FOOD AND DRUG ADMINISTRATION

+ + + + +

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

8479 '00 MAR 27 A10:18

+ + + + +

VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

+ + + + +

MEETING BY TELECONFERENCE

+ + + + +

FRIDAY,

MARCH 10, 2000

+ + + + +

This transcript has not been edited or corrected, but appears as received from the commerical transcribing service. Accordingly the Food and Drug Administration makes no representation as to its accuracy.

OPEN

ORIGINAL

The meeting was held at noon in the Kennedy Room of the Holiday Inn, 8777 Georgia Avenue, Silver Spring, Maryland, Dr. Harry B. Greenberg, Chair, presiding.

PRESENT:

HARRY B. GREENBERG, M.D.	Chair
ROBERT COUCH, M.D.	Temporary Member
ROBERT S. DAUM, M.D.	Member
THEODORE EICKHOFF, M.D.	Temporary Member
MARY K. ESTES, Ph.D.	Member
WALTER L. FAGGETT, M.D.	Member
L. PATRICIA FERRIERI, M.D.	Temporary Member
BARBARA LOE FISHER	Member
DIANE E. GRIFFIN, M.D., Ph.D.	Member
CHARLES HOKE, JR., M.D.	Temporary Member
ALICE S. HUANG, Ph.D.	Member
EDWIN KILBOURNE, M.D.	Temporary Member
STEVE KOHL, M.D.	Member
MARTIN MYERS, M.D.	Temporary Member
DIXIE E. SNIDER, JR., M.D., M.P.H.	Member
DAVID S. STEPHENS, M.D.	Member
NANCY CHERRY	Executive Secretary
DENISE ROYSTER	Comm. Mgmt. Spec.

A-G-E-N-D-A

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

(12:03 p.m.)

MS. CHERRY: The following announcement addresses conflict of interest issues associated with the sessions of the Vaccines and Related Biological Products Advisory Committee on March 10, 2000.

Based on the agenda made available, it has been determined that the committee discussions for the influenza virus vaccine formulation for 2000-2001 and the briefing of the vaccine safety action plan present no potential for a conflict of interest. Dr. Alexander Klimov has been invited as a guest to participate in this discussion.

The Director of the Center for Biologics Evaluation and Research has appointed Drs. Claire Broome, Robert Couch, Theodore Eickhoff, Patricia Ferrieri, Charles Hoke, Edwin Kilbourne, and Martin Myers as temporary voting members for the discussion on the flu formulation.

In the event that the discussions involve specific products or firms not on the agenda and for which FDA's participants have a financial interest, then the participants are reminded of the need to exclude themselves from the discussions. Their refusals will be noted for the public record.

With respect to all other meeting participants, we ask in the interest of fairness that you state your name and affiliation and any current or previous financial involvement with any firm whose products you wish to comment on.

Now, let me check one more time because I think somebody else came on the line. Dr. Daum? Dr. Faggett?

DR. FAGGETT: Dr. Faggett is here.

MS. CHERRY: Good. Welcome.

DR. FAGGETT: Good morning.

MS. CHERRY: Dr. Kim. Dr. Broome. Okay. Well, I hope they will join us as we go through. That's all I have, Dr. Greenberg.

DR. GREENBERG: Okay. Let me look at my agenda here. What am I supposed to be doing next here, Nancy?

One note that I would like to just simply say to the advisory group around the telephones, that obviously it is harder to coordinate statements and questions in this venue then when we're in person. What I would just ask is that we all be tolerant of everybody else because it's complicated. Also that you spend a little extra time formulating your question or your thought so that we do it as

efficiently as possible.

I guess with that admonition, I will turn over the discussion to Roland who is going to review the current situation.

DR. LEVANDOWSKI: Okay. Thank you, Dr. Greenberg. Good day to everybody. I just would like to review a little bit about things that have happened in the past. As you will recall, as the January meeting the committee recommended that the A/New Caledonia/20/99 strain would be used as the H1N1 virus for the 2000-2001 influenza virus vaccine for the United States.

However, at that time the recommendations for the H3N2 Influenza A and the Influenza B viruses were deferred so that additional information could be collected and analyzed.

In February new information was presented and discussed at the World Health Organization and recommendations were made by WHO at that time. I believe you should have gotten a copy of the WHO recommendations. The WHO recommended as published in the February 25 "Weekly Epidemiologic Record" that vaccines for the 2000-2001 influenza season of the northern hemisphere should contain an A/New Caledonia/20/99 H1N1 like strain, an A/Moscow/10/99

H3N2 like strain, and a B/Beijing/184/93 like strain.

Those recommendations are the same as those that were previously made in September of 1999 for the southern hemisphere where that influenza season is about to begin and manufacturing has been accomplished.

As you may know from previous discussions, the A/Moscow/10/99 H3N2 virus has been found to be unsuitable for vaccine manufacturing and that's because the wild-type virus does not grow well enough and no suitable reassortant was obtained after considerable effort was expended in a number of laboratories to try to make a high-growth reassortant.

However, the A/Panama/2007/99 H3N2 virus is considered to be an A/Moscow/10/99 like strain and several high-growth reassortants with potential for use in manufacturing have been produced. That was also noted by WHO in their publication.

The B/Yamanashi/166/98 virus, which is an B/Beijing/184/93 like strain is being used for manufacturing as the B strain in most areas of the world.

Earlier this week on March 7 representatives of member countries of the European Agency for Evaluation of Medicinal Products met to complete their

recommendations for strains to be used in influenza virus vaccines next season in Europe.

European scientists from national regulatory authorities and manufacturing groups confirmed the selections that were made by WHO by choosing A/New Caledonia/20/99 as the H1N1 virus, A/Panama/2007/99 as the H3N2 virus, and B/Yamanashi/166/98.

In the case of the A/Panama/2007/99 strain, five high-growth reassortant viruses are being considered as potential vaccine candidates and it is expected that work will be completed in the next two weeks to determine which of those candidate viruses might be best suited for overall manufacturing purposes.

Our purpose for today is to complete the recommendations for influenza virus strains to be used in vaccines for the United States during the upcoming season. Specifically the committee and consultants are gathered on this teleconference to make recommendations for the H3N2 Influenza A virus and the Influenza B viruses. I'll just read the questions as they are listed in the agenda.

No. 1 is what strain should be recommended for the Influenza B component of the vaccine? Question 2 is what strain should be recommended for

the Influenza A (H3N2) component of the vaccine.

Having said that, unless there are some other comments from anybody, to begin we would like to provide some additional data for the committee's consideration starting with additional surveillance information from the CDC. Standing by at CDC will be either Dr. Alexander Klimov or Dr. Nancy Cox to fill us in on information on surveillance.

DR. FAGGETT: Do we have this information in our packet?

DR. LEVANDOWSKI: Yes, that information should have been sent to all the committee members as part of the most recent package of information. I would suggest that you do follow along with the handouts wherever possible.

DR. GREENBERG: Roland?

MS. CHERRY: It was faxed.

DR. GREENBERG: Roland, I assume this packet is the packet where the first page says CDC Information for FDA Advisory Panel March 10, and it's a 17-page packet. Is that correct?

DR. LEVANDOWSKI: That should be correct. I'll just confirm that with the CDC colleagues.

Sasha? Nancy? Are you there? Hello.

MS. CHERRY: CDC?

DR. KLIMOV: Can you hear me? Hello.

MS. CHERRY: Yes.

DR. LEVANDOWSKI: We're having trouble hearing you.

DR. KLIMOV: Can you hear me now?

DR. LEVANDOWSKI: Yes.

DR. KLIMOV: This is Dr. Klimov from CDC. Nancy Cox is not available right now. She might join us later. Do you hear me clearly?

DR. LEVANDOWSKI: Yes.

DR. KLIMOV: Okay. Should I start, Dr. Greenberg?

DR. GREENBERG: You should start but I asked a question which you could answer first, and that is I am assuming that the information that the panel members will be following is in a packet that starts with something saying, "CDC Information for FDA Advisory Panel, March 10," and it is a 17-page document?

DR. KLIMOV: That's correct.

DR. GREENBERG: Okay.

DR. KLIMOV: I will start with brief update on the U.S. Surveillance and national influenza activities we can ignore in the U.S. Most states or territorial epidemiologists reported widespread

influenza activities this week.

Only five of them reported original activity. The proportion of patients with visits to sentinel physicians for influenza like illness is within the baseline level in the U.S. You know there are issues (indiscernible). I'm sorry. Can you hear me?

DR. LEVANDOWSKI: Sasha, we're not hearing you because there was a lot of interference there for a second or so. There was some sort of crunching noise. Could you please repeat that?

DR. KLIMOV: So, as I said, the proportion of patients with visits to sentinel physicians for influenza like illness is within the baseline level in the whole U.S. now. You also know from the January meeting that there are pharmacological issues existing for the pneumonia and influenza mortality. This mortality is deeply down now but also is still slightly above the threshold for this period of the year.

The dominant one this year was Influenza A (H3N2). You can look at the page 2 which has a graph indicating that the peak of the Influenza A (H3N2) activity was between first and second week of this year. You could notice as well that at the very end

of this season there is an increasing number of Influenza A (H1N1). Totally we received like 45 to 50 Influenza A (H1N1) within the last five weeks. I am going now to the page 4.

DR. KOHL: Can I ask a question about that?

DR. LEVANDOWSKI: Dr. Kohl has a question, I think, for you Sasha.

DR. KLIMOV: Okay.

DR. KOHL: The H1N1 isolates, were they from a particular part of the United States? Were they those Carolina/Kentucky isolates that are featured on the next page?

DR. KLIMOV: The Kentucky isolates and Carolina isolates but not only from those regions. We have them from Hawaii, Nevada, California, Wisconsin, Kentucky as you said, and North Carolina as well.

DR. KOHL: Thank you.

DR. KLIMOV: And the hemagglutination inhibition test presented on page 4 for Influenza H1N1 viruses actually validates the decision which was made in January about H1N1 vaccine component. As you can see from this table in two sort of difference frames, we have now in the United States two variations of Influenza H1N1 circulating. The first group is so-called Beijing/262-like or we can call them now A/New

Caledonia-like viruses. This is antigenic and genetic group.

The other group of viruses we found in North Carolina and Kentucky. They are similar to the previous year's Influenza H1N1 which circulated in the United States. They belong to so-called Bayern group or, according to the vaccine strain, to the A/Johannesburg/82/96 antigenic and genetic lineage.

The Beijing/262-like or New Caledonia-like viruses, you can see that within this group Beijing/262 ferret antisera which is A antisera on this table will not cover well all new strains and in particular some strains from Hong Kong, Bangkok, and Philippines. There is more than four point difference between the homologous titer and the titer against those (indiscernible). At the same time you can see that New Caledonia/20 ferret antisera did well with all the viruses in this set.

As you can see from the table also, the Johannesburg/82/96 or Bayern-like viruses, are close to each other and to the previous years of Johannesburg/82. I would like to remind you all that Johannesburg/82-like viruses are distinct antigenically to the A/Beijing/262/95-like viruses. However, the Beijing/262 produces five types of

antibodies that cross-react well with all A/Bayern/7/95-like viruses.

Now I'm going to move to the Influenza B viruses. I would like to ask you to turn to page 6 of our package.

PARTICIPANT: It's difficult to hear you. Could you speak up, please.

DR. KLIMOV: Okay. I'm trying to speak as loud as I can. Can you hear me?

PARTICIPANT: It's a bit better.

DR. KLIMOV: Okay. I will try keeping louder. This page 6 and the following page 7 represent recent hemagglutination inhibition data on some recent viruses. As you can see, most of those viruses continue to belong to B/Beijing/184/93 and B/Yamanashi/166/98 group.

The test on page 6 includes some recent viruses from China. As you remember, during the January meeting we mentioned that we just received at that moment a package from China. From the table on the page 6 you can see that some of those new viruses from China are poorly covered with Beijing/184 antisera.

As you remember during the January meeting we mentioned the Shenzhen/654/99 at that moment

possible variant which we hope will cover most of the viruses. You can see from the table on page 6 this antisera (indiscernible) so it looks like the China has some new variations but there is no one particular group of viruses in this region.

DR. GREENBERG: There is somebody who is eating an apple into their phone or something.

MS. CHERRY: It may help if you put your phone on mute while you're listening.

DR. KLIMOV: Okay. So page 7 represents the data which we received from Dr. Alan Hampson from London. We have similar data, just his collection is a little bit wider. The test includes recent viruses from Hong Kong. I forgot to mention that unfortunately we do have just a few viruses from China so far. We've had very few come to the U.S. this season.

The table on page 7 clearly shows that the new virus is from Hong Kong definitely Yamanashi/166/98-like and this Yamanashi antisera reacts well with the strains from that region.

The next page 8 presents data --

PARTICIPANT: Sasha, can I ask a question? Do we have much epidemiologic information yet about the Shangdong/07 being so far out?

DR. KLIMOV: Not too much actually. We are talking more about what I call B/Victoria-like viruses. We did not receive this virus from China but we do know that some countries like Japan and Taiwan do have B/Victoria-like viruses with the B/Beijing/184. As you all know, the B/Victoria-like viruses are in the United States for many, many years.

PARTICIPANT: Thank you.

DR. KLIMOV: Page 8 represents the evolutionary relationships among Influenza B hemagglutinin genes. This is about the same shown to you all at the January meeting except new viruses on the top of the tree, Shenzhen/652, Shenzhen/654. The majority of recent viruses are within the bottom part of this tree. In other words within the B/Yamanashi/166 genetic group. They are genetically close to B/Yamanashi.

The viruses on the top of this figure which I mentioned is from so-called Harbin/7/94 genetic sublineage. I should mention that viruses from this sublineage wasn't found in the United States. They continue to circulate a little bit in China but even in China they have more B/Yamanashi-like viruses at this moment genetically.

The next table on page 9 is actually the

same table we have shown during the January meeting but we put this in the package just to remind you all that B-Yamanashi/166/98 virus is the closest virus to so-called consensus amino acid sequence of the hemagglutinin.

You can see, for example, that Beijing/184 has 9 amino acid differences. Harbin/7/94, which used to be the same strain for several years, has 12 amino acid differences but B/Yamanashi/166/98 still has only 2 amino acid differences from the consensus sequence. This is an indication that we do not have considerable antigenic change of the hemagglutinin of recent Influenza B viruses.

If you have questions about Influenza B please go ahead. Otherwise, I will go to Influenza A (H3N2) viruses.

Okay. Influenza A (H3N2) virus. We have a few which is similar to what we saw during the January meeting or before January meeting. Most of the viruses are still close to Sydney/05/97, Moscow/10/99, and Panama/2007/99.

If you look at the hemagglutination inhibition table on page 11 of your package, you can see that the viruses are close to Sydney, Moscow, and Panama. But at the bottom part of the table, you can

see that there are some new viruses.

For example, in this particular case, from Indiana, Texas, Florida, which are low to Sydney/05 to the homologous side. Also you can see that there is a tendency that Moscow antisera or Panama antisera cover those new viruses better than Sydney/05 antisera does.

The next table on page 12 includes some new viruses from U.S. and other areas. This also represents the data of hemagglutination inhibition activity caused by ferret antisera raised against several Panama high-growing reassortants. Those reassortants are so-called Resvir-16, Resvir-17 as prepared in Dr. Levandowski's lab, and also NIB-41 which was prepared by Dr. John Wood in London.

Once again, from this table you can see at the bottom of the table there are some recent viruses which are low to Sydney/05 antisera but they are followed pretty well with Moscow/10 or Panama/2007 antisera most of them.

Also this table shows that antigenically all three high-growing reassortants are similar to each other and acceptable by their antigen as potential vaccine reassortant. They work as well as wild-type Panama virus does.

The next page, page 13, represents a genetic evolutionary relationships data among recent Influenza A (H3N2) viruses. You can see that definitely the viruses of this subtype are undergoing genetic changes. They are quite high now from Sydney/5/97 genetically.

In the middle of this graph you can find Panama/2007/99 virus. Actually, all recent viruses belong either to the A/Panama/2007 branch on this tree or to the branch which is on the top of this picture. I should mention that antigenically those viruses from those top two branches it is impossible to distinguish between them. As I said, antigenically they are pretty similar to A/Panama/2007.

If you move to the next page 14, you can see that Panama/2007/99 is the virus which is one of the closest to the consensus amino acid sequence of the hemagglutinatinin of recent Influenza A (H3N2) viruses. For example, the Sydney/5/97 had 9 amino acid differences from the consensus. Panama/2007 had just 3 amino acid differences which actually provides additional support to Panama as a potential vaccine candidate from our point of view.

The last page of the package, page 15, presents the data on evolution of the neuraminidase

genes of recent influenza viruses. You can see from this graph the new variations of Influenza A viruses like reassortants 16, 17, etcetera.

They belong to a sublineage which is different from the sublineage of where the Sydney/5/97 neuraminidase is. In other words, the neuraminidase of recent viruses is genetically different from the neuraminidase of Sydney/5/97-like viruses.

As a sort of conclusion about the H3 part of my presentation, I should repeat that antigenically and genetically the data which we gained after the January meeting are similar to what we have shown during the January meeting about vaccine selections. Genetically we definitely see that the new age of Influenza H3 antiviruses are most harm in comparison to Sydney/5/97 vaccine strain.

Also, I would like to mention that we may sort of vary on how many viruses we received this year from people who were vaccinated. We call them vaccine tailors. How data indicate that if two years ago we received approximately 3.8 percent of viruses from vaccinated people. Last year we received 4.1 percent of strains from people who were vaccinated.

This year this figure is double so in this season 47 of 542 viruses we received so far. It was

9 percent, 8.7 percent of viruses we received from people who were vaccinated this last year. We do not ask specifically people to send us the knowledge of viruses circulated from vaccine tailors so this is just random figures which we have.

Probably I will stop here and ready to answer your questions.

MS. FISHER: This is Barbara Fisher. I have a question.

DR. LEVANDOWSKI: Yes.

MS. CHERRY: Go ahead.

MS. FISHER: Okay. Sorry. What you're saying then is that those who were vaccinated and came down with the flu, we don't know which strain was associated with that failure?

DR. KLIMOV: You know, my most cases, antigenically those viruses are pretty close to Sydney to Moscow to Panama, the recent viruses. Genetically they are withdrawn.

MS. FISHER: I have one more question. In the last meeting you talked, or someone talked about increased mortality associated with the flu this season. Do we have anymore data about the health and vaccination history of those who died including their ages?

DR. KLIMOV: This data is still in the collection stage. I know that our edit section is working on this right now but I do not have any finalized data about this issue.

DR. GREENBERG: Let's clarify something just for the record here because I'm not sure I understand the response. It was my impression that the data that was stated was that this year --

PARTICIPANT: You're breaking up, Harry. We can't hear you.

DR. GREENBERG: Is that better? Sasha, hold on a second. What I heard you say was that this year approximately 9 percent of the isolates sent to the CDC appeared to come from people who were vaccinated as opposed to the past two years where approximately 4.5 percent came from people who were vaccinated.

DR. KLIMOV: It's about 4 percent.

DR. GREENBERG: You said nothing that I am aware of of differences in sequence or antigenicity of the two types of isolates. I think that was what Ms. Fisher was asking.

DR. KLIMOV: Okay. Once again, the tables which are in our package indicate that we do see a definite percentage of viruses which are low to Sydney now.

DR. GREENBERG: Sasha, the question is are those viruses specifically obtained from people who were vaccinated?

DR. KLIMOV: Okay. Every year we receive some number of viruses. We made a query how many -- when we receive some viruses in some cases they have a remark that the virus was from a vaccine tailor or from vaccinated person. When we made these calculations, we realized that this year --

DR. GREENBERG: Sasha, you're not listening I don't think. I understand what you're saying.

PARTICIPANT: Harry, permit me. It's just a simple question. Are the isolates from vaccinees the same as from none vaccinees?

DR. KLIMOV: In general, yes. In general, yes.

DR. GREENBERG: Thank you. Because that was what Ms. Fisher, I think, was asking and, I think, your answer confused me. Okay.

DR. KLIMOV: Okay. I'm sorry.

DR. GREENBERG: Go on.

PARTICIPANT: I have two questions. I have to say I am not terribly impressed with differences away from the Sydney in terms of antigenicity. If you look at page 12 again and compare Sydney/5 at the top

as A with NIB-41, which I gather is a Panama reassortant, I don't see really significant differences among those ferrets here.

I think you probably only used a couple of ferrets per observation point. Don't you? I just wonder that we're always moving too fast here and relying more on sequence and antigenicity, antigenicity being the definitive thing as far as I'm concerned still. The tendency is interesting but probably academic in terms of protection.

DR. KLIMOV: As you can see from the table on page 12, there is a four-fold difference one way between Sydney and Panama but not the other way, between Panama and Sydney as you can see on this particular table but we don't see this in all the tests so it's a one-way difference between Sydney and Panama-like viruses.

Yes, indeed, there is no dramatic difference between Sydney and, let's say, Panama for example. But as you can see, nonetheless, from the table on page 12 on the bottom part quite a number of viruses on this table are more than four-fold down to Sydney but not to Moscow and not to Panama but all of them are reacting extremely well with Panama or Moscow. The percentage of low reactors to Panama or to Moscow

is lower than percentage of low reactors to Sydney.

PARTICIPANT: Yes, but the group I would be concerned about, which would be numbers 20 through 28, the data looks very much the same to me as I scan those data in terms of protection by any of those ADCD antisera at the top.

DR. KLIMOV: Exactly. That's what I'm saying. Antigenetically all reassortants with Resvir-16, 17, and NIB-41 are similar to wild-type Panama virus.

PARTICIPANT: As far as I'm concerned, it becomes academic about changing away from Sydney even though our instincts tell us probably why. I have one other question, Sasha. Do you have any information about the neuraminidase antigenicity? You've shown us a genetic tree there. Is there any information about any significant antigenic differences among those N2s?

DR. KLIMOV: We don't have this here at CDC but there is data which indicated antigenic properties of recent neuraminidase are different from the Sydney/5-like neuraminidase.

PARTICIPANT: I see. That might begin to explain some of the differences you will be seeing this year in terms of vaccine failure. Are you going to be looking for that?

DR. KLIMOV: That's correct.

PARTICIPANT: Okay.

DR. LEVANDOWSKI: Okay. This is Roland Levandowski. Are there other questions?

DR. KOHL: Yes, this is Kohl. I'm a little concerned about the H1N1 at the end of the season. And also about the isolation of a considerable number of low neflodation strains from the southern part of the United States.

DR. KLIMOV: As to the first question, the number of H1N1 viruses in the United States in the recent weeks, it's hard to predict right now will it continue to increase. We do know that Japan, Taiwan had wide outbreaks of H1N1 viruses this season. We do know that Canada, for example, had in recent weeks also outbreaks of Influenza A (H1N1) viruses.

Once again, it's difficult to say whether it's going to be what we call a wide base and small peak at the end of the season but this is the fact right now. There is an increasing number of H1N1 viruses which we did not see before during the preceding weeks of the influenza season.

DR. KOHL: And a portion of those H1N1s will not be well covered by this strain we chose in January.

DR. KLIMOV: It is well covered. It is well covered.

DR. LEVANDOWSKI: Dr. Kohl, let me just -- can I clarify? This is Roland Levandowski. Can I clarify? You're looking at the table from page 4 and you are referring to the antigens No. 17 through 21?

DR. KOHL: Correct.

DR. LEVANDOWSKI: Those antigens are really Johannesburg/82/96-like strains. I think we should emphasis that the CDC's ferret antisera are very good at detecting the difference between those two lineages, between the Beijing/262 vaccine lineage and the older Johannesburg/82/96 lineage.

We're not presenting the data here but we have data from people who have been immunized which indicate very well that the antibodies produced in response to Beijing/262 and people do cross-react very well with those Johannesburg/82/96-like strains.

Although we don't have data on these specific strains, I think we would expect that we would see the same if we did the serologies with those. Partly that would be because most people have been exposed in the past to the Johannesburg/82/96-like strains.

DR. KOHL: Thank you very much.

DR. COUCH: That data is in your handout.

DR. LEVANDOWSKI: I wasn't really going to emphasis it later.

DR. COUCH: But the concern arises and it's covered by your serology table.

DR. LEVANDOWSKI: Okay. This is Roland again. Are there other questions or comments?

DR. DAUM: Bob Daum speaking from Chicago.

MS. CHERRY: Hi. Welcome, Dr. Daum.

DR. DAUM: Welcome to you. Hi. In terms of failure isolates, return to that for just a moment. Two questions. First of all, do we know anything about the reporting system or the likelihood that someone would send you an isolate from a failure patient versus a nonfailure patient and has that possibly changed in the last three years?

Secondly, I may have blanked but did you give us any breakdown by serotype of the failure isolates?

DR. KLIMOV: As to the first question, there is not actually a system of sending us viruses specifically for people who failed to be protected with the vaccine immunization so they us randomly. As I mentioned before, we do not request specifically to send us data from such patients.

MS. CHERRY: Dr. Klimov, you are being hard to hear. Can you speak up?

DR. KLIMOV: Okay. Okay. Is this better?

MS. CHERRY: Yes.

DR. KLIMOV: Okay. Once again, we do not have any specific system of tracking viruses from vaccinated people, just people that sent us what they consider to be interesting to send. Once again, there is no specific system. Just, as I said, we notice that this year the percentage seems to be higher than two years ago.

As to the second question, I didn't quite understand what you mean about serotyping. They are all H3N2.

DR. GREENBERG: Again, I think it's important for all of us --

PARTICIPANT: You're breaking up again.

MS. CHERRY: Harry, we're losing you.

DR. GREENBERG: I would just like to make sure that everybody once questions are answered try to ask a new question because it's hard enough to pay attention to this thing, at least on my phone, because it's breaking up so much. Are there any more questions?

DR. COUCH: Harry, Bob Couch. As long as

you've stopped for a moment, I'm going to have to leave the call in about 10 minutes. I am responsible for our noon conference. Just in general, I think Ed's points are well taken but I think the decisions are fairly straightforward but it's probably too early for an opinion. In 10 minutes from now I'm going to leave you but if you want me to say anything at that time, feel free. Otherwise, I'll try to join you if you're still going when it's over.

DR. GREENBERG: Okay. I might since you have a lot of experience and probably --

DR. COUCH: You've got other people there that do, too, though.

DR. GREENBERG: No, no. I might ask you your opinion so if you could just indicate when you are about to leave.

DR. COUCH: Okay. Okay.

DR. GREENBERG: Roland.

DR. LEVANDOWSKI: Okay. If there are no further questions, then we'll just continue. I would like to get some information, just some refresher information about serologic responses and the availability of strains and reagents. I will try not to take too long. I'll refer you to the handout from the Center for Biologics that is dated current to

March 7, 2000. I don't want to call your attention to too many tables in there but I will call your attention to a few.

I don't have a handout that has all the individual serologic studies that were done from the participating labs to save space so the ones that are included in the handout are just intended to give some examples for people who wanted to take a look at them.

My main goal is going to be to try to summarize the work that has been done by the four labs that are involved in doing serologic testing; CDC in Atlanta, WHO Melbourne in Australia, National Institute for Biological Standardization and Control in London, and CBER-FDA in Bethesda.

Overall I would like to point out that this collaboration is very extensive and labor intensive. The effort is to try to collect as much information as we can on the performance of vaccines with respect to antibodies that will inhibit recently identified strains relative to the current vaccine strain. You will see on these tables that we've got more than 50 different influenza viruses that we've taken a look at this year. I'll call your attention to some specific ones.

A lot of the information has been previously

described. I'm not going to talk about the H1N1 strains at this point. I'm going to restrict my remarks to the H3N2 and the B viruses. There's a table on page 3 of the handout which indicates the H3N2 Influenza A viruses that have been examined and you'll see if you look at that that the list is very extensive. It includes strains from all of the antigenic and genetic backgrounds that have been identified.

In particular, the list includes some viruses that were collected during the current influenza season in the United States such as the A/Michigan/27/99 and the A/California/32/99, as well as some strains that are genetically more closely related to the A/Moscow/10/99 and A/Panama/2007/99 such as the A/Victoria/358/99 and A/Philippines/26/99 strains.

If you'll turn to the summary table, which on page 16 of the handout, you'll see a table that shows a number of serologic tests that were done indicating whether a 50 percent or greater reduction in antibody titer occurred as compared to the A/Sydney/597 vaccine strain. Here again we're using the 50 percent or greater reduction as a cut-off point since it represents a two-fold reduction in titer.

In some instances on this table, the tests were done with the Resvir-13 A/Sydney/597 reassortant that was used in the vaccine. In some instances the wild-type A/Sydney/597 virus was used for comparison.

You'll notice that there is some variability in the results between the laboratories but in several instances the majority of tests indicate that there is a 50 percent or greater reduction in the antibody titers such as the results for A/Victoria/358/99 and A/Philippines/26/99.

In other instances there is little or no reduction such as with the A/Michigan/27/99 strain and with the A/Shenzhen/510/99 strain. Overall we think that the results indicate that the current H3N2 Influenza A vaccine strain is imperfect in its coverage of recently circulating influenza viruses.

Turning to the -- I'll just continue and if there are questions, I'll take them all at the end I think. Turning to Influenza B, the table on page 4, flipping back to page 4, indicates the viruses that were used for serologic testing. You'll note that most emphasis was placed on viruses that are similar to the current vaccine strain which is B/Yamanashi/166/98. The strains tested are representative of a wide geographic range and they

include the new variant B/Shenzhen/654/99.

The summary on page 17, flipping back one more time, shows the number of serologic tests that were done that showed a 50 percent or greater reduction in antibody titer as compared to the B/Yamanashi/166/98 vaccine strain or its equivalent. Again, the results are somewhat mixed. For the new variant strain B/Shenzhen/654/99, for example, the geometric mean titers were reduced by more than 50 percent in the majority of tests.

In addition, results for B/South Australia/5/99 were also reduced. In looking at other strains that are similar to that one such as the B/Shanghai/180/99 and the B/Johannesburg/5/99 there was little or no evidence of reduced titers. Taken all together the results indicate that antigenic changes that are occurring can be detected in some cases including in the case of this variant B strain.

That's really all I have to say about the serologies at this point. If there are questions, I'll take them.

One further comments would be that these data are really not so different from what we were discussing in January, although there was a lot of additional information that was collected. If there

aren't any questions about that, then I'll just go on and make a few comments about the availability of strain reagents.

The Influenza A/New Caledonia/20/99 (H1N1) high-growth reassortant virus, the IVR-116, is currently being used for manufacturing. Information on the yield of the strain suggest it to be a moderately high yielding strain. For the benefit of manufacturers, the specific antisera and antigen for performing the potency test for A/New Caledonia will be available from the Center for Biologics within the next two weeks.

The antigen is in the last stages of calibration for use and both it and the specific sheep antiserum are being prepared for distribution even today as we're speaking. These reagents are available at an earlier time this year than usual for a new strain because of efforts to support manufacturing for vaccines being distributed in the southern hemisphere and we think that's actually a good thing for helping us smooth out the difficulties with making strain changes.

There are five high-growth reassortants of the A/Panama/2007/99 (H3N2) virus that are being evaluated. As Sasha Klimov was pointing out, all of

these appear to be antigenically equivalent. Even though he didn't have all five listed in the table, they are all antigenically equivalent. Two of these appear to be higher yielding than the others.

Additional information is being gathered on those to determine whether one or the other of those strains might be better suited to downstream processing which is an issue also.

Potency reagents are not currently available for the Panama/2007 strain, although immunization of sheep has been begun in anticipation that strain might be a potential vaccine candidate. Potency reagents for the A/Panama/2007 strain would not be available until sometime in May which is typical time for these.

Of course, we do have the reagents for the A/Sydney strain currently available and in the event that a Panama strain was chosen for manufacturing, those reagents could be used in the interim, although they would be expected to give a falsely high estimate of how much vaccine was being produced.

The B/Yamanashi/166/98 virus and potency reagents are currently available. However, here we don't have as much of a choice in terms of the practical issues. Work that's been done earlier in the United States and Europe with the

B/Johannesburg/599 strain and in Australia with the B/South Australia/599 strain suggest that neither of those strains would be suitable for manufacturing because of their poor growth characteristics. Really we don't have any other candidate, Yamanashi-like strains at this time.

One further comment about the B/Shenzhen/654/99 strain is that working with it in the laboratory it seems to have, at least in some laboratories, some unusual properties in that when the antigen is split with ether whereas normally we would expect the hemagglutinin titer to increase substantially it sometimes goes down and that's a little bit concerning.

That's all that I have to say about the strains and reagents unless there are some questions or comments.

DR. FAGGETT: One question. This is Dr. Faggett in Washington. You said there were two strains that had a high yield because they were antigenically -- there were two strains of those?

DR. LEVANDOWSKI: We're talking about the A/Panama/2007/99 reassortants that I believe you are referring to. Those two strains are designated as Resvir-17 and NIB-41. They are both reassortants that

were produced using the A/Panama/2007/99 virus as the wild-type parent.

PARTICIPANT: Roland, has just one high-yield reassortant on the New Caledonia been distributed to manufacturers?

DR. LEVANDOWSKI: That has been and at this point we don't anticipate using any others mainly because of the issues about making the reagents specific for the strain. We have noticed in past years recently that there can be some differences in the behavior of the behavior of the potency reagents for different isolates, even though when they are related by the wild-type parent.

PARTICIPANT: I just wondered if in the manufacturer's hands if you looked at the other New Caledonia candidates they might be higher yielding.

DR. LEVANDOWSKI: I believe there may be some information on that but I don't have it at hand.

PARTICIPANT: Okay.

DR. SNIDER: Roland, this is Dixie Snider. You went over it rather fast, at least with regard to the B reassortants that might be available. What I took away was that there was no B/Yamanashi strains that were viable. Then you started talking about Shenzhen I lost you.

DR. LEVANDOWSKI: I'm sorry. I do tend to talk pretty fast when I'm excited like I am today. There are no reassortants for the B strains at this point. The manufacturers rely entirely on the wild-type strain and in producing vaccine that often is one of the biggest problems, to get a wild-type influence of B virus that grows well.

What I meant to point out but maybe didn't do well enough was that the strains that have been examined by manufacturers so far which include the Johannesburg/599 and the South Australia/599 did not appear like they would be of practical use in manufacturing.

The Shenzhen/654 strain has not been examined as far as I know but, as I was mentioning, there are some concerns that come out of just the laboratory testing of the strain about whether that would be a suitable strain or not.

DR. COUCH: Harry, would you permit me? Bob Couch.

DR. GREENBERG: It would be my pleasure.

DR. COUCH: I will just be brief and I'm sure you'll have other discussions and there may be different views as well. I think probably our decisions are not very complicated.

Regarding B, I would like to have known more about the influence of the B strain variation and the epidemiology of what's going on in China with regard to questions like Shenzhen and South Australia, but I think our information otherwise is fairly straightforward that I would recommend that we stay with B/Yamanashi again for the coming year.

Regarding the H3N2, I agree with Ed. I don't think it's absolutely clear that there is a distinct change that requires a change. But, on the other hand, as he said, I think we have that as a knee jerk response and I think we need a little fine tuning if that's what we have in store on the H3N2.

I'd feel a little bit better with Panama in view of the suggested changes in the neuraminidase as well even though we don't have antigenistic data. I'm a little more comfortable with changing that H3N2 and Panama looks like our best bet in that regard. That would be my recommendation on H3N2.

DR. GREENBERG: Thank you very much, Bob.

DR. COUCH: And I'll have to run.

DR. GREENBERG: Okay. Have a good noon meeting.

DR. COUCH: Thanks.

MS. CHERRY: Thanks, Dr. Couch.

DR. GREENBERG: Roland, back to you.

DR. LEVANDOWSKI: Okay. Are there other questions at this point? If there weren't, I would be prepared to make a summary of this and give some options for what the strain choices might be.

MS. CHERRY: Please do.

DR. GREENBERG: Yes.

DR. LEVANDOWSKI: For the 2000-2001 influenza vaccine, just to summarize the information about the H3N2 and the Influenza B viruses starting with the H3N2 Influenza A.

In the case of the H3N2 Influenza A viruses, it's pretty clear that antigenic drift is continuing. Most of the strains are antigenically similar to the A/Sydney/597 and A/Panama/2007/99 strains. However, we have some evidence that suggest that the neuraminidase of the more recent strains is different from that of the current vaccine strain which is A/Sydney/597. That can be debated some.

Ten to 15 percent of the strains, no matter what the choice is, are not well inhibited by the ferret sera but those low reactors, as we emphasized in January, don't fall into any particular genetic background.

Whereas the CDC normally receives 2 to 3

percent of its influence isolates from persons who are immunized, this year the percent seems to be higher, about 9 percent of the isolates, which is a substantial increase from people who got this year's vaccine and nevertheless were infected. That was without particular effort to try to collect those strains.

Some of the H3N2 viruses are not very well inhibited by antisera from people who are immunized with the current vaccines that contain the A/Sydney/5/97 strain. Again, the current vaccine strain, A/Sydney/5/97, has been around already for two years which is quite a long time by modern standards for an H3N2 strain given the continuous antigenic drift.

Finally, the high-growth reassortants of A/Panama/2007/99 are available. They appear to grow well. It looks like they would be possible to use in manufacturing.

The options for the H3N2 strain, the first option would be, of course, to continue to use the current vaccine strain which is A/Sydney/5/97. In favor of that, I would say that the manufacturing is very well worked out and the yield is highly predictable. In addition, many of the viruses this

year are A/Sydney/5/97-like.

Again that is that there is antigenic drift that is continuing. The vaccine strain, again, is relatively old for an H3N2 strain. More than the usual number of H3N2 isolates are from persons who are immunized with the current vaccine. A consistent minority of all the strains, however, are not well inhibited by the sera produced against the current vaccine.

This brings me to the second option and I think there are only two here. The second option is to change the current vaccine to a strain that is more representative of the currently circulating viruses such as the A/Panama/2007/99. In favor of that a more recent strain would provide a closer match with the hemagglutinin and the neuraminidase of contemporary strains.

There are some alternative high growth reassortants that could be chosen. Against that we really don't know that a new strain would be superior in coverage for the low reactors in terms of its comparison to A/Sydney.

Turning to the Influenza B viruses --

DR. GREENBERG: Roland?

DR. LEVANDOWSKI: Yes.

DR. GREENBERG: Do you want to do both of these and then have discussion or do you want to have any discussion about your H3N2 and then have a vote on that?

DR. LEVANDOWSKI: If it's simpler to go ahead with the H3N2, I think that might be the way to go if that's what you're suggesting.

DR. GREENBERG: It's up to you but I think that might be simpler since it's totally fresh and you just went through the options and people can ask you a question and then we can vote.

DR. LEVANDOWSKI: Okay. That's perfectly fine with me.

DR. GREENBERG: Are there any further clarifications that anyone would like of Roland or anybody else?

DR. SNIDER: Well, Harry, this is Dixie. I was just going to mention that this week's MMWR also points out that although this past season has not been out of line with the kinds of epidemics we've had in the past five seasons, it has been shall we say one of the more severe seasons. I think that is also a factor that would indicate to me that it would be wise to try to keep up with this drift if it continues to occur.

DR. GREENBERG: Thank you, Dixie. Does anybody have anything else to say before we call a vote?

DR. FAGGETT: This is Walt Faggett. That would be pushing towards changing the Sydney, right? Is that what you're saying?

DR. SNIDER: Yes.

DR. FAGGETT: So that 9 percent probably was due to that.

DR. SNIDER: Yeah, and what I'm saying is that we had other indicators of the severity of the epidemic during this past year. Although we've seen numbers like we've seen this past year in some previous seasons, you would have to say it was a bad season.

DR. GREENBERG: Okay.

MS. CHERRY: Dr. Greenberg, I think it's only fair we open the floor for an open public hearing before we vote.

DR. GREENBERG: Okay.

DR. KOHL: This is Dr. Kohl. I would just like to comment before we do that. I'm more concerned in the H3N2 story in that, as was mentioned, this will be the third year we have a Sydney-like virus in the vaccine. Last year was a more severe epidemic and

would possibly suggest that the vaccine maybe wasn't working quite as well, although that is jumping a little bit.

The problem, of course, is that we don't have another virus to go to that looks like it's a leading candidate. I think there is some concern in our two options.

DR. GREENBERG: I agree with you, Dr. Kohl. Of course, I don't think there has ever been a flu season where anybody knowing the way flu works doesn't have some concern. Are there any other questions or comments?

DR. FERRIERI: This is Pat Ferrieri, Harry. I just wanted to echo some of the concerns about the current -- if we would retain the Sydney/597. I'm totally opposed to doing that based on the background noise that we've been hearing on clinical failures. I think we do have a reasonable substitute.

DR. GREENBERG: Thank you, Pat. Anybody else want to weigh in before we open it up to the public?

DR. ESTES: This is Mary Estes. I concur with Pat.

DR. GREENBERG: Thank you, Mary.

DR. EICKHOFF: This is Ted Eickhoff. I will

take a contrary position and simply point out it's really stretching the science considerably to infer that the severity of the outbreak this year was due to continuing antigenic drift. It may have been but there certainly may have been other factors also.

Furthermore, that 9 percent figure for strains submitted from "vaccine failures" is subject to a whole lot of selection by us about which we know very little or nothing.

DR. KILBOURNE: This is Ed Kilbourne. I agree with Ted absolutely on both points. I also have to say that I'm in agreement with that and also with the way Bob Couch analyzed the situation. I think I'm particularly disturbed by the evidence of possible neuraminidase change. I would probably go along with change.

DR. GREENBERG: Thank you both, Dr. Eickhoff and Dr. Kilbourne. Are there any other comments?

MS. FISHER: I have one comment. Barbara Fisher. I think there has to be a more competent investigation into genetic and other differences in those individuals who suffer vaccine failure and those who don't, those who die from the flu and those who don't. It may be that we're talking about something that has to do with the individual versus the vaccine.

DR. KLIMOV: This is Dr. Klimov. That is exactly what we are doing right now. We tried to investigate as much as we can about the history of some vaccine failures as well as about the genetic characteristics of those viruses.

DR. GREENBERG: Thank you, Ms. Fisher and Sasha. Any other comments? Okay.

Nancy, you said you had people there in the audience who might want to make a comment?

MS. CHERRY: Well, I think it's only fair before we take a vote.

DR. GREENBERG: Yeah. We can't see who's there.

MS. CHERRY: If there is anyone in the room that would like to make a comment, we do have some microphones. Well, I do not see a rush to the microphone so I guess we can proceed.

DR. GREENBERG: Okay. Nancy, could you call a roll call vote because you know who's currently here and who is not and I don't.

MS. CHERRY: Well, there are a few I'm not sure of but let's start -- well, do we need a motion, Harry?

DR. GREENBERG: Yeah. I am going to make a motion, I guess, which is that -- we can go on to a

second motion if this doesn't work, and that is I make a motion that we recommend that the H3N2 component of the coming year's vaccine be switched to the Panama/2007/99-like virus.

PARTICIPANT: I second that.

DR. GREENBERG: Is that okay?

PARTICIPANT: Second.

DR. GREENBERG: Thank you. So that's the motion.

MS. CHERRY: Okay. Now, I will go down the list then and read them off. Dr. Kohl.

DR. KOHL: I agree.

MS. CHERRY: Dr. Huang.

DR. HUANG: I agree.

MS. CHERRY: Dr. Daum.

DR. DAUM: I agree and wonder if it's possible to consider a more outreaching collection of viruses from failure patient strategy to avoid the selection bias that I think Ted Eickhoff rightly raised as a possible concern.

MS. CHERRY: Okay. Dr. Stephens.

DR. STEPHENS: I agree.

MS. CHERRY: Dr. Faggett.

DR. FAGGETT: I agree.

MS. CHERRY: Ms. Fisher.

MS. FISHER: I abstain.

MS. CHERRY: Okay. Dr. Kim, are you there? Okay. He's not. Dr. Estes.

DR. ESTES: I agree.

MS. CHERRY: Dr. Snider.

DR. SNIDER: I agree.

MS. CHERRY: Dr. Griffin.

DR. GRIFFIN: I agree.

MS. CHERRY: Dr. Greenberg. Obviously you agree. It was your motion.

DR. GREENBERG: Just to be contrary I could change my mind.

MS. CHERRY: Don't do that across 3,000 miles. Dr. Broome, are you there? No. Okay. Dr. Eickhoff.

DR. EICKHOFF: I support the update. I agree.

MS. CHERRY: Okay. Dr. Ferrieri.

DR. FERRIERI: I agree.

MS. CHERRY: Dr. Myers.

DR. MYERS: I agree.

MS. CHERRY: Dr. Katz.

DR. KATZ: I agree.

MS. CHERRY: Dr. Hoke.

DR. HOKE: I agree.

MS. CHERRY: Dr. Couch is gone but we had his. And Dr. Kilbourne.

DR. KILBOURNE: Yes.

DR. GREENBERG: I have a question. This may be procedural. I would like a clarification. Ms. Fisher?

MS. FISHER: Yes.

DR. GREENBERG: On the abstention is your abstention -- the vote was how to pick a new influenza strain and I'm just curious whether your abstention is you're feeling that you don't have enough information --

PARTICIPANT: I wasn't voting on that. I was voting on --

DR. GREENBERG: No, no. I was speaking to Ms. Fisher.

MS. FISHER: My abstention is I don't feel comfortable participating in the vote. I just don't think that it is something that I can vote on at this point.

DR. GREENBERG: Is that because you don't think there should be an influenza vaccine?

MS. FISHER: Oh, no.

MS. CHERRY: Harry, it's all right. I don't think she really needs to explain.

DR. GREENBERG: Okay.

MS. FISHER: It was not that at all. Just that I don't feel comfortable participating in this decision.

DR. GREENBERG: Okay.

PARTICIPANT: Dr. Greenberg, I'm sorry but I was voting on what I thought was a motion to approve a change.

DR. GREENBERG: Yes.

PARTICIPANT: You're stating a lot of other things in your repetition of that motion. I just want to be sure I wasn't voting on a lot of things including problems of selection and so forth.

DR. GREENBERG: No, I think, as I understand it, you were simply voting on the motion which was to change next year's strain to A/Panama/2007/99-like strain.

PARTICIPANT: Okay.

DR. GREENBERG: So, as I understand it, we've completed one half of our selection. Now, Roland, I would love you to go through the pluses and minuses of our questions for the B.

DR. LEVANDOWSKI: Okay. I think the B selection may make itself but let me just summarize what information we have.

The antigenic drift is clearly continuing in Influenza B viruses as well. Most of the strains worldwide are related to the current vaccine strain which is B/Yamanashi/166/98. Within that group there is a new variant represented by the B/Shenzhen/654/99 but it's not really clear how extensively that strain is spreading. I don't think we have good information to suggest that it is at this point but it's just a little bit fuzzy.

There is no evidence that the spread of the B/Victoria/287-like strains and it's my understanding that those appear to be declining in frequency at the present time, although they are still being found in some parts of Asia where they had been found previously.

Some Influenza B viruses that are related to the current vaccine strain are not well inhibited by antisera from people who are immunized with the current vaccines that contain the B/Yamanashi/166/98 strain. However, the B/Johannesburg/5/99 and B/South Australia/5/99 strains that were identified as being potentially capable of giving broad coverage for most of the Influenza B viruses don't grow very well and they would not be good choices for manufacturing. We don't really have other additional vaccine

candidate strains at this time.

The options for Influenza B, the first option would be to retain the current vaccine strain which is B/Yamanashi/166/98. In favor of that, again, most of the Influenza B viruses are clearly related to the current vaccine strain. In addition, manufacturing is well defined and it's predictable.

Contrary, or on the negative side, there is a new variant strain that has been recently identified and we're not always sure where those things are going. Some of the Yamanashi-like strains are also not well inhibited by the post-immunization antisera.

That leads me to the second option. The second option would be to change the current vaccine strain to a more recent B/Yamanashi-like strain. In favor of that would be that the vaccines might provide broader coverage for the currently circulating Influenza B viruses. Contrary to that is that there aren't any true alternate vaccine candidate strains and those that have been looked at really are not going to be adequate for large scale manufacturing.

Those are the options and if there are questions or --

DR. GREENBERG: Roland, can I ask you a question? It seems to me you've postulated a

hypothetical option but not a real option. A hypothetical option is actually not an option. If I understand it correctly, there is no chance to change because we don't have anything to change to. Is that correct or do I have it wrong?

DR. LEVANDOWSKI: I think we can always make an attempt to catch up with a strain that is identified as being a significant new variant that really requires a response. In the past you might remember that in 1986 there was a new H1N1 virus that was identified only toward the end of March and an attempt was made to make vaccines for that.

It's very, very difficult this late in the year for manufacturers actually to turn around and gear up to make a change for a strain they haven't had a chance to work with yet. From a practical point of view, I would say that if there were great urgency to do so, we would certainly want to make the attempt to do it.

Given the current circumstances where we don't have information that suggest that great urgency, I think it would be hard to postpone the decision to try to fine some other strain which also might turn out not to grow very well.

DR. GREENBERG: Okay. Are there any other

questions?

MS. CHERRY: I guess then let's open the floor again in case anyone wishes to comment here before the vote.

PARTICIPANT: Question on the floor.

MS. CHERRY: Again, I do not see anyone. I'm sorry. Who had --

DR. HUANG: May I make a motion? This is Alice.

DR. GREENBERG: Yes, Alice. Make a motion.

MS. CHERRY: Alice?

DR. HUANG: I would like to move that we remain with the current vaccine strain, the Yamanashi, for the B.

DR. SNIDER: Second.

MS. CHERRY: Who was that?

DR. SNIDER: Dixie.

MS. CHERRY: Okay.

DR. GREENBERG: Okay. We have a motion.

MS. CHERRY: Would you like me to read the list?

DR. GREENBERG: Yes, please.

DR. FERRIERI: May I ask a question first, Harry?

DR. GREENBERG: Sure.

DR. FERRIERI: Does this permit the -- does exclude the possibility of choosing a recent isolate of B/Yamanashi to use as Roland suggested or does this confine us to the precise strain used in this year's vaccine?

DR. GREENBERG: Roland, could you answer that?

DR. LEVANDOWSKI: Yes, I will. Yes, it would require us. We would be using what's the current vaccine strain. It would not be another similar strain.

DR. GREENBERG: No, I think what Pat asked was does this mean if all of a sudden a new B isolate appeared two days from now that clearly looked very different and looked like the right choice, would we not be able to change? Isn't that what you were asking, Pat?

DR. FERRIERI: Yes, that, you know, has relationship genetically to B/Yamanashi but it's a recent isolate that has some evidence of drift. You hinted, Roland, that we might use that as an option.

DR. LEVANDOWSKI: Well, I guess I would have to answer that by saying that I don't really know of another strain at this point that has qualities that from the outset would make it look suitable for

manufacturing. I think that's what I was trying to point out, that we have made an attempt to find some egg isolates of newer Influenza B viruses that might be suitable for manufacturing and we've not been able to do that.

DR. SNIDER: Roland, this is Dixie. Isn't there another issue here which would be that if we came up with another B strain, we would have all three new components? How long would that take to manufacture?

DR. LEVANDOWSKI: Well, that issue I wasn't going to get into but, yes, it would be somewhat difficult for manufacturers to change all three strains in one year if it's not really necessary. If it were necessary, we would make an attempt to do that but it would mean that vaccines would be delayed for a longer period of time than it normally takes to produce them. It would be difficult to make that change.

Although this year we are in a somewhat different situation where we have for the first strain that was selected as a different strain we were able to get reagents together at an earlier time.

DR. SNIDER: Right, for the southern hemisphere. But, nevertheless, I mean, that is an

issue I think that is important to have on the table.

DR. GREENBERG: Are there any other comments?

PARTICIPANT: Yeah. Roland, is there still work ongoing looking for a more suitable B isolate that will grow?

DR. LEVANDOWSKI: I don't know of the actual work that's going on. I do know that all of the WHO influenza centers are continuously examining strains that come in and I believe that our colleagues from CDC could answer if they thought they had found any additional strains up to this point that might be candidates.

I don't believe that's true. One of the difficulties for us is finding strains that are egg isolates. In current times a lot of the strains that come in for antigenic characterization are from tissue culture isolates which we have not really found suitable for manufacturing.

PARTICIPANT: So you're saying that it's extremely unlikely within the next month, for instance, that there will emerge a candidate that could be used in manufacturing the vaccine.

DR. LEVANDOWSKI: I think it's not too likely but it's possible. I mean, it's always

possible that a new strain will be identified.

PARTICIPANT: And is it possible, Harry, for us as a committee to leave that door open?

DR. GREENBERG: I assume. That was the original question to Roland who opened this situation. I assume that it's always possible to alter what's going into the vaccine assuming that epidemiologic information has changed. This is simply, I think, our best recommendation at this point in time.

PARTICIPANT: Well, this is an unusual situation. I think it sounds like we have epidemiological information that there are new Bs out there that would be better covered by a virus but we don't have one that grows well enough to cover it.

DR. GREENBERG: I thought we do not have compelling evidence of a new B variant. That's the issue, that there is some noise out there and it might be that a new B one is what we want but it's not an overwhelming picture.

Roland, can you clarify this for me and the committee?

DR. LEVANDOWSKI: I'll try to answer that. The B/Shenzhen/654/99 strain does represent apparently -- if Dr. Klimov and Dr. Cox are available, they will need to comment, too, but I believe we should view

that as a true new variant of Influenza B virus. What we don't really have evidence of at this point is that that strain is spreading and displacing the majority strains which are still quite clearly B/Yamanashi/166/99-like but that could change, as always, that the epidemiology is always moving on.

PARTICIPANT: Roland, a B/Shenzhen isolate would also cover the B/Yamanashi-like isolate?

DR. LEVANDOWSKI: Dr. Klimov will probably want to comment on this but from his tables, and I'm not sure which page that's on at this point to tell you the truth, I think suggest that the B/Shenzhen strain would not necessarily produce at least a ferret sera that covers all the B/Yamanashi strains that well. In fact, it might not be a good choice for that reason.

DR. GREENBERG: That was my impression. Even if such a --

DR. KLIMOV: On page 6 you can see the table which includes the Shenzhen/654/99 ferret antisera. You can see that this antisera definitely do not work well against new viruses. Still Yamanashi seems to be the best one that works reasonably well with the majority of viruses circulating at this moment.

DR. GREENBERG: Okay. Thank you for

clarifying that. Are there more questions? I think then we can if we don't have anymore questions -- Nancy, I take it nobody in the open hearing got up?

MS. CHERRY: No one has. Let me give them one last chance. No, no one is rising from their seat.

DR. GREENBERG: So we have a motion from Alice. Nancy, can you call the roll call?

DR. FAGGETT: And repeat the motion, please.

DR. GREENBERG: The motion from Alice, I think, if I have it right, Alice, and correct me, was that we recommend that we stay with the current B/Yamanashi virus for the coming season, the 166/98.

DR. HUANG: That's right, Harry.

MS. CHERRY: Okay. Here we go. Dr. Kohl.

DR. KOHL: I support the motion.

MS. CHERRY: Dr. Huang, obviously. Dr. Daum.

DR. DAUM: Support.

MS. CHERRY: I'm sorry?

DR. DAUM: I support the motion.

MS. CHERRY: Okay. Dr. Stephens.

DR. STEPHENS: I support the motion.

MS. CHERRY: Dr. Faggett.

DR. FAGGETT: I support the motion.

MS. CHERRY: Ms. Fisher.

MS. FISHER: I abstain.

MS. CHERRY: Okay. Dr. Kim. Dr. Estes.

DR. ESTES: I agree.

MS. CHERRY: Dr. Snider.

DR. SNIDER: Yes.

MS. CHERRY: Dr. Griffin.

DR. GRIFFIN: I agree.

MS. CHERRY: Dr. Greenberg.

DR. GREENBERG: I agree.

MS. CHERRY: Dr. Broome. Dr. Eickhoff.

DR. EICKHOFF: I agree.

MS. CHERRY: Dr. Ferrieri.

DR. FERRIERI: I agree.

MS. CHERRY: Dr. Myers.

DR. MYERS: I agree.

MS. CHERRY: Dr. Katz.

DR. KATZ: I agree.

MS. CHERRY: Dr. Hoke.

DR. HOKE: I agree.

MS. CHERRY: Dr. Couch is gone. Dr. Kilbourne. Dr. Kilbourne? Dr. Kilbourne?

DR. KILBOURNE: I agree. I'm sorry. I was muted.

MS. CHERRY: Okay.

DR. GREENBERG: Thank you for being so mute.

DR. KILBOURNE: It rarely happens.

MS. CHERRY: That's the end of the voting.

DR. GREENBERG: Okay. I would like to thank all of you for moving through that so expediously.

Nancy, as I look at the agenda, correct me if I'm wrong, we now have something that says Open Session, Vaccine Safety Action Plan.

MS. CHERRY: Yes. As we move into that, that will be Dr. Egan speaking. I want to remind the committee that we did not screen you for this because this was to be a case where we are giving you information rather than asking you for advice so there was no conflict of interest screening. You certainly are welcome to ask questions but, again, our sign is not hanging out for advice.

DR. GREENBERG: Nancy.

MS. CHERRY: Yes.

DR. GREENBERG: I'm just going to ask my other committee members. I know I have to just get up for a minute or two and I just wondered whether we could take like a three minute break to let anybody do anything they need to do before Dr. Egan gets started.

MS. CHERRY: Absolutely.

DR. GREENBERG: Is that okay, folks?

PARTICIPANT: Good idea.

PARTICIPANT: Sure.

DR. GREENBERG: Okay.

MS. CHERRY: And when Dr. Greenberg gets back then we will reconvene.

DR. GREENBERG: I have about a hundred yard run. If we can get this wound up and people can get on their way, that would be terrific.

(Whereupon, at 1:29 p.m. off the record until 1:36 p.m.)

DR. GREENBERG: We should probably get started.

DR. EGAN: Thank you. As I just mentioned, what I'm planning to do is just give a little bit of an update to the committee about the Department's vaccine safety action plan and implementation plan.

MS. CHERRY: Can you hear him well enough?

PARTICIPANT: Yes.

DR. EGAN: Although concerns about safety have always attended the use of vaccines, these concerns have loomed somewhat larger in recent years. The increased number of vaccinations that are available and that are required is obviously one of the reasons for this increased concern about safety.

Paradoxically, also the very success of

vaccines is another reason. The diseases that vaccines have been designed to prevent are gone and are no longer perceived as much of a threat as before. Attention thus turns to the adverse events that may accompany vaccines.

On this overhead I've listed a number of vaccine concerns. Most of these concerns are fairly recent, Hib vaccines and diabetes, for examples. Some of them are quite old, the progressive vaccinity that accompanied smallpox. Some of these are clearly linked to vaccination. Oral polio vaccine and vaccine associated paralytic polio as an example.

Others are not clearly linked. Measles and autism for example. Some may be very specific to the vaccine strain as with mumps vaccine and aseptic meningitis. This has been linked to the Urabe strain but not to the Jeryl Lynn strain that is in use in the United States.

This is a small list of concerns that have been expressed in recent years concerning vaccine safety. I can list a good number of additional concerns and put up many, many more slides. Assessments of these concerns certainly need to be done. However, these take resources and these resources are limited and prioritizations need to be

made.

I would like to make a few points about these concerns. These safety issues can stem from the vaccine itself. For example, again, VAPP and polio or aseptic meningitis and the Urabe strain of the mumps vaccine. They can stem from an adventitious agent in the vaccine. For example, SV40 that was found in the oral polio vaccine. They can stem from additives or adventitious materials that are found in the vaccine.

Some recent work in our own laboratories indicate that the thrombocytopenia that is associated with the measles vaccine may derive from an adventitious protein that is a protein from cell substrate that is present in the vaccine.

One can also look at adverse events due to LPS, DNA, antibiotics and what have you, that make their way into the vaccine. For some of these concerns causality has been established. For some the most evidence is against them. For some the evidence is uncertain.

What is certain, however, is that an increased emphasis needs to be placed on and increased resources need to be devoted to vaccine safety activities. We need to better address the problems that are or may be associated with vaccines. We need

to do this in a prospective fashion and retrospective fashion.

The vaccine safety implementation plan is a departmental plan to address this need. It also includes a component on vaccine communication. The plan itself arose as a result of a report that was presented to Secretary Shalala from the task force on Safer Childhood Vaccines. The Secretary then directed the National Vaccine Program Office to develop an action plan for implementing the needs that were addressed in the report.

This was done through the National Vaccine Program Office's interagency group. This is a group of various Government agencies including the NIH, the FDA, CDC, and HRSA. This interagency group, which was co-chaired by myself and Dan Salomon, developed a vaccine safety action plan. This was presented to the National Vaccine Advisory Committee and later to the Surgeon General, Dr. David Satcher, the Dep. Sec. of HHS, Mr. Kevin Thurm.

This Vaccine Safety Action Plan, which is extremely comprehensive, evolved into the vaccine safety implementation plan which was more of a focused and immediate implementation of the action plan. Our highest priority activities were identified and, to

the extent possible, plans were made to implement these in the current fiscal year.

I will note that stable funding for this plan is being pursued. However, this is a quite difficult issue and whether this gets done through the vaccine trust or by setting up an additional trust fund or through continuing funding through the normal allocation process is still not settled.

There are five goals that have been identified for the vaccine safety action plan. These are given on the current overhead which is to increase effort to detect potential vaccine safety problems. Two is to improve the response to and understanding of vaccine safety concerns. To improve the risk management of vaccines in clinical settings. To increase and improve communications about vaccine risks and benefits. To obtain and maintain a state of the art vaccine supply.

This vaccine safety implementation plan was chaired by Dr. Roger Bernier. The development of this implementation plan was chaired by Dr. Roger Bernier from the CDC's National Immunization Program and done through the National Vaccine Program.

Let me say a few words about some of the immediate action steps that were identified and these

are on the following overheads.

With regard to detecting potential safety problems, the most immediate needs were to improve laboratory testing of vaccines and evaluate vaccine safety and purity, and to develop new approaches for the presence of unknown or previously undetected agents in vaccines. An example of the latter is, for example, one could develop generalized PCR methods not for specific viruses but for families of viruses.

With regard to improving response and understanding of vaccine safety concerns, it was thought there was a need to evaluate the VAERS reports more adequately to improve scientific understanding of the reports and to carry out a more timely review of newly hypothesized vaccine safety concerns.

For example, have a standing board or committee, presumably investigative scientists outside of the Government, that could be presented with a vaccine safety concern and they could make some assessment of how important it would be to immediately investigate that concern or if the evidence didn't support it that well. Then to study possible causal links between vaccines and specific diseases in expanded vaccine safety data link population.

With regard to improving risk management of

vaccines in clinical settings, we felt it was very important to finalize the decision rules for vaccine policies so that any unnecessary repeat doses are not administered, to update the standards for pediatric immunization practices, and to include a focus on safety related issues and practices.

With regard to increasing improved communication, the need to improve the exchange of information between healthcare providers and parents. That's healthcare providers on all levels. And for obtaining and maintaining state of the art vaccine supplies and to develop safer alternatives for current vaccines. This could include both the vaccines themselves and excipients or adjuvant that are used in these vaccines. For example, changing preservatives, different preservatives; changing adjuvants, for example, from aluminum to another type of adjuvant.

That's the plan in a nutshell. I think there is much that we need to do to make vaccines safer and to promote the safe use of these vaccines. If I could just close with a quote from Sir Graham Wilson from his classic book, The Hazards of Immunization.

I quote, "It is for us and for those who come after us to see that the sword which vaccines and

antisera have put into our hands is never allowed to tarnish through over confidence, negligence, carelessness, or want of foresight." Thank you.

DR. GREENBERG: Thank you, Bill, for an excellent presentation. I guess now I would open it up to committee members who have any questions of Bill.

DR. FAGGETT: Harry, Walt Faggett. One question. Excellent presentation. The matter of stable funding, you mention it's going to be stable but you don't give the source. I'm not clear how stable it's going to be if you don't have a source of funding at this point.

DR. SNIDER: Harry, this is Dixie. I wanted to make an observation about that. As a federal official I hope I don't step over the line but there has been a lot of difficulty, Walter, and everyone else, in trying to nail down some stable funding.

Through all of these meetings we have really had no major problems in convincing people that this is an important thing for us to be doing. I mean, all of us, the agencies involved and all professional societies and so forth.

The situation is such that those who are concerned about having adequate money for vaccine

purchase are obviously in this environment from which we are having new vaccines come on line that are higher priced than earlier vaccines, are very concerned about trying to redirect funds from vaccine purchase to vaccine safety.

Those who are concerned about having adequate funds available for vaccine compensation are understandably reluctant to have any of those funds reprogrammed for vaccine safety. Those who are concerned about this are concerned about increasing appropriations for vaccines.

CDC has this year reprogrammed some of its money to increase our efforts on vaccine safety but they fall far short of what is needed. I think there is some real concern about how we get over the hump in terms of getting some resources.

As some of you may know, there has been an interest in reducing. Since the vaccine compensation has a goodly amount of money in it, there has been some interest in reducing the excise tax on vaccines and some discussion of redirecting some excise tax money into a vaccine safety arena but that would take some legislative action which is obviously difficult to pull off.

DR. GREENBERG: Thank you, Dixie.

DR. EGAN: I would just like to say thank you very much for that response, Dixie. My comments about seeking stable funding was seeking stable funding specifically for vaccine safety because we don't have the ability, the monies, to redirect existing funds from existing activities such as the vaccine purchaser.

MS. FISHER: Barbara Fisher here. I think the vaccine safety plan is a really good first step to addressing some of the outstanding concerns about vaccine safety, but I think it might be useful to take another look at the conclusions of three reports issued by the Institute of Medicine in 1991 and '94, particularly those talking about the lack of research investigating the biological mechanisms underlying adverse events following natural infection as well as immunization.

Also to review the report of the April 1, 1996, Institute of Medicine Vaccine Safety Forum Workshop, which also identified biological mechanism and research needs.

I know that the greatest concern to parents right now is the lack of scientific information on the cumulative effect of multiple antigens on the developing immune and neurological system,

particularly and potentially genetically susceptible populations. In other words, those children who may be susceptible to developing autoimmunity or immune-mediated neurological dysfunction.

Further, whether some of this might be influenced by genetic recompenation caused by exposure to viruses and other toxins including additives in vaccines, as you mentioned, Dr. Egan, like mercury and aluminum. There is private money being raised right now to fund this kind of research.

I think that if the FDA takes the lead, it would have public support because it would pave the way for development of screening techniques to identify high-risk children and it would lead to modification of that policy to make them safer. I just would like to say, however, that the suggestion of taking money from the funds, the trust fund, that was set up for vaccine-injured children would be vigorously opposed.

I think the other funding sources need to be identified, but I think there would be public support for it especially if the CDC and FDA and NIH makes this a priority that the funding the vaccine safety research, particularly basic science research, is a priority in our society. You will receive grants or

support for that but there will be opposition to using the trust fund money.

DR. EGAN: Thank you, Mrs. Fisher, for those comments. I would like to add that in the vaccine safety action plan there were a number of items that related to many of the issues that you brought up, particularly looking for susceptible populations, investigating the realm of adverse events and genetic susceptibility to those adverse events.

The particular action steps that I put up here were those ones that we could begin immediately this year. Those very, very difficult studies on genetics with adverse events are certainly elements of the action plan. Thank you.

DR. GREENBERG: Are there any other comments from the panel?

DR. KATZ: Harry, I would like to make three comments. Is that all right?

DR. GREENBERG: Yes. Could you identify yourself?

DR. KATZ: Sam Katz. Three comments and two for Bill. The first one is scientific in accuracy. When you talk about SV40 you limited it to OPV. SV40 was found in IPV also.

DR. EGAN: My mistake, Sam. I meant to say

IPV because it never was in the licensed OPV. It was only in the IPV. Thank you for correcting that.

DR. KATZ: Secondly, I don't know if this is for publication or just this meeting but it is sometimes misleading. You made the statement that diseases are gone. Only smallpox is gone. We know very well that diphtheria continues in eastern Europe, that measles is in the Netherlands, that polio is in Sub-Saharan and much of Asia. We mislead the public when we say the diseases are gone. They are gone from the United States but not from the world. No place is further than a jet plane ride away from wherever one sits today.

DR. EGAN: Thank you for that comment. Certainly for many of these, barring smallpox, they are seen. There's a case or two of diphtheria every year in the U.S. Measles has reemerged and so on. My point was more that they are not prevalent and immediate to everybody as they were and not everybody was seeing the devastation.

DR. KATZ: Our worst enemy sometimes. A third question for Ms. Fisher. I sat the last few years on the Advisory Commission on Child Vaccines. It runs very effectively. The commission is made up of parents and of attorneys who prosecute these cases

and only a couple of physicians and nurses.

Basically they have done an excellent job in rewarding appropriate cases that have been adjudicated by medical experts and reviewed very carefully. Nevertheless, with the current excise tax they've had more than enough money to pay all the claims that were adjudicated. With the trust funds it has continued to increase over a billion dollars that just sits there.

It isn't even used to compensate these families because they get enough funds from the excise tax. I think that still stands without anyway eroding the compensation program as a possible avenue for safety which seems to me perfectly compatible. It's what the program is set up for.

MS. FISHER: Barbara Fisher here. A GAO report has just been issued in the last few months looking at the implementation of the National Childhood Vaccine Injury with respect to the compensation program.

Congress is taking a look at it and I think that there are still outstanding questions about the rules for compensation and the way it is being implemented and whether or not in the future there will be an opportunity for more awards if the terms under which compensation are given are changed.

I think it's a mistake to assume that the excess amount that is now in the trust fund is not going to be utilized in the future and a terrible precedent would be set to go into that fund and use it for any other purpose than what Congress originally intended it for in 1986 which is to compensate vaccine-injured children.

DR. EGAN: This is Bill Egan. I think that the point here is that we need stable funding for vaccine safety research. I don't think we are going to settle in this meeting where that's going to come from. The issue is that the stable funding is needed and a variety of sources are being discussed and debated. I think we've just heard some of the points that have been made in that debate.

DR. GREENBERG: Hold on a second. I would like to get some other panel members who might have something to say involved here.

DR. MYERS: Harry, this is Marty. Could I add something from the National Vaccine Program perspective?

DR. GREENBERG: Yeah.

DR. MYERS: I think the point that Bill was making is a very important one, that the Department is looking at a variety of options and the trust fund is

only one of the many that the Department has been considering for stable funding.

It's understood that stable funding is necessary but the process is likely to take some time given the manner in which appropriations are managed and decisions are made concerning long-term funding of initiatives such as this.

What this implementation plan that Bill has been describing is those things we thought were so urgent they shouldn't wait for that process and the different agencies, as Dixie said, reprogrammed funds to help support these activities of which CDC, NIH, FDA, and NDPO with its unmet funding have done to get a number of these enhanced safety activities initiated.

For example, one of the ones that Bill mentioned was there is contracting underway with potential external review groups to consider timely reviews and hypothesized vaccine safety concerns, somebody that would be outside of Government.

Another that was discussed extensively at the recent NVAC meeting was a workshop to identify and discuss more effective approaches to vaccine benefits and risk communications which is going to occur in the fall. I think this is looked at as we're getting

started the issue of stable funding is very important but it won't come quickly.

DR. GREENBERG: Thank you, Marty. Are there any members who have not yet spoken who would like to add something? Are there any members who have spoken who would like to add something?

DR. FAGGETT: Harry, Walt Faggett. Just one quick one for Bill Egan. Do you have a budget projection on what is needed for some of the very impressive activities you are planning for vaccine safety?

DR. EGAN: For the whole package these are really very, very rough estimates. For everything combined it's numbers on the order of up to $50 million dollars per year. Activities like, you know, the vaccine safety data link which is absolutely essential in all of these. Those are very, very expensive computer systems to keep up. They cost millions of dollars per year.

DR. FAGGETT: They are mandated under 2010 so that should give you some hope.

DR. SNIDER: Harry, this is Dixie. I have a question for Bill or Marty or anyone who has been involved in thinking about vaccine safety implementation plan. Getting back to this committee.

The question would be what could this committee do as part of its role in helping to move vaccine safety issues forward? Are there other specific -- is there a specific charge or some specific recommendations coming out of this Planning Activity Board or the Vaccine and Related Biological Products Advisory Committee?

DR. EGAN: Dixie, I think this presentation right now was simply to advise the committee of what was going on within the Department. I think the individual members can always act on their conscience and act as advocates for whatever they see fit. We weren't asking for any kind of action at this time. This was simply a briefing or update.

MS. FISHER: I have a question. Barbara Fisher. Is it allowed under committee rules for individual members of the committee to meet with FDA staff to review concerns about priorities, for example, on this plan? Is it appropriate or is it allowed under the rules for committee members, for example, like me to meet with an FDA staff to communicate the parent concerns and priorities or what they think priorities are for vaccine safety?

DR. EGAN: Mrs. Fisher, it's allowed and appropriate for anyone, member of the committee or

not, to call me, to meet with FDA to express their concerns, and to give us their opinions and advice.

MS. FISHER: Thank you.

DR. MYERS: Harry, just to respond to Dixie and your query. It would seem to me like the NVAC would be useful to have the advisory committee go on record in support of a stable long-term funding.

DR. GREENBERG: I think we've been --

OPERATOR: Conference operator. How may I help you?

MS. CHERRY: I'm sorry. We're still meeting.

DR. MYERS: To Mrs. Fisher, in addition to the FDA one of the attempts of this workshop this fall is to -- one of the specific objectives is to establish meaningful mechanisms for meaningful discussions to address various concerns by a variety of different constituents. I think participation in that would be very useful.

DR. GREENBERG: Thank you, Marty. I would like to make a comment myself. This is simply as a panel member, not as a chair. That is that this is to me an incredibly important area. I think all of you as panel members, and many of you who are scientists, need to realize that there is going to have to be

priorities set even in such an important area as safety as to where you are going to get the most benefit and where you need to put your biggest efforts and where other efforts go.

To some degree because this is such a hot potato that's hard because everything is important but, as you've heard, there's not money for anything it sounds like. What I would ask of all of you is to think is this wonderful list that Bill presented, is this what is needed for vaccine safety?

Begin to think in your own mind where we are going to get the most improvement most quickly and what are longer terms and perhaps slower investments and share that information or that thought with Bill. I think it's a very -- it's easy to say we are all for safety but it's pretty hard to figure out exactly what is the most important thing to do, the next most important thing to do. That requires a lot of thought.

DR. EGAN: Just let me emphasize, too, that this plan is a departmental plan and all of the agencies that are part of the interagency group of the National Vaccine Program. I would also like to thank again Dr. Roger Bernier from CDC who worked so very, very hard to develop this implementation plan which I

simply present today.

DR. GREENBERG: I would imagine that a number of you are beginning to get antsy so I would like to know if there are any other questions of Bill or thoughts?

DR. KOHL: Harry, Dr. Kohl. Would it be appropriate to have a committee motion to strongly urge stable funding for this plan?

DR. GREENBERG: As far as I'm concerned, that's just fine. Nancy, are there any prohibitions of that?

MS. CHERRY: Well, this was unplanned and I don't know where the motion will go from here.

DR. GREENBERG: Well, I'm not sure where it will go either.

MS. CHERRY: I mean, you can go on record as making that motion.

DR. GREENBERG: I'm happy to be on record as we've been a number of times in the past on record for stable funding for the research mission of the FDA. It's never clear to me where those motions go either.

DR. FAGGETT: Walt Faggett. I'd like to second that motion.

DR. GREENBERG: Okay. Why don't you just quickly take a vote.

MS. CHERRY: Okay. Shall I go down the list again?

DR. GREENBERG: Yeah.

MS. CHERRY: Okay. Kohl.

DR. KOHL: Yes.

MS. CHERRY: Huang. She's gone. Daum.

DR. DAUM: Yes.

MS. CHERRY: Stephens.

DR. STEPHENS: Yes.

MS. CHERRY: Faggett.

DR. FAGGETT: Strongly agree.

MS. CHERRY: Okay. Fisher.

MS. FISHER: Yes, strongly agree but oppose any use of the trust funds for the children.

MS. CHERRY: Okay. Kim. He never made it. Estes.

DR. ESTES: Yes.

MS. CHERRY: Snider.

DR. SNIDER: Abstain.

MS. CHERRY: Abstain? Okay. Griffin.

DR. GRIFFIN: Yes.

MS. CHERRY: Greenberg.

DR. GREENBERG: Yeah.

MS. CHERRY: Broome. Eickhoff.

DR. EICKHOFF: I agree.

MS. CHERRY: Ferrieri. Dr. Ferrieri? Okay. Dr. Myers.

DR. MYERS: Abstain.

MS. CHERRY: Katz.

DR. KATZ: Agree.

MS. CHERRY: Hoke. Couch is gone. Kilbourne. Gone.

DR. GREENBERG: So we are beginning to lose people so I would like to --

MS. CHERRY: Well, not all of those were actually --

DR. GREENBERG: Yes.

MS. CHERRY: Some of those were temporary voting members.

DR. GREENBERG: I totally understand. I would like to get everybody's -- let everybody express their opinion but if we don't have any more opinions, maybe we could move towards closure here.

MS. CHERRY: Okay. Before we do, we need to open the floor one more time.

DR. GREENBERG: I understand that, Nancy. I'm trying to see whether there are any more comments on Dr. Egan's presentation. No? Great. So, Nancy, can you check the floor there.

MS. CHERRY: Okay. Would anyone like to

address the committee? I guess not. Back to you, Dr. Greenberg.

DR. GREENBERG: Okay. I think the safety issue is obviously incredibly important. Without safety we will not -- without real safety and the perception of safety we will not have utilization of vaccines the way they should be used. I think we all need to think long and hard about it and how to improve it.

Bill, that was a good first start. Again, I suggest all of you to think about ideas that you have and to relay those to Bill. Are there any last comments on safety?

If not, I would like to thank all of you for joining on this telephone conference. It worked fine. I know you are all very disappointed that you could not spend the last two days in Washington but you'll just have to live with that.

MS. CHERRY: We did have nice weather had you come.

DR. GREENBERG: Okay.

MS. CHERRY: I would like to thank everyone also, particularly for the abrupt change in plans. Thank you for being flexible enough to go along with us.

DR. GREENBERG: Okay. Thanks again and I guess we'll be seeing you in May.

MS. CHERRY: Okay.

(Whereupon, at 2:13 the teleconference was concluded.)

CERTIFICATE

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

Before: DHHS/FDA/PHS/CBER

Date: March 10, 2000

Place: Silver Spring, MD

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