U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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VACCINES AND RELATED BIOLOGICAL PRODUCTS

ADVISORY COMMITTEE

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MEETING ON INFLUENZA VIRUS VACCINE FORMULATION FOR 1999-2000

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Thursday,

March 11, 1999

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The Advisory Committee met by teleconference, coordinated from Room 121, Building 29, National Institutes of Health, Bethesda, Maryland, at 12:30 p.m., Dr. Harry Greenberg, Chair, presiding.

PRESENT:

HARRY GREENBERG	Chair
ADAORA ADIMORA	Member
ROBERT DAUM	Member
KATHRYN EDWARDS	Member
MARY ESTES	Member
WALTER FAGGETT	Member
DIANE GRIFFIN	Member
ALICE HUANG	Member
STEVE KOHL	Member

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TEMPORARY VOTING MEMBERS:

ROBERT BREIMAN
REBECCA COLE
ROBERT COUCH
THEODORE EICKHOFF
PATRICIA FERRIERI
EDWIN KILBOURNE
GREGORY POLAND

ALSO PRESENT:

NANCY CHERRY
NANCY COX
ROLAND LEVANDOWSKI
JOHN O'BRIEN
STEVE SALMON
CAPTAIN DAVID TRUMP

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

(12:44 p.m.)

DR. GREENBERG: I'd like to welcome all of you to this conference call, which is an important one, to try to help the FDA pick the correct constituents of next year's influenza vaccine. This, as all of you know, is my first term at leadership. I'm very happy that Dr. Ferrieri is still among us, and Pat, please correct me when I stray from the procedures.

DR. FERRIERI: Don't worry about a thing, Harry. You're doing fine.

DR. GREENBERG: What I would like to say -- you should have all, all of you in front of you should have an agenda. What I would like to do is make sure that all of us are here, and I guess, Nancy, the operator is going to do that confirmatory call?

MS. CHERRY: Well, I expect to hear from the operator, and I was going to ask for a roll call at that time.

DR. GREENBERG: Why don't you, Nancy, because you have it there, simply ask for a roll call now, and if the operator breaks in, we can do it over again, but I think it's important that we all in front of us know who is out there.

MS. CHERRY: Okay. First of all, Captain Trump, are you there?

CAPTAIN TRUMP: I just walked in.

MS. CHERRY: Oh, he just -- son of a gun. The operator is probably trying to reach you. Okay. Dr. Greenberg?

DR. GREENBERG: Here.

MS. CHERRY: Dr. Ferrieri?

DR. FERRIERI: Here.

MS. CHERRY: Poland?

DR. POLAND: Here.

MS. CHERRY: Adimora?

DR. ADIMORA: Here.

MS. CHERRY: Mrs. Cole?

MS. COLE: Here.

MS. CHERRY: Estes?

DR. ESTES: Here.

MS. CHERRY: Huang?

DR. HUANG: Here.

MS. CHERRY: Edwards?

DR. EDWARDS: Yes.

MS. CHERRY: Daum?

DR. DAUM: Yes.

MS. CHERRY: Couch?

DR. COUCH: Was that Couch?

MS. CHERRY: Yes.

DR. COUCH: Here.

MS. CHERRY: Eickhoff?

DR. EICKHOFF: Here.

MS. CHERRY: Cox? Nancy Cox?

DR. COX: Yes, I'm here.

MS. CHERRY: Okay. Kilbourne?

DR. KILBOURNE: Here.

MS. CHERRY: Griffin?

DR. GRIFFIN: Yes.

MS. CHERRY: Faggett?

DR. FAGGETT: Here.

MS. CHERRY: Kim? Oh, that's right, he's not -- Breiman?

DR. BREIMAN: Here.

MS. CHERRY: Kohl?

DR. KOHL: Here.

MS. CHERRY: Goldenthal? Okay, she's on our staff, and she should be tying in. Parkdale?

UNIDENTIFIED PARTICIPANT: Parkdale is here.

MS. CHERRY: Okay. Penat (phonetic)?

MR. PENAT: Here.

MS. CHERRY: Medeva?

MR. MEDEVA: Yes.

MS. CHERRY: Okay, I think that's it.

DR. GREENBERG: Okay, well that's great. Thanks for joining us, and what I would like to do now is actually hold the meeting --

MS. CHERRY: Well, I have an announcement.

DR. GREENBERG: Yes. So Nancy, an announcement.

MS. CHERRY: Yes.

UNIDENTIFIED PARTICIPANT: You've got to do five.

MS. CHERRY: I could not let you get by without reading the wonderful statement.

This announcement is made a part of the record at this meeting of the Vaccines and Related Biological Products Advisory Committee on March 11, 1999. Pursuant to the authority granted under the committee charter, the Director of the Center for Biologics Evaluation and Research has appointed Mrs. Rebecca Cole and Drs. Robert Breiman, Robert Couch, Theodore Eickhoff, Patricia Ferrieri, Caroline Hall, who is not with us, Edwin Kilbourne, and Gregory Poland as temporary voting members. I should note, too, that we are joined in the room by a guest, Dr. David Trump.

Based on the agenda made available, it has

been determined that all committee discussions at this meeting for the influenza virus vaccine formulation for 1999-2000 present no potential for a conflict of interest. In the event that the discussions involve specific products or firms not on the agenda for which FDA's participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement. Their exclusion will be noted for the public record.

With respect to all other meeting participants, in the interests of fairness, we ask that you address any current or previous financial involvement with any firm whose products you wish to comment on.

And that's the end of the meeting statement. I would add, though, please help Dr. Greenberg. This is a teleconference, so any time you wish to speak, please state your name before you speak. Also, please do not put us on hold, because that causes unpleasant results for us.

DR. FAGGETT: Nancy, Dr. Faggett. Was I -- did I miss my name as a voting member?

MS. CHERRY: You're a member of the committee, Dr. Faggett, so you automatically get a vote.

DR. FAGGETT: Thank you.

MS. CHERRY: Okay. Then, I just want to repeat that if you get disconnected, there is a number to call. 1-800-545-4387, and ask for confirmation number R37481. For the international people -- excuse me. Oh, they call the same number. And with that, then, I will -- Dr. Greenberg, I'm tossing it back to you.

DR. GREENBERG: Nancy, could you just state that number for everybody one more time?

MS. CHERRY: Of course. 1-800-545-4387, then you have to state a confirmation ID, R37481. And actually I see here that, for Medeva, if you get disconnected, you call the same number, but you give a confirmation ID of AR52984.

MR. MEDEVA: Thank you.

DR. GREENBERG: Okay. Well, we are actually a little ahead of schedule already. I commend you all for that. What I would like to do now is turn over the meeting to Roland Levandowski, who is going to introduce and review the subject matter, and then he and Dr. Cox will lead us through the data that we are going to need to have to evaluate how to move forward. Roland?

DR. LEVANDOWSKI: Okay, thank you Dr.

Greenberg. This is Roland Levandowski --

DR. GREENBERG: Roland, we're not hearing you.

DR. LEVANDOWSKI: Okay, I'll try to speak louder. This is Roland Levandowski. Can you hear me now?

DR. GREENBERG: No.

UNIDENTIFIED PARTICIPANT: Is the green light on?

DR. LEVANDOWSKI: The green light is on.

DR. GREENBERG: Roland, it's the same problem we were having earlier. It's not the loudness, you're garbled. You're electronically messed up, so you need to figure that out.

DR. LEVANDOWSKI: How about now?

DR. GREENBERG: It's garbled.

DR. LEVANDOWSKI: Am I too close? How about if I get farther away?

DR. GREENBERG: Better.

DR. LEVANDOWSKI: Too close. Can you hear me now?

DR. GREENBERG: Still a problem.

UNIDENTIFIED PARTICIPANT: Still a problem.

MS. CHERRY: Roland, come on my side of

the table. We're going to switch places.

UNIDENTIFIED PARTICIPANT: We can hear you now well, Nancy.

DR. LEVANDOWSKI: Okay, how about me?

DR. GREENBERG: No.

DR. LEVANDOWSKI: No.

(Laughter.)

DR. GREENBERG: It's not not hearing you. It's sort of like you're talking through --

UNIDENTIFIED PARTICIPANT: Marbles.

DR. GREENBERG: Yes, marbles.

DR. LEVANDOWSKI: Well, that should make me speak better, I guess, if I use a few marbles. I'm not sure what to do. I'll keep talking, but if you can't hear me, it's sort of --

DR. GREENBERG: It's okay.

DR. LEVANDOWSKI: -- not so good. Okay, I'll keep talking. You'll have to tell me when you miss something you think is important. Is that okay?

DR. GREENBERG: Not great. You know, you've got to figure this out, because we are going to have to hear the information, and it's really not -- it's not perfect, Roland.

UNIDENTIFIED PARTICIPANT: Can you talk into a phone, instead of a speaker?

DR. LEVANDOWSKI: I would if I had one available.

MS. CHERRY: No.

DR. LEVANDOWSKI: At the moment, all I have is the speakerphone. We don't have a handset.

DR. GREENBERG: Something is peculiar, because Nancy is sounding fine, but you're not.

MS. CHERRY: See if the cord is being pinched.

DR. LEVANDOWSKI: Okay, I'll try a different microphone. Is that any better? Hello? I guess not.

DR. GREENBERG: Nancy?

MS. CHERRY: Yes? Harry, can you hear me?

DR. GREENBERG: I think we've had this problem before. It's actually going -- needs to be mastered.

MS. CHERRY: Well, I don't know. Let me see, maybe the cord is being pinched here on the bottom.

UNIDENTIFIED PARTICIPANT: Whatever you just did made it better.

MS. CHERRY: Okay, now how is it?

DR. GREENBERG: Better.

MS. CHERRY: Okay, let me try Roland

again.

DR. LEVANDOWSKI: Testing, testing, 1, 2, 1, 2. Is this thing on?

UNIDENTIFIED PARTICIPANT: Yes.

DR. LEVANDOWSKI: Okay. I'll start, and I'll just keep going until you tell me stop the next time.

DR. GREENBERG: You're doing good.

UNIDENTIFIED PARTICIPANT: Whatever you're doing now is good.

DR. LEVANDOWSKI: All right.

UNIDENTIFIED PARTICIPANT: What you were doing.

DR. LEVANDOWSKI: Thanks very much.

DR. GREENBERG: Don't move and don't breathe. Just talk.

DR. LEVANDOWSKI: Okay, I'll try to do my best on this. What we are here for today, of course, is to try to complete the recommendations for the influenza viruses to be used in the vaccine for 1999 to 2000. And, of course, there are some questions for the committee, and they will seem pretty obvious when I state them, but I will state them anyway.

We have two questions. What strains should be recommended for the influenza A(H3N2)

component of the vaccine, and what strain -- and the second question is, what strains should be recommended for the influenza B component of the vaccine.

DR. GREENBERG: Roland, this is not going to work for me. Are other people having trouble?

PARTICIPANTS: Yes.

UNIDENTIFIED PARTICIPANT: He's breaking up real bad.

UNIDENTIFIED PARTICIPANT: How much money are we saving by doing it this way?

UNIDENTIFIED PARTICIPANT: Can't you get to another line?

MS. CHERRY: Well, they've gone to call the operator to see if the operator can do anything.

(Whereupon, the foregoing matter went off the record at 12:54 p.m. and back on the record at 1:00 p.m.)

DR. LEVANDOWSKI: I'm speaking to you by space satellite.

DR. GREENBERG: It's perfect. Go on.

DR. LEVANDOWSKI: All right, I'll get started. I won't repeat the questions, but the two questions really are what should be the other two components of the influenza vaccine for next year. And I just wanted to remind everybody that we had sent

out materials as background for the meeting today, and we will be speaking from those materials. It would be good for people to try to follow along.

The three pieces include Weekly Epidemiologic Record, which has the WHO recommendations; there's a package of data on string characterization from CDC; and there's a summary of serologic data that was used for the WHO that we put together here at the Center for Biologics.

Based on the data that were available at the time in January, the committee recommended that we retain the A Beijing 262/95 strain for the H1N1 component of the vaccine, and at that time the committee indicated that additional data would be useful to determine whether a change would be needed for the H3N2 influenza A or the influenza B components of the vaccine. The committee also indicated, by its discussion at least, that the initial data suggested the possible need for a change in both the H3N2 and the influenza B strains.

Subsequent to that, as you know, the WHO held its meeting on February 15th and 16th, and recommendations from that meeting were published on February 26th in the Weekly Epidemiologic Record, which was sent out. Based on the information that was

available at that meeting, including the data that were not available at the end of January, WHO recommended that a trivalent vaccine contain an A Beijing 262/95-like H1N1 virus, an A Sydney 5/97-like H3N2 virus, and either a B Beijing 184/93-like or a B Shangdong 7/97-like virus. That B recommendation is a bit unusual, and it acknowledges the fact that there are differences in the epidemiology of influenza B viruses around the world at the moment.

Whereas B Beijing 184/93-like viruses continue to be found in all areas of the world, viruses that are related to B Shangdong 7/97, which is the other lineage, have been confined to parts of Asia, and although in past years the frequency of these viruses like the B Shangdong were not so much, they have been increasing, and in the case of Japan, those viruses appear to make up more than 80 percent of the isolets.

To really start to describe how those recommendations came about, the information that was used for those recommendations, and to permit us to complete our recommendations, we want to review the pertinent data that would supplement what we had available to us in January, and so to start I'm going to ask Nancy Cox if she'll present some information on

the characterization of strains. Nancy, are you there? Can you hear me?

DR. COX: Yes. I'm here. Can you hear me?

DR. LEVANDOWSKI: I can hear you.

DR. COX: Good. I was going to give a brief update of the influenza activity that's -- ongoing season, actually, because activity may be starting to decline, but there's still a lot of influenza activity going on in the U.S., and then go on to the strain characterization. I thought the Committee would be quite interested.

We'll have a publication, an influenza update, in the -- in MMWR, which will be published on March 12th. And this MMWR summarizes the activity through February 27th. We have a bit of updated activity for the subsequent week which indicates that influenza activity is declining a bit, but to give you some of the numbers.

We should have expected that influenza activity might occur a bit early this year because of the large, rather remarkable outbreak that was investigated in Alaska during the summer months, but in fact the season started off a bit later than in some recent years. And what we can see from our

surveillance information is that influenza activity in the U.S. began to increase in mid-January, and has remained elevated in most regions of the country through the week ending March 6th, or March 4th.

Percentage of patient visits to the sentinel positions has been above the baseline for seven consecutive weeks, and since the week ending January 23rd, at least 25 states have reported either widespread or regional activity each week. For the most recent week for which we have data, 37 states reporting widespread or regional activity. The week ending February 13 where 43 states -- regional or widespread activity.

Now, we always look at the severity of the season, examining mortality, and we now have four consecutive weeks where C and I mortality has been above the threshold. That includes this week for which we have the most recent data, ending March -- last Friday.

So I think that what we can say is that we have had a fairly active influenza season. There have been a total of 6,000 -- over 6,500 influenza viruses detected in the U.S. so far. The majority of those that have -- roughly now 78 percent are A's, 72 percent are B's, and roughly 12 H1 out of the A's. 40

of the A's are really H3N2, and that's for our discussion later.

Now influenza A has predominated overall, but in the west north central, the east north central, and east south central regions, 35 and 45 percent of the influenza isolets are type B, so there really is some regional variation in the circulation of A's and B's.

Also reporting in the MMWR, results of an investigation undertaken by the California Department of Health Services, and the important thing for the Committee is that because a fairly low percentage of the staff have just gone from care facilities, have been vaccinated, it was possible to estimate vaccine effectiveness against influenza-like illness. Outbreak was H3N2 -- have been characterized, some of them, four isolets have been characterized as Sydney-like viruses. Vaccine effectiveness was estimated -- among the 47 staff members. So I think that will be relevant to our discussions later, and I just wanted to mention that MMWR will be coming out.

Now if you would please turn to the CDC portion of the material that was sent out to you, I would just --

UNIDENTIFIED PARTICIPANT: Say what the

estimate of efficacy was?

DR. COX: Sorry. 72 percent.

UNIDENTIFIED PARTICIPANT: And you said that was in staff?

DR. COX: It was in staff. Because the residents were so highly vaccinated, it was impossible to estimate vaccine effectiveness.

We have a table, the first page of the information from CDC -- type table, has H1N1 strains in it. We have had only 12 H1N1 isolets reported from the entire United States. One of those isolets is shown on the test dated February 5th, and that's the Florida-12 strain. It looks very much like the strain from Michigan -- at the time of the meeting, in that it is clearly a Zairean-like strain, and is low inhibited by the reference antisera in that group.

We also included in this table viruses from Asia, some of the most recent strains that we had not tested previously. The -- of special note are the viruses from Nanchang, from the seasonal that we have the date listed, date collected, pardon me, listed as unknown. We do know that these viruses were collected -- season. The reason we wanted to put this in is basically to reassure the Committee that the situation has not changed -- at the end of January, so we don't

really want to make any major point, but the -- really hasn't changed.

I think we can just skip over the frequency table for H1N1, to the next page, and go on to the H3N2 tables. Now, we have two additional H3N2 tables -- generated in February, and these tables include some of the most recent strains that we analyzed -- come from, some from the U.S., and some from Europe, and on the first page we have quite a number from Asia.

As you have seen at our meeting in January, the majority of strains are Sydney-like. They are very well inhibited by the Sydney antiserum. But there are some strains which are -- inhibited by the Sydney sera, and they are represented by antigen 11, 12, 15, and 19. We have looked rather carefully at whether the antisera Sichuan -- you that we were able to identify a couple of Sichuan variants, which are listed as antigens 6 and 7 in the reference antigen section. And those viruses can be distinguished one way from Sydney and a Chile and Argentina, which are all Sydney-like viruses, but if you look at the antiserum, these viruses, they do inhibit the Sydney -- reasonably well, so the activity, cross-reactivity is in one direction. The

difference is they are in one direction.

And we have looked rather carefully at whether there is better coverage of the lower reactors with the antiserum to the Sichuan viruses, and I would say that our antiserum produced here at the CDC does cover these variants marginally better overall. However, antisera produced at Mill Hill in London, at the WHO center in Melbourne does not bear out this finding. In other words, if they use the Sydney -- I'm sorry, the Sichuan antisera in Australia to look at some of the low reacting viruses that they have isolated in Australia, and likewise if they use the Mill Hill serum, the -- actors from Europe. It's the poorer coverage, not better coverage, antisera generated to the Sichuan strain. So -- see marginally better coverage and they -- poorer coverage.

The other thing that I want to mention is that the genetic analysis of the Sichuan viruses indicate that they form -- and we have --

DR. GREENBERG: Could you say that again? I heard a beep. I missed what you said.

DR. EDWARDS: This is Kathy Edwards. I was cut off, but I got reconnected. So, that was the beep.

DR. COX: Okay. The genetic analysis

shows that the Sichuan viruses are quite a tight genetic group, with some signature amino acid changes not shared by other viruses, and we have only a total of 12 strains -- can't prove. They are all from Sichuan. They are not from anywhere, not from any other city in China or any other country, Asia or anywhere else, and they were isolated in the period between April of '98 and September of '98. In other words, we don't have any more recent strains after September -- into this group.

So I think that if you turn the page to the next table that was generated --

DR. KOHL: Before we turn the page, strains 11, 12, 15, and 19, which look like the low -- this is Dr. Kohl -- look like the low Sydneys, I'm not impressed that there's much higher activity with the Sichuans. Is this what you are talking about, marginally better?

DR. COX: Exactly. That's what I'm talking about.

DR. KOHL: Okay. It's not very impressive, is it?

DR. COX: It's not very impressive at all.

DR. KOHL: Thank you.

DR. GREENBERG: Not impressive and not

reproducible.

DR. COX: That's correct. So, we --

MS. CHERRY: Please remember to state your name.

DR. COX: -- and look at the second HI test that we put into the package, which was dated on the 18th of February. -- don't have the Sichuan 346 in this particular test. We have the Shenzhen antiserum in, which was representative of another group. But again, you can see that in this test, O reacting viruses -- the Sydney antiserum, those that are less well inhibited by the Sydney antiserum, which include antigens 9, -- teen, 17, and 18, aren't really better covered by the Shenzhen, not by the Shenzhen nor the Sichuan 418 antisera.

So, I think that we should, with that, go on to look at the -- table, and just see what proportion of strains are really down with the Sydney antiserum overall. Now, in the material which we sent you, we had a total of -- strains, I characterized, that were isolated during the period October '98 to February '99, actually the end of February, and since then we have actually tested additional viruses up to a total of 401 strains. Now this is about -- because the influenza season got a fairly slow start, they

looked to -- we've been able to analyze about two and a half times the number of strains -- data for when we presented for the FDA meeting at the end of January. I think sometimes there's a feeling that we really generate a lot more information in that additional month or so, but I think you can see that we really have generated a lot more information this year.

What we -- the bottom line is, -- been with these additional strains that we've analyzed -- extensive stable -- that we still have only ten percent of strains are reduced in titer with the Sydney antiserum. So I think that our feeling is that Sydney -- we really didn't expect that the China viruses would be Sydney-like. When we -- anticipating their arrival, we were sort of speculating that they might look either like Sichuan or perhaps even something entirely new. That hasn't really been borne out.

We looked very, very carefully at the genetic data, and -- we would say is that we have some things that are beginning to fall out for the H3N2 strains, but there is really no clear direction -- viruses -- feel that Sichuans really are not representative, but we've been seeing more frequently.

Are there any questions?

DR. BREIMAN: Nancy, this is Rob Breiman. What, I missed what you said was following out the genetic material. What's being suggested?

DR. COX: There are some groupings that are falling out, but within each grouping we have viruses which are reacting normally to antiserum. Also viruses that are reacting a bit lower. So there's not a clear signature sequence that tells us that these are viruses which are moving antigenically. So the viruses are quite heterogeneous in terms of the genetic analysis -- not a clear direction yet.

Are there any other questions?

DR. KOHL: Could you tell us historically, when you see a pattern like this --

DR. GREENBERG: Identify yourself, please.

DR. KOHL: I'm sorry, Dr. Kohl. When you see a pattern like this, with a two year predominance of one type of virus, the Sydney in this case, what are the chances that the third year is going to be the same, historically.

DR. COUCH: Unprecedented.

DR. KOHL: Unprecedented.

UNIDENTIFIED PARTICIPANT: Who said unprecedented?

UNIDENTIFIED PARTICIPANT: That was Couch.

UNIDENTIFIED PARTICIPANT: Dr. Couch.

DR. COUCH: We've seen two H3N2 years in a row at least once, clear cut. Chalmers Victoria years for two in a row, and then we had a break before Texas. And since we've been monitoring it here, two years in a row is the most we've seen.

DR. KOHL: This is Dr. Kohl again. Dr. Couch, when there is a change in the third year, is it a shift of that virus, or is it a completely different virus or something? Do we have a track record on that?

DR. COUCH: When it reappears?

DR. KOHL: No, no. What happens in the third year, after you see --

DR. COUCH: Oh, third year it's B, or it was H1.

DR. KOHL: Okay, so it's not a shift or a drift from that same --

DR. COUCH: No, no. It's not a third year, there has not been a third year of H3 as the major virus. And I think that's correct. Isn't that, Nancy, are you aware of any three years in a row?

DR. COX: I don't think we really have three years in a row where H3N2 has been predominant, but we've had three years in a row where we had

significant amounts of H3N2 activity, and usually when we've had circulation of the H3N2 subtype for a couple of years, we have kind of a signal that the virus is moving in one direction or another.

DR. COUCH: Yes, we were able to identify that. You know, we put the label Harold Wave --

DR. GREENBERG: Identify yourself.

DR. COUCH: Couch, Couch here. We were able to identify viruses ahead, and we put the label Harold Wave on them, and the Texas virus was present in the Victoria epidemic. I remember that one very well. And yet was not the major virus until two years after that, but was more prominent during the subsequent year, which was either H1 or B, I'm forgetting at the moment, and then a year after that it became the dominant virus. But Nancy has suggested that things are -- there are some viruses there, but not one you can put your finger on.

DR. COX: I think that in the past, you know, during the past decade, we've been -- put a great deal of effort into improving surveillance in Asia and specifically in China. We've been rather fortunate in that we've been able to detect the variant that was subsequently responsible for epidemics a couple of years, some cases, in advance of

the times that it actually produced the epidemic in the U.S. and Europe. And so we were able to really first detect the virus and then monitor its spread, and get high growth reassortants ready, and so on and so forth.

That was not the case for Sydney. That was a surprise. And in fact, we see now that at least northern China didn't experience a Sydney outbreak until this winter. -- had a Sydney outbreak in the U.S. before we had Sydney, and now -- the many surprises that influenza has in store for us.

DR. EDWARDS: This is Kathy Edwards. The decision by WHO, does that make it very difficult for us to choose something different, just practically, with vaccine manufacturers trying to make one vaccine for one country or a group of countries and one for another. Is that an issue that's important for us to understand?

DR. COX: Roland, do you want to comment on that?

DR. LEVANDOWSKI: This is Roland Levandowski. There can be difficulties when there are different strains that are chosen, and it's not just even for the manufacturers. It's also for use of the vaccines. In many instances, people are traveling,

workers are traveling back and forth across continents, and I think in some sense it probably is helpful, not only for standardization of vaccines and for manufacturing the vaccines, but just for the use of the vaccines, that they -- that there is some coherence in what is in the vaccine.

DR. EDWARDS: Thank you.

DR. COX: And the only thing I would like to add to that is that there is really no scientific reason for differences for vaccine composition for Europe and North America.

DR. GREENBERG: This is Harry Greenberg. Nancy, I have two questions. If I got this right in summary, despite how unusual the situation is, as finely read as you can make it, you could see no indication of what new H3N2 strain could emerge. There's no -- there's nothing in the tea leaves at this moment.

DR. COX: There's nothing in the tea leaves. If we were to choose the Sichuan, which is probably the best characterized of the viruses that are a bit different from Sydney, we might be in a worse situation than we would be if we just stuck with the Sydney.

DR. GREENBERG: And I have one other

question, and maybe I'm getting ahead of myself here. Certainly anecdotally in California, much the way Dr. Kohl mentioned at the last meeting, I now have seen many people with flu-like illness, not documented flu, mostly, who have been vaccinated. What you seem to say is, despite that anecdotal observation, it does not look like the vaccine was working poorly where it's been studied scientifically. Is that correct?

DR. COX: I think we have very limited data, but I think that what, in this one long term care facility, where vaccine effectiveness could really be examined, and it was just against -- and it wasn't against confirmed influenza, but it was effectiveness against influenza-like illness, there was a 72 percent effectiveness calculated for that -- for the health care workers. So I think that there always are vaccine failures. We know it's not a perfect vaccine, but there are abundant antigenic characterizations -- would indicate that there is a very good match with the majority of isolets that are circulating, that it's a tiny percent of the isolets that are circulating, and we know that there are other respiratory agents circulating -- else.

I think it's a combination of factors. There are more people getting vaccine now, and there

are multiple respiratory pathogens circulating, and it's not a perfect vaccine.

DR. FAGGETT: Speaking anecdotally again, in terms of studies in the long term -- this is Dr. Faggett -- were there any instances of Guillaume-Barre identified, either in the California or the long term facility?

DR. COX: Any -- no, I don't believe so.

DR. FAGGETT: Thank you.

DR. LEVANDOWSKI: Okay, we're getting a little bit behind time. This is Roland Levandowski. I guess I should be pushing our -- reminding the speakers, that's me and Nancy, basically, that we should keep on track and keep moving. So Nancy, are you prepared to go on with the B?

DR. COX: Sure. I'm prepared to go on with the B. If you would to the page with the first HI test of influenza B. Test -- on the 11th of February. You'll see that we have tested with eight different antisera, and the thing that I would to point out is that we tested rather a large number of viruses in the United States that were isolated this season. These are primarily from January.

And if you concentrate on column number two where we have the antiserum with the Harbin

strain, that's a titer of 640, this antiserum does not inhibit -- very well. We have a number of titers of 40, 80, and 160. RS is switched. All of which would be fourfold down or more to the -- the homologous titer.

We have been looking at a variety of additional strains and antisera. I think I'll just move very quickly through the second table. You can see that there is a similar pattern there. Then we have a lot a viruses from the U.S. A test that was generated on the 25th of February. Then we have a number of strains which are reduced fourfold or greater in titer with the Harbin serum in column two.

On this test, we see that the Yamanashi antiserum does a bit better. It has a somewhat lower homologous titer, but we don't have that many viruses that are twofold down from it. Also -- that -- better. Georgia 02 is not terribly good, we've found, in -- not the C's test, but a number of other tests. It's not as good as the Yamanashi or Bucharest.

DR. KOHL: This is Kohl. The Yamanashi, just eyeballing it, doesn't look any better than the Beijing 184.

DR. COX: Actually, it does. Oh, Beijing 184. Beijing 184 is the prototype strain, and it is -

- it has been very consistently good, but it did not grow well enough for the vaccine manufacturers to use, and was not considered satisfactory for vaccine production at the time. That's why we moved to the Harbin, because it grew quite well. At the time, we hadn't tested it nearly as much, and we considered it antigenically equivalent.

As things have moved on and our analyses have progressed, we note that there are differences -- viruses on this -- there are, of course, two separate lineages of influenza B viruses circulating -- of the viruses -- lineage -- really two groups. One group is related to Beijing 184, and the other is the Harbin. Now, the Beijing 184 lineage appears to be predominating.

DR. KOHL: Dr. Cox, isn't the Beijing 184 what's recommended by the WHO?

DR. COX: Yes, but all countries have used Harbin.

DR. KOHL: Okay. Thank you.

DR. COX: So Yamanashi would be considered a Beijing 184-like strain. In other words, if we were looking for a strain that was more contemporary than Harbin 94, and which gave us better cross protection than the actual vaccine strain, Harbin -- we would

still, we could still be using a Beijing 184-like strain.

DR. GREENBERG: The WHO, if you just read it, it says, "Beijing 184-like," and like is the Harbin.

DR. KOHL: Right. Okay.

DR. COX: If we could move on to the -- table, I think that's probably the most informative.

DR. POLAND: This is Greg Poland. I've been paying attention, when there's a short pause, Nancy, the next word drops. When there's a longer pause, it doesn't drop.

DR. COX: Okay. I'll try not to pause -- just pause longer.

The frequency table that we sent out had a total of 108 influenza B viruses that were isolated between October '98 and February '99. And we've updated that number with some recent stuff that we have done. Now we have 138. There are only 50 -- characterized at the time of the FDA meeting, so we really do have a lot more information.

And what we've seen is that now, with a total of 138 strains, seven percent of them are reduced in titer to the Harbin vaccine strain at least fourfold.

DR. EDWARDS: What was that number?

DR. COX: 67 percent.

DR. EDWARDS: 67.

DR. COX: That's correct. So it has been varying between about 65 and 75 percent, depending on the latest information, but it certainly has increased compared to the period April '98 to September '98. If you look at the next section on the frequency table, you'll see that approximately 35 percent of a smaller number of -- were reduced at titer to Harbin serum.

DR. HUANG: Are they more like the Shangdong strain? This is Alice.

DR. COX: No, they're not.

DR. HUANG: They're not, okay.

DR. COX: No. The viruses -- there are only two strains that we've examined that are like the Shangdong, and they are listed on this table as Victoria-like. And those two are from Asia, as you can see, they are in the Asia column.

Okay, so we actually looked through a fairly large number of tests, and tried to see which -- which of the strains, more contemporary strains might offer better cross protection against the currently circulating influenza B viruses. And -- found that -- Yamanashi strain actually looked better

than Bucharest and Georgia 02, which were the two other contemporary strains that we have the most information for.

So in contrast to -- at the time we did the calculations, we had about 74 percent of strains down to Harbin, and only 13 percent of strains -- to the Yamanashi antiserum.

Okay, I think that finishes up what I had to say, unless there are any questions.

DR. KOHL: This is Kohl. Is the Yamanashi a good grower.

DR. LEVANDOWSKI: This is Roland Levandowski. The answer -- the short answer is yes, and I'll give a little more information on that a little bit later.

DR. COUCH: But the Yamanashi with ferret sera would still be -- would it not be still classified as a B Harbin-like strain?

DR. COX: Yes, it would be B Beijing or 184-like.

DR. COUCH: Or 184 as you choose.

DR. LEVANDOWSKI: Okay, are there other questions?

DR. KOHL: So, Bob, this is Kohl again, does that mean that the Yamanashi would probably

perform just as poorly as the Beijing Harbin?

DR. COUCH: Well, I guess I mean by that, we can see if Nancy and Roland do, it's somewhat unpredictable that it would be a better strain.

DR. KOHL: Okay.

DR. FERRIERI: This is Pat Ferrieri. Nancy, I missed the points on the Bucharest strain. Why would that one not be so good?

DR. COX: Actually -- counted the number of strains that were reduced fourfold or greater in titer with the Harbin antiserum, with the Yamanashi antiserum, the Bucharest antiserum, and with the Georgia antiserum. And the numbers are 74 percent, 13 percent, 31 percent, 51 percent respectively. We have fewer data for the Georgia 02, but we were really trying to look at a strain that is more representative of the contemporary strains, either better cross reacting antibody at least with the ferret sera, and the Harbin current vaccine strain appears to do it.

Now, the only other thing I would like to add is that there are data from Europe which confirm our findings, and those data come from the Netherlands, from France, and from the U.K.

DR. GREENBERG: Okay, Roland, are you going to continue?

DR. LEVANDOWSKI: Yes, I think we should. We are getting a little bit behind, and I'm feeling nervous about it, and I'm sure you probably are, too. There will be time for some further discussion and questions on all these points, so I don't think we'll miss anything.

I'll go ahead then and describe some serologic data, and if you want to turn to the handout that CBER put together, this handout is a summary of data that was compiled from haemagglutination inhibition antibody testing that was done at the centers that participated. Those are listed at the beginning of the handout. I don't think we need to go into that part of it.

I'd like to call your attention to the tables that start on page 5 of the handout. And the tables on page 5, 6, and 7 indicate strains that were used for serologic testing during the last couple of periods, extending back to September of '98 for different WHO recommendations that have been made.

There are tables on page 8, 9, and 10, and those tables summarize where we have data from at least two laboratories have tested a strain. You will see that there are quite a few -- there are fewer strains that were tested widely, and I will point out

that for the antigens and the strains that are listed for serologic testing, not all of these strains, of course, were tested in every laboratory, and that's mostly because of the timing and the logistic constraints of getting these strains shipped from place to place to do the testing.

Some of these strains were tested in a single laboratory, and sometimes it was with a single serum panel, so that what's shown, what I am going to try to describe from the listing of the different strains used for serologies takes a little thinking about.

The data as they have been accumulated really reflect the fact that the current influenza season has been developing at a later time than in other recent years, and so that's another thing that has impacted on our ability to get a lot of data at different places.

On page 5, the H1N1 strains used for the serologies are shown, and the strains are subdivided into A Beijing 262/95-like strains at the top and A Bayern 7/95 like strains at the bottom. Vaccine strain on this table is shown with an asterisk, and the strains that are underlined are those for which at least one test in at least one laboratory showed a 50

percent or greater reduction in the geometric mean titer compared to the vaccine strain.

You'll note that there are a number of strains that showed a reduction compared to the vaccine strains, but overall the reductions were not uniform in most instances, and I'll call your attention now to page 8, which has data for the H1N1 strains that were tested in multiple laboratories. And these tables will all be somewhat similar. The table on page 8 summarizes the data from four labs, from the four labs listed. It shows how many sets of sera gave a 50 percent or greater reduction for the newer strains in comparison with the vaccine strain. The upper two strains there are actually Beijing 262/95-like.

I'd like to call your attention to the one that is shown as A Hong Kong 4847/98. You'll see that three labs tested the strain, and you can see that a few of the tests from two of the labs were low, but overall the reduction that was found was less than 50 percent. And you can see that only about 25 percent of the tests really looked like they were low.

Similarly, for the A Michigan 24/98 strain, you can see that there were some tests that were low, but overall, again, it didn't look -- it

didn't appear to be, not a consistent finding among the different tests that were done.

So I'd say in summary about the H1N1's, and not to belabor this, although some of the tests were reduced, the overall data don't indicate that there was a major antigenic change in the H1N virus, as at least demonstrated from these human serologic data.

Moving on to the H3N2 viruses on page 6 of the handout, going back to page 6 of the handout, the H3N2 strains that were tested are shown. And these strains are broken down into groups based on genetic and antigenic characterization. Nancy Cox did not emphasize the genetic characterization, but did mention it. The strains in the upper group are those that are most like A Sydney 5/97, and you see there are quite a few of those.

The bottom group is most antigenically distinct from the A Sydney strain, and that's the A Sichuan-like viruses, which seem to be off by themselves somewhat, and then there are others in between that at least genetically appear to be forming their own little groups.

The underlying strains, again, are those that show at least one lab and at least test finding

of 50 percent or greater reduction, but you can see that there are some strains -- and you can see that there are some strains in all the groups that were low on occasion, but you can see that the majority of the strains tested did not show a reduction. And, again, calling your attention to the Sichuan strain on page 9, the summary table where more tests were done, this has been updated somewhat since January, not by much, but with the additional data that were available. And you can see that for Sichuan 346/98 there were some tests that were low for all of the laboratories, but calling your attention to the last two columns, overall you can see that less than half of the tests were reduced by 50 percent or greater, and overall the reduction based on all of tests was not quite 50 percent.

So, again, in summary, for the H3N2 viruses I would say that there were some reductions that were seen, but for the majority of viruses that were tested representing the broad diversity of the strains that were examined, the current vaccine strains induced reasonably good antibodies, and I'd say the bulk of the data again do not indicate a major antigenic change in the H3N2 viruses.

On page 7, going back to page 7, the

antigens here for the influenza B viruses. And the antigens are broken up into the B Beijing 184/93-like viruses at the top, and the B Shangdong 7/97-like strains at the bottom. I should mention that B Shangdong 7/97 is very much related to the B Victoria 2/87 strain that Nancy was talking about.

In most instances, these serologic tests were done with ether disrupted virus, but one of the four laboratories involved performed all the tests with whole virus, and I don't know that it actually made any difference here. The underlined strains are those for which at least one lab found a reduction in at least one test. And, reductions actually were found for both the ether disrupted and the whole virus antigen in some of the tests.

Although some of the B Beijing 184/93-like viruses gave reduced responses compared to the vaccine strain, which here was B Harbin 7/94, most of the results were very comparable to those with B Harbin 7/94. However, as has been previously true for several years, all of the strains that were related to B Victoria 2/87, and here it's the B Shangdong 7/97 predominantly we're talking about, they showed consistently reduced responses in most of the tests.

And on page 10, the summary of that, if I

just call your attention to the next to the last column, and just looking again at the B Shangdong 7/97 antigen, you can see that in more than 80 percent of the tests performed there was a reduction, and in the case of the B Shangdong and related viruses, that reduction was reasonably substantial.

Not shown in any of the material except as described briefly in the WHO recommendations, there was also a study that was done using a trivalent vaccine, contained a B Shangdong 7/97 B component. That vaccine was made by Pasteur-Merilleux, and the vaccine was administered to 60 adults and 60 elderly in Australia. The pre- and the post-immunization sera -- and that was done in the fall -- the pre- and the post-immunization sera have been collected from the study participants, but the serologic testing has not yet been completed as far as I know, and the data presented at WHO were for about half of the sera that have been collected.

But, for the sera that were tested, the antigens included B Shangdong 7/97, which in that case was the vaccine strain, and it was compared to a vaccine that included B Harbin 7/94. And, in this particular test, there were several other recent B Beijing 184/93-like viruses that were looked at,

including the B Romania 318/98, the B Delaware 2/98, and the B Foshan 396/98, representing a strain -- several strains from different continents.

The preliminary data indicate that the vaccine was immunogenic, in that it produced antibodies that are similar in titer for the vaccine virus, and in the case of the B Shangdong containing vaccine, the titers were similar for the B Beijing 184/93-like viruses.

There's one important item that I'd like to mention in relation to that study. The study does not include children or any immunologically unprimed individuals, and I point out that based on previous experience in unprimed children, it's not likely that antibodies, the B Beijing 184/93-like viruses, would be induced very well, if at all, by a B Shangdong 7/97 vaccine, and therefore for children, where B Beijing 184/93-like viruses are prevalent, a vaccine containing something that's like B Beijing 184/93 would be a much closer antigenic match.

I'll stop there. If there are any questions, I'll try to answer them.

DR. FAGGETT: This is Walt Faggett. With the children, so that would still be a two shot series with Beijing 184?

DR. LEVANDOWSKI: Yes, for children under, I guess it's age 9, if they have not been previously immunized or infected.

DR. FAGGETT: So there are no studies of children that we can refer to?

DR. LEVANDOWSKI: Doing immunization studies in children -- yes, they are fairly difficult to come by, unless they've been arranged in advance. It's a population that is hard to enroll, and there's a lot of work that has gone into preliminaries to have it set up, but we do not have any information specifically on the B Shangdong 7/97 vaccine, or on a B Beijing 184/93-like vaccine in recent years.

In the past, we have looked at strains that are on the B Beijing 184/93 -- in that lineage, and we have seen there also that those vaccines do not induce antibodies that cross react with the other lineage as represented by B Shangdong 7/97 or B Victoria 2/87.

DR. KILBOURNE: Could you remind us again what population base we are talking about?

DR. LEVANDOWSKI: I'm sorry. This is Roland. I don't understand the question.

DR. KILBOURNE: The question is, the data you have shown us -- populations are represented?

DR. LEVANDOWSKI: Oh, I see. For all the serologies that were done. These sera, the sera that are shown in the studies here, are all from adults and elderly. The adults and the elderly were on three different continents. There were some number of sera -- there were 172 some odd serum pairs altogether, and there were populations from Europe, from the United States, and from Australia represented in both the adults and elderly in separate serum panels. Does that answer the question?

UNIDENTIFIED PARTICIPANT: Who asked the question?

DR. LEVANDOWSKI: That was Dr. Kilbourne.

DR. GREENBERG: If there are no further -- Roland, or -- do you have any more questions from the committee?

DR. LEVANDOWSKI: Okay, I actually have some additions -- this is Roland again -- I have some additional information, and there are a couple of other items that we would like to address before the discussions of the committee, if that's okay?

DR. GREENBERG: Sure.

DR. LEVANDOWSKI: I did want to touch on availability of strains and reagents, just to let you know where those things stand, and at that point it

might be reasonable if there were some comments from the manufacturers about their view on some of these strains, to let us know.

Also, I have asked, invited to our meeting somebody from the Department of Defense, Captain David Trump from the Office of the Assistant Secretary of Defense for Health Affairs, because it was thought that it might be useful to have some input from the Department of Defense on what their view is on some of the issues that may come up, but I'll go ahead first with the availability of strains and reagents, and just say generally that for any strains that are currently in the vaccine, of course, we already have the reagents, and there aren't any problems or seed viruses that are available. The manufacturers know how to handle the strains well. Everything that needs to be done can be done.

If there are any new strains that are chosen, we do not have reagents for those things in hand at the moment, and based on previous experience, we would anticipate that the reagents would not be ready for use until sometime in May.

For H3N2 viruses, there really are no new suitable candidate strains that have been identified since January. There is a high growth reassortant of

the A Sichuan 346/98 strain, which is RESVIR 14 from our lab, and Dr. Kilbourne may have something from his lab that I don't know about, but the strain that we know about has not yet been fully characterized antigenically and genetically, and we're not really sure whether it would be appropriate even if it were selected.

For the influenza B viruses, among the B Beijing 184/93-like virus, there are several strains that have been partially evaluated and appear promising, and among those strains, the B Yamanashi 166/98 and B Romania 318/98 appear to grow quite well, and in some reports they may grow better than the current vaccine strain, the B Harbin 7/94.

Some of the other strains that were being discussed have been looked at also, including B Bucharest, and we have a little bit less information there. That strain, from what I know, appears to be somewhat lower growing, although that is somewhat variable. There are some reports that it may be reasonable.

For the B Shangdong 7/97 virus, of course that strain has already been used for making an experimental vaccine, and from everything we know from other manufacturers who have had a chance to examine

it, it appears to be quite good growing.

I guess I would stop there on that, and see if there are any questions, and if there aren't any questions, there may be questions that the manufacturers might need to address. I might ask the opportunity for any manufacturers who feel like they have some set of information about strains that they have been looking at, or strain collections, if they might be willing to do that. And I guess if there aren't any voices raised, or hands raised for anybody who might be in the room where I am not, then I guess --

MS. CHERRY: No hands raised here.

DR. LEVANDOWSKI: Okay. Then I guess, Dr. Greenberg, I might ask if Captain David Trump, who I mentioned is with the Office of the Assistant Secretary of Defense, Health Affairs, might be willing to give us some comments from the Department of Defense point of view.

DR. GREENBERG: I think that's great. Dr. Trump, I would ask you to be concise.

CAPTAIN TRUMP: Yes, sir. This is Dave Trump. Can you hear me?

MS. CHERRY: Yes.

CAPTAIN TRUMP: It's working fine here in

the state where I am. Historically, we do not differ as far as the vaccine that's been used for the military, at least in the last several years if not longer, from the national recommendation, and that is something that -- differing from that would not be a decision that DoD would make very lightly. The recommendation coming out of the WHO certainly with its geographically based recommendations raises some concerns and questions.

We have about 100,000 military personnel who are at any one time in the Asian area of operation, the majority of them based either in Korea, the Republic of Korea, or in Japan.

DR. GREENBERG: You're breaking up. I guess we'll just try to go with it, but it's hard.

CAPTAIN TRUMP: I'll keep it short. 100,000 primarily in Japan, Okinawa included, Guam, and Korea, and on ships. Probably another 200,000 who are either getting ready to move into that area or would be on standby to move there, and about 75,000 family members. And so a recommendation for the nations of Asia that would recommend one vaccine, and then what would be here in the United States for us recommended, would be a challenge about deciding what to do for those who are in Asia. We certainly will

await your recommendations, and the decision from this group and from the advisory committee next week.

This most likely will be a question that we'll pose to our Armed Forces Epidemiological Board, and Dr. Poland and Dr. Eickhoff are very familiar with that group.

DR. GREENBERG: Roland, can I get a clarification?

DR. LEVANDOWSKI: Yes.

DR. GREENBERG: The charge to our committee is to make a recommendation for vaccination in the United States, or for recommendations for vaccination in something more than the United States?

DR. LEVANDOWSKI: My understanding is that our committee would make the recommendation for the U.S. Public Health Service, and my belief is that that recommendation would reflect what's best for the civilian population. Historically, as Dr. Trump was mentioning, I think I was having trouble hearing also, the Armed Forces Epidemiological Board has made its own recommendations, and there have been occasions in the past where the military has required a vaccine that was somewhat different from the vaccine that was used in the United States. There is precedent for that, and that can be accommodated, and as I've

discussed with others, licensing of vaccines that might be different for the military can probably be accommodated in the current system. It's a matter of having the reagent available to be able to produce the vaccines, so -- I'm rambling on here, but I believe that our recommendation is for the civilian population.

DR. GREENBERG: And I have one other question, personally, here. It's my impression that the B Shangdong-like viruses have been present in Asia, or in Southeast Asia, for a long time. What is the change to make this a bigger question for the military here?

DR. LEVANDOWSKI: This is Roland. Do you want me to answer that one?

DR. GREENBERG: Yes. Whoever can answer quickest.

DR. LEVANDOWSKI: I would say that what would spur this would be the fact that the percentage of B Shangdong or B Victoria 2/87-like viruses occurring in Asia seem to be increasing, but Nancy Cox I think should maybe answer that with some of the frequency data that she was describing earlier.

DR. COX: I think that the percentage of viruses that are B Victoria-like or B Shangdong-like

in China has decreased, and the difference is that the viruses -- Victoria or B Shangdong-like viruses are circulating in Thailand on -- but they have been, and they may be predominating in these two countries. But I don't think that the epidemiology has changed very much since last year.

But what's happening at the WHO level is that we're trying to take into account the fact that a lot more influenza vaccine is being used in Asian countries now -- likely to be used in Asian countries in the future. So we want to take that fact into account and make appropriate recommendations for those countries to sort of encourage their -- increasing use of influenza vaccine.

DR. GREENBERG: Nancy.

DR. COUCH: Couch. An interest question. Does -- what B strains have been used in the vaccines, say in the last couple of years, in Japan and in Australia?

DR. COX: In Australia, B Harbin has been used. In Japan, I believe that two years ago they had a tetravalent vaccine, a B Harbin-like and a B Beijing 184-like -- Victoria -- like strain, so they had two B components.

DR. COUCH: I see.

DR. COX: Now that they didn't have very good immunogenicity -- for this past season went back to a B Beijing 184-like, so they had a trivalent vaccine for this past year.

DR. GREENBERG: Roland?

DR. LEVANDOWSKI: Yes, sir.

DR. GREENBERG: Do you have any additional comments before we open this up to committee discussion.

DR. LEVANDOWSKI: I think it would be good if, maybe, Nancy Cox would be willing to summarize what the options are at this point. Would that be okay?

DR. GREENBERG: That would be terrific.

DR. COX: Okay, I'll start with the H3N2 viruses. What we know is that -- viruses have -- worldwide, both in 1997-98 and the 1998-99 influenza seasons, and widespread outbreaks have been reported in a number of countries in Asia, Europe, and North America. -- sense of H3N2 activity overall. -- type tests with post-infection ferret sera, the majority of influenza A -- Africa, the Americas, Asia, Europe, and Oceania.

Our -- hopefully related antigenically through Sydney 5/97. Of the portion of viruses, that

is about 10 percent that are antigenically distinguishable from Sydney, however these viruses -- heterogeneous -- analyses have not revealed the emergence of a representative variant that's the geographic -- . Options for that C component -- retain the Sydney component -- the advantages would be that most current strains are Sydney-like -- ours has known characteristics, or to update the Sydney component, the H3N2 component, and -- know that this variant has already circulated widely for two years, and that H3N2 viruses cause more hospitalization and mortality than viruses from the other two groups, but I think that we are a bit stuck -- that Sichuan 346 variant that really hasn't proven to be representative of the currently circulating strains.

For the influenza B viruses, if I could just quickly go on, we do have viruses from both the B Victoria or B Shangdong and Yamagata or B Harbin when it is circulating worldwide, but I could qualify that by reemphasizing the B Victoria-like viruses have been seen only in Asia for the past nine years.

Influenza B activity has been moderate worldwide. However, some countries in Europe actually had influenza B strains predominating. -- some of the FDA meeting, we had 12 of 34 U.S. isolets -- titered -

- B Harbin antiserum. Now at the present time we have 53 of 96 U.S. strains which are reduced in titer with the B Harbin strains.

As Roland mentioned, the current influenza B component -- this antibody that cross reacts with many of the Harbin or B Beijing-like viruses -- all of these studies, and we know that we lack test data to these components in 1995.

Our options for the B vaccine component are to retain the B Harbin -- a C strain seems to cover most of the current related strains in the -- studies it has known characteristics. Or we could update the B Harbin 7/94 component, and we would be looking for a B Beijing 184-like strain. -- to do this on the basis that there is a reducibility of the Harbin ferret serum to inhibit the current strain, as I mentioned before, and we've looked at a whole variety of strains, and the B Yamanashi does appear to be sturdier to the B Harbin vaccine component. And, of course, the third alternative is to update the B Harbin component -- on the B Victoria lineage, because these viruses continue to circulate in Asia, and there is a susceptible population in the United States. However, both the virology and the epidemiology argue against this option, because there is very, very

pronounced antigenic differences between viruses on the Victoria or Shangdong lineage -- lineage, and the genetic differences among these viruses are very great. It's approximately 30 amino acid differences between the two lineages.

So I think I will stop there.

DR. GREENBERG: Nancy, did I miss H1N1?

DR. COX: We had already decided the H1N1 part, so I thought in the interests of time I would just skip over that.

DR. GREENBERG: Fine. Roland?

DR. LEVANDOWSKI: That's it from us, Dr. Greenberg. We'll turn things back to you and the committee for discussion.

DR. FAGGETT: So Dr. Greenberg, Dr. Faggett, Nancy said that I was to sign on the H1N1, so that's A Beijing 262?

DR. COX: Yes, that's correct.

DR. FAGGETT: Okay, thanks.

DR. GREENBERG: And that was pretty much decided at the last meeting, and there's been no new information, as I understand it, to make that decision -- on, and that's obviously a WHO decision as well.

I'd like to open up this conversation now for an open discussion of the committee. That could

be a little complicated on a conference call. I think we've had an excellent presentation from the CDC and the FDA, and I think we have all the information that one can have. I am -- all of you feel we don't have all the information you would like, and -- frequently is, we have to make a decision -- late, and I think we're going to have to do it with what is available.

So what I would do now is just open this up. People identify themselves, and ask questions or give statements, and after we've exhausted that, hopefully -- they vote.

DR. COUCH: Harry, this is Couch. Would you like me to start you?

DR. GREENBERG: I'd love you --

DR. COUCH: Not with a statement. I was going to suggest a motion, and just maybe a comment about the motion, and then see if there is discussion.

DR. GREENBERG: I actually have to go to the bathroom, so if we can move this quickly, this would --

(Laughter.)

DR. COUCH: Well, it seems to me that the H3N2 doesn't require much discussion, that we've had major Sydney two years in a row, and while the desirability would be to pick an H3N2 strain and

anticipate what's going to happen, perhaps to some extent, next year and may be significant the year after, we can't do that. We don't have strains in place that say that there is a justifiable change in A Sydney, so my motion would be that we retain A Sydney as the vaccine strain.

DR. GREENBERG: Do I have a second?

DR. FERRIERI: Pat Ferrieri seconds it.

DR. GREENBERG: Can I have a vote, then, of the members, and --

DR. FERRIERI: May I just say something, Harry? I'm really glad that we didn't make the decision in January. We sort of teetered on the brink of doing it then. I'm very happy we waited to hear the data, and even though our decision is probably the same as what we would have done in January, I appreciate hearing all this information today.

DR. COUCH: Couch. I will always second that. The latest possible data insures our -- reassures that we are going in the right direction. This time, as you say, it's a good change, but sometimes it's not.

DR. GREENBERG: And I underline that. Can -- should I, Nancy, can you call out the roll call for votes?

DR. KOHL: Can I ask a question? This is Kohl.

DR. GREENBERG: No. Yes, you can.

DR. KOHL: What I gather we are doing is we're saying that it is very unlikely that A Sydney is going to be circulating next year, or an A Sydney-like is going to be circulating next year, and --

DR. COUCH: Or, if so, it's not going to be the dominant virus producing the epidemic.

DR. KOHL: Okay. And the only reason we're not changing is because we don't know what to change to, is that correct? If there were something that was sticking out, we would probably change.

DR. COUCH: Well, that would be my preference. If we had clearly a clear cut Harold Wave with epidemiologic significance of a strain that is changed, of an H3N2, but was not dominant, that would be the kind of thing that I would have been looking for, and with all of the supporting data that goes with that for a recommended change, but we don't have that.

DR. GREENBERG: Dr. Kohl, I think that's always the case, that if there is a clear indication that a new strain is coming and we know what it is, we are likely to make that recommendation.

DR. COUCH: Actually, that's well said, Harry. That's sort of a generality.

DR. GREENBERG: So can, Nancy, can you call a roll call?

MS. CHERRY: I will. Dr. Poland? Okay, Dr. Adimora?

DR. ADIMORA: I agree with the motion as presented.

MS. CHERRY: Mrs. Cole?

MS. COLE: Yes, I agree also.

MS. CHERRY: Dr. Estes?

DR. ESTES: I agree.

MS. CHERRY: Dr. Huang?

DR. HUANG: Yes.

MS. CHERRY: Dr. Edwards? Dr. Edwards?

DR. GREENBERG: I think she went to clinic.

MS. CHERRY: Okay. Dr. Daum? Dr. Couch?

DR. COUCH: Agreed.

MS. CHERRY: Dr. Eickhoff?

DR. EICKHOFF: Agree.

MS. CHERRY: Dr. Kilbourne?

DR. KILBOURNE: Yes, I'd like the opportunity to say something now. That is, I don't think we should be embarrassed about this

recommendation, and I think that -- the best we can do at the moment to bear in mind that even if a new strain appears, we are going to have some significant, perhaps heterovariate immunity, so we are not leaving the country unprotected.

DR. COUCH: Absolutely not. I agree, Henry.

MS. CHERRY: Okay. Dr. Griffin?

DR. GRIFFIN: I agree.

MS. CHERRY: Dr. Faggett?

DR. FAGGETT: Could you repeat the motion? I'm sorry, I didn't hear -- I was off the line.

MS. CHERRY: The motion was to retain the Sydney 5/97.

DR. FAGGETT: I heard Bob Couch say --

DR. COUCH: As the H3N2 component.

DR. FAGGETT: Thanks. Definitely, yes.

MS. CHERRY: Okay. Dr. Kim, are you there yet? No. Okay. Dr. Breiman?

DR. BREIMAN: Yes.

MS. CHERRY: Dr Kohl?

DR. KOHL: Yes.

MS. CHERRY: Okay, and Dr. Ferrieri?

DR. FERRIERI: Yes.

DR. GREENBERG: And for the record, I also

vote yes, and so I think we've picked one of our two choices, and I thank you for being -- thank Bob Couch for being so expeditious. Perhaps, Bob, since you seem to have a knack for this, you can start us off on the group B's.

DR. COUCH: Me? Couch, did you call on me for that?

DR. GREENBERG: I sure did.

DR. COUCH: That one's not quite as easy, but I think -- but I know what I think we ought to do. Well, Nancy, I couldn't hear all of Nancy's options. I'm sorry about that, but I think we know what they are. I suppose the only -- well --

DR. GREENBERG: Do you want me to summarize the options, Nancy's options for you.

DR. COUCH: Let's not -- I don't need them, if everybody else heard them all right. My recommendation will be, without a whole lot of conversation, that we retain B Harbin as the vaccine strain. If we were looking for a change in this lineage, why, as I read the data, if Yamanashi and Foshan and Georgia 02, and there was one other there that looked like they may be candidates, but when you look at the ferret sera and what we knew about them, I wasn't convinced that there was enough data to

suggest change in the B Harbin component, and that would be my recommendation.

I suppose the data from Australia is a little disturbing with Shangdong, but on the other hand, they were dealing not with children, they were dealing with adults, and we might expect something like they saw in the way of cross reactivity. The only other consideration would be that a bi-component of influenza B, and we've discussed that, I think, at least two or three years in a row, and I would not support that, even though I think some argument could be made for it. It's interesting that the Japanese went that direction at one time in the past.

So, I would think that monovalent Shangdong would be the one that I would reject. Bivalent, or B Harbin, or updated B Harbin, and of those three, it looks to me like the only one that's reasonable is to continue B Harbin as is. So that would be my recommendation, and we'll see what happens to the discussion.

DR. GREENBERG: Okay.

DR. HUANG: Harry, could I break that up into a different kind of motion that may move us along a little faster. This is Alice. I think that it would be easier to first consider whether we want a

Beijing 184-like virus versus the Shangdong, and then later go to the specific strains, that is --

DR. GREENBERG: I think that's an excellent idea, Alice. So could you make your motion?

DR. HUANG: So the motion is that we prefer a Beijing 184-like strain for the B virus.

DR. GREENBERG: I need a second to that motion.

DR. EICKHOFF: Eickhoff. I'll second it.

DR. GREENBERG: So Nancy, could you call the roll?

MS. CHERRY: Yes, I will.

DR. GREENBERG: So, just so everybody knows, what Alice has done is said we haven't picked the exact strain, but she said this year, like years in the past, although we know that Shangdong is out there and is in Asia, we know that that is not the primary choice to be in the vaccine for the U.S. population, and that it still should remain a Beijing 184-like virus. The precise choice of that virus remains to be chosen by us. That's what we are voting on now.

MS. CHERRY: Okay. Dr. Poland?

DR. POLAND: Yes, I agree.

MS. CHERRY: Okay. Dr. Adimora?

DR. ADIMORA: I also agree.

MS. CHERRY: Mrs. Cole.

MS. COLE: Yes, I agree.

MS. CHERRY: Dr. Estes?

DR. ESTES: I agree.

MS. CHERRY: Dr. Huang?

DR. HUANG: Yes.

MS. CHERRY: Dr. Edwards. No, still not there. Dr. Daum?

DR. DAUM: Yes, I agree.

MS. CHERRY: Okay. Dr. Couch?

DR. COUCH: I agree.

MS. CHERRY: Dr. Eickhoff? Was that a yes?

DR. EICKHOFF: Yes.

MS. CHERRY: Okay, it didn't come through very well. Dr. Kilbourne?

DR. KILBOURNE: Yes.

MS. CHERRY: I'll have to go back and look at my list a minute. Dr. Griffin?

DR. GRIFFIN: I agree.

MS. CHERRY: Dr. Faggett?

DR. FAGGETT: I agree.

MS. CHERRY: Dr. Kim, you're not there? Okay, Dr. Breiman?

DR. BREIMAN: Yes.

MS. CHERRY: Dr. Kohl?

DR. KOHL: Yes.

MS. CHERRY: Dr. Ferrieri?

DR. FERRIERI: I agree.

MS. CHERRY: And Dr. Greenberg.

DR. GREENBERG: And for the record, I also agree, and thank you, Alice, for doing it that way, which will speed this up. And now, I think we are in the home stretch, and I can't last much longer, so what I would like some discussion of -- if I heard Nancy Cox correctly, and she broke up for me too, I think her impression was that maybe the Yamanashi strain did represent a better choice than sticking with the B Harbin from her reading of the serology.

I also got the impression she had a bit more serology in front of her than we have in front of us, so maybe I could ask Nancy and Roland to reiterate or give a hint of what they think one more time, and then I'll open it up for the committee.

DR. COX: Roland, do you want to go first, or do you want me to?

DR. LEVANDOWSKI: I don't have as much to say, probably, so maybe I could go first. I would say that the choice originally back five years ago, if we

could have done it, would have been for a B Beijing 184/93-like virus. The B Harbin -- the use of B Harbin 7/94 was kind of a fallback position that resulted from the fact that the B Beijing 184/93 virus itself did not grow well enough for manufacturers to be able to make a vaccine, and we were fortunate to have that strain available to us at that time.

There has not been a compelling reason to change that strain in the interim, or at least not as much of a compelling reason to change that strain in the interim, and although the data as they exist from human serologies don't necessarily indicate that the current vaccine is ineffective, the data from the ferrets does suggest that we can detect what we would expect, a continuing antigenic drift of the B Beijing 184-like viruses. And in the respect that we possibly have an opportunity to change a strain that otherwise we might be in a hard position to do, I think I should remind everybody that it is not a light undertaking to change any strain for the manufacturers. It's particularly hard, and -- because it's totally unknown, but it's almost impossible to make three changes in one year.

And if we make no change at all this year, I worry that we would be in a position in coming years

where if we wanted to update the B strain, we might be a little more stuck, and then maybe Nancy should say what she's got to say.

DR. COX: Okay, thanks, Roland. What I would say is that we are seeing about the same pattern of antigenic variation that we saw when we updated the vaccine from the Panama 90 strain to the B Beijing 184-like recommendation back in '95. And it makes us feel fairly uncomfortable here at CDC when we have viruses rolling in from the United States and other parts of the world that are really not well inhibited by ferret antiserum, that is, when the titers are reduced by four to sixteenfold, as the current B strains are.

And we actually went back and looked very carefully over data that we had accumulated over the last year and a half, and found that we had a good consistency with a couple of different lots of ferret antiserum that had been used very extensively in our labs, and that it was very clear that the number of virus -- the proportion of viruses that are reduced in titer with the actual -- with the antiserum for the actual vaccine strain is increasing over time. And this, I think, is something that always makes us feel nervous. We are reluctant to report these viruses out

as being Harbin-like in that instance. You know, there's clearly when they are Beijing 184-like, or Yamanashi-like, but they are not -- they are reduced in titer before they are greater with the Harbin serum.

So, I think that having looked at the B data over a number of years, we are getting to the point where we were when we changed from B Panama to B Beijing 184, and it -- so it makes us here at CDC feel that it is time for an update of a few components.

DR. KOHL: This is Kohl. Dr. Cox, at one point in your presentation, you summarized the fourfold decrease in percentages, going from Beijing on to Bucharest. Can you repeat those summaries of fourfold decreases?

DR. COX: Yes. I'll start with Beijing 184. That's 7 percent. Harbin, 74 percent. Yamanashi, 13 percent. Bucharest, 31 percent. And Georgia 02, 51 percent. And I should mention that we have fewer data with the Georgia 02 antigen and antiserum.

DR. GREENBERG: Okay, I'd like to open this up. This is obviously the most difficult part of our decision. But I'm glad Nancy and Roland clarified

their point of view, because I do think that we are hearing at least from them that they are, in their very discreet ways, saying that they think it is time for a change. Do I have any comments from the committee or any further questions?

DR. ESTES: Harry, this is Mary Estes. I have a question. I had the impression from Roland that if we decide we would like to make a recommendation, there are some possibilities of strains, the Yamanashi, he said, and the Romania may actually grow better than the Harbin. But how soon will it be known if those are really viable alternatives? And how quick -- I mean, if we don't make a final decision today, is there still time to evaluate those and have them be able to be used by the manufacturers.

DR. LEVANDOWSKI: This is Roland. I'll try to answer that partly. I think Nancy might need to jump in on this one also. It's always difficult for the manufacturers to make a change. They have to start everything over anew, but they are looking at these strains already. These all have been -- many of these influenza B strains have been distributed to manufacturers, and they have had an opportunity to see at least what the growth characteristics are.

They don't really know how these things will go through the process altogether. They don't have as much information as they would have for, say, B Harbin. But, from their experience, it sounds like some of these strains do grow well enough that they would be acceptable, and for some reports it sounds like the Yamanashi strain might be as good or better than the Harbin strain.

We -- if you don't make a decision on the actual strain today, that I guess could be accommodated. We're not -- I don't know that we have all the information in hand to be firm about which of these strains would be the optimum one, to tell you the truth, and we have been anticipating getting some information from our European colleagues in that respect to know exactly what they are thinking about strains.

But what I have heard informally from Europe is that they too see that the Yamanashi and Romania strains look like they grow pretty reasonably well, and if there is not a problem with these things from antigenic or genetic characterization, then they would probably be useful.

DR. GREENBERG: Roland? So a recommendation could be for a B 184-like strain that

more closely approximated circulating isolets than the B Harbin. Would that be what -- that would be -- that would not specify the specific strain, but I think encompasses what you and Nancy are saying.

DR. LEVANDOWSKI: I guess that would be the sense of it, yes.

DR. GREENBERG: Okay, any comments? Any additional questions?

DR. FERRIERI: This is Pat Ferrieri, Harry. I think that what you have just stated could stand as a motion, essentially.

DR. GREENBERG: I was trying to sneak one in there.

DR. FERRIERI: And I second it as a motion.

DR. KOHL: I want to clarify the question to the FDA. Kohl. You did not require us to select a specific strain at this point, is that what you are saying? Is it the sense of the committee that it should be something better than Harbin?

DR. LEVANDOWSKI: Actually, yes. There is precedent for that in the past, where we have had multiple strains to consider, we would like to, as much as possible, optimize the antigenic characteristics and also the growth properties. We do

want to pick a strain that seems to be best for most of the manufacturers. We understand that there's nothing that's perfect for every manufacturer, but we would like to try to optimize that, and they do provide information. That is one of the comments that we would like to have from the manufacturers, in fact. So, yes.

DR. GREENBERG: Do I have any other comments or questions from the committee?

DR. DAUM: Yes. This is Daum from Chicago. I'd actually like to ask Dr. Couch to comment on his original view that we should not change in light of the discussion that has gone on since he spoke.

DR. COUCH: The ferret sera suggest a minor difference in the strains, whereas, as Nancy pointed out, there are -- frequently they are fourfold lower, which you don't like to see. The Harbin vaccine serologic responses, when you look at some of the strains -- I don't remember seeing Yamanashi, it wasn't one of the strains used, but Foshan and other strains were used, and the serologic responses using those different strains following vaccine were identical, almost, to the responses following Harbin, were not different in terms of their reactivity with

those strains.

So that, you know, there's some rumblings out there that B is changing, but I don't mean anything critical by the comment, but I think Roland's phrased it very well, that, gee, if we don't maybe do something now, it may be too difficult to do it next year, and let's sort of anticipate and get ahead a little bit of the game, but I don't think there's a strong argument at this end to doing that for another basis. But on the other hand, the practical aspects of this business are very appropriate.

DR. GREENBERG: Nancy?

MS. CHERRY: Which one?

DR. GREENBERG: Nancy Cox.

DR. COX: Yes?

DR. GREENBERG: You know, both you and Dr. Couch have a tremendous repository of knowledge about this, and I'm getting a slightly different feeling about it from the two of you.

DR. COUCH: Oh, no, I don't differ with the recommendation.

DR. GREENBERG: Okay.

DR. COUCH: No. I just meant that all of the ducks are not in place that strongly support that, but I thought Roland justified it in a very

appropriate way.

DR. GREENBERG: Bob, is that satisfactory to you?

DR. DAUM: Yes.

DR. GREENBERG: Are we ready to vote on the motion, then?

DR. ADIMORA: This is Ada Adimora. Could you please just restate it again?

DR. GREENBERG: I think the motion as I stated it is that our recommendation is for a B Beijing 184/93-like virus that better fits kind B isolets than the B Harbin strain does.

DR. ESTES: If an appropriate isolet that can be made into a vaccine becomes available.

DR. GREENBERG: Right. Thank you, Mary. Nancy Cherry, can you call a roll?

MS. CHERRY: Okay. Dr. Poland?

DR. POLAND: Absolutely agree.

MS. CHERRY: Dr. Adimora?

DR. ADIMORA: Agree.

MS. CHERRY: Mrs. Cole.

MS. COLE: I agree.

MS. CHERRY: Dr. Estes?

DR. ESTES: I agree.

MS. CHERRY: Dr. Huang?

DR. HUANG: Me, too.

MS. CHERRY: Dr. Edwards. Oh, she's gone. Dr. Daum?

DR. DAUM: Yes. Agreed.

MS. CHERRY: Dr. Couch?

DR. COUCH: Okay.

MS. CHERRY: Dr. Eickhoff?

DR. EICKHOFF: Yes.

MS. CHERRY: Dr. Kilbourne?

DR. KILBOURNE: Yes.

MS. CHERRY: Dr. Griffin?

DR. GRIFFIN: I agree.

MS. CHERRY: Dr. Faggett?

DR. FAGGETT: I agree.

MS. CHERRY: Dr. Breiman?

DR. BREIMAN: Yes.

MS. CHERRY: Dr. Kohl?

DR. KOHL: Yes.

MS. CHERRY: Dr. Ferrieri?

DR. FERRIERI: Yes.

MS. CHERRY: Dr. Greenberg?

DR. GREENBERG: For the record, I agree. Does this mean that we are close to the end?

MS. CHERRY: I think so. Roland?

DR. GREENBERG: I thank all of you for

making my first turn at this very, very easy. I guess our next meeting is going to be -- when is our next meeting, Nancy?

MS. CHERRY: Our next meeting is May 10 and 11, but I don't have information for you on that yet, but I expect it to be a meeting here in town, and until we meet and decide, I think you'd better plan on both days.

UNIDENTIFIED PARTICIPANT: Couldn't hear a thing.

DR. GREENBERG: The next meeting is May 10th and 11th, and you should expect a two day meeting.

UNIDENTIFIED PARTICIPANT: Thank you.

MS. CHERRY: Hang on, I just don't want you to close the meeting before we have open public hearing. I just want to remind you of that.

DR. GREENBERG: I'm just biting the bullet here.

DR. DAUM: Harry, Mr. Chairman?

DR. GREENBERG: Yes.

DR. DAUM: This is Bob Daum from Chicago. While everybody who -- there seems to be a lot of expertise on influenza on the telephone here, and I would like to make a call for there being more studies in place to monitor the efficacy of this vaccine in

years to come. I'm a little disappointed that there isn't more that we were able to hear today, and maybe it's too early in the season to have it, and lots of things are in place.

But someone made the comment that they have an anecdotal experience, there's lots of vaccinated people with pretty nasty disease this year. I have the same anecdotal observation, and I recognize that it doesn't mean 72 percent isn't right on the money. Boy, I'd sure like to know more about how this vaccine is performing in different populations.

DR. KOHL: This is Kohl. I would add to that. I think that it really is important that we try to get in place a mechanism for studies in children, which are a fairly large percentage of people who -- or a significant percentage of people who have serious influenza infections.

DR. FAGGETT: This is Walt Faggett. I just want to second that comment. It's really critical.

DR. GREENBERG: Are our colleagues at the FDA listening?

DR. LEVANDOWSKI: This is Roland. I'm listening.

DR. COX: -- at the CDC are also

listening. This has been a recurring theme at many of our meetings, and we are actually in the process of doing -- looking back at vaccine effectiveness, at least elderly populations, and we know the importance of also looking in younger populations. We have a study that we have been doing in a day care population for a number of years.

But it is difficult to find the funding to do these studies properly, but we do recognize the need, and are proceeding to get the information, even if it is a bit later than would be ideal.

DR. KOHL: I would like to propose that you hear that the committee says that they think that this is an important item, that funding should be aggressively sought for it.

MS. COLE: This is Rebecca Cole. I think in children really should be a priority.

DR. COX: We will take that up the line here, and work as hard as we have over the past few years -- continue to work as hard as we have over the past few years to get funding for such studies, but we certainly appreciate your support for this type of endeavor.

DR. LEVANDOWSKI: This is Roland Levandowski. I'd like to say something about that,

too. We also very much appreciate the comments along those lines that -- you probably don't know, but the FDA for about 20 years did fund clinical trials on a very regular basis every year to look at issues of efficacy and also to look at safety issues for influenza vaccines, and unfortunately the budgetary constraints at the FDA have prevented those from continuing. But obviously it's something that has been of great interest to FDA for a long, long time, and part of the reason for that is that, of course, the influenza vaccine changes every year, so it is always a moving target trying to keep up with it.

But while the military are here as our guests, I think it should be pointed out that they, too, in the past have had more substantial support for doing efficacy trials, and a lot -- in fact, much of the most important information we have on efficacy, including the original studies that were done to get the vaccines licensed in the first place were supported by the military. There have been somewhat of a general complacency about influenza because it has been thought to be so well controlled, and in defense of that, I would say that every study where someone has tried to show efficacy for influenza vaccine almost routinely shows that.

DR. GREENBERG: I would like to move it. I think these are all very good points, but I would like to, unless somebody has another -- I think we've made our point here. I would like to move on to the open public hearing.

MS. CHERRY: Let me ask, is there anyone in the room that would like to make a statement? I'm not aware of anyone here in the room. In that case I guess I can declare the open public hearing session closed.

DR. GREENBERG: In that case, I would again to thank all of you for taking your precious time and devoting it to this useful service --

DR. SALMON: This is Steve Salmon at Parkdale. Can I say something for a minute, please.

MS. CHERRY: Oh, yes.

DR. SALMON: Okay, yes, we appreciate the fact that the Sydney was chosen, and that does give us something to work on. It is important that a choice be made on the B well, well in advance of the May meeting that is scheduled. If you wait until the May meeting to make that kind of decision, you will limit the number of doses that will be available in the marketplace this year.

DR. GREENBERG: It was my impression, and

maybe I got this completely wrong, that the precise choice of the strain will come from work that the CDC and the FDA and the manufacturers do, and that's an operations choice, and really doesn't need to come back to the committee. Do I have that wrong?

DR. LEVANDOWSKI: That's correct.

UNIDENTIFIED PARTICIPANT: I think you have it right.

DR. GREENBERG: Okay. So it doesn't have to wait to the May committee. The May committee is not involved in that choice.

DR. SALMON: Okay, so a choice will be made in the next several weeks, then?

DR. LEVANDOWSKI: This is Roland again. It could be in the next several hours.

DR. SALMON: Okay, very good. Thank you.

DR. GREENBERG: Again, I'd like to thank everybody, and if nobody has anything else to say, we'll have this meeting adjourned.

(Whereupon, the foregoing matter concluded at 2:39 p.m.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: MEETING ON INFLUENZA VIRUS VACCINE FORMULATION FOR 1999-2000

Before: FDA/CBER VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

Date: MARCH 11, 1999

Place: BETHESDA, MARYLAND

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

John Mongoven