DR. COUCH: How about Japan?

DR. COX: They didn't make any mention of using reverse genetics. At the WHO meeting I did discuss our plans.

CHAIRPERSON OVERTURF: Any other comments, questions?

(No response.)

CHAIRPERSON OVERTURF: We are about a half an hour ahead. So I thought we would just go ahead and take the break now, reconvene at three o'clock, and we'll try to answer the questions for the vaccine selection.

(Whereupon, the foregoing matter went off the record at 2:33 p.m. and went back on the record at 3:01 p.m.)

CHAIRPERSON OVERTURF: Okay. I'd like to call the meeting to order again.

First of all, I'm going to have -- Roland is going to give us a breakdown of the options for strain selection. He's going to answer all questions at this point.

(Laughter.)

DR. LEVANDOWSKI: Okay. If you're expecting me to boil this down to one number, I don't think I can do that.

Something has happened to my slides here. Where are we? Sorry for that.

Okay. So just to summarize a little bit before I go into what the options might be here, for H1N1 Influenza A viruses, as we heard this morning, there are relatively few Influenza A H1N1 viruses that have been circulating around the world, and at this point in time, there is no firm evidence that there is any H1N2 viruses that are still circulating.

There have been isolates sporadically from a number of areas, including Africa, the Americas, Asia, Europe, Oceania, basically everyplace, and there has been a single outbreak that was reported in Tunisia.

The HAs of the H1 strains are antigenically all very similar to the current vaccine strain, which is A/New Caledonia/20/99, and the H1 viruses that are currently circulating are also generally well inhibited by antisera from people that

have been immunized with vaccines that contain A/New Caledonia/20/99.

The high growth reassortant of A/New Caledonia/20/99 is available. It grows well. It manufactures well, and it's a well know entity for the last several years. So for H1N1, of course, the first option is to retain the A/New Caledonia strain as the vaccine strain.

And in favor of that, as I just mentioned, most of the H1 viruses are the most recent H1 viruses, the most recently isolated H1 viruses are A/New Caledonia-like by their antigenic characterization. The current vaccines do appear to be well matched for the HA of the current strains, and manufacturing is very well worked out.

Against this might be only that there have been so relatively few strains to analyze at this point in time, and the influenza season isn't exactly over yet.

For the second option, the second option would be to use a more recent H1N1 virus for manufacturing, and this probe here is, I think, a

fairly weak one. There might be a closer match with a hemagglutinin and a neuraminidase of contemporary strains. I think that's more likely in a genetic than in an antigenic sense.

Against this option would be that a new strain, of course, we're never really sure that it's going to provide any superior immunogenicity or efficacy compared to current vaccine strain, and certainly nothing has been done to investigate what might need to be done to support manufacturing for any new virus that would be chosen.

A third option would be to defer the recommendation, and in favor of that, that there might be or I guess there could be some hope that there would be some other contemporary strains that might be identified that would look closer to what we might expect for next year.

But based on what's happened so far, I don't think we have any true expectation that there's going to be any new forthcoming information on H1N1 viruses so that that would not point to a good option.

For the H3N2 viruses, the H3N2 viruses

have predominated globally during this season, and that has actually been going on for quite a long time, the global predominance of the H3N2 viruses.

A new variant that's represented by the A/California/7/2004 strain has been identified already in many areas of the world, although it has only been recognized relatively recently. In January, I think, is when it really became obvious and clear from analysis of the strains that were being collected that there was this new variant that was developing.

The HA, most of the strains have been identified, not all, but most are antigenically distinguishable from either the A/Wyoming/3/2003 or the A/Wellington/1/2004 vaccine strains that have been currently in use.

And as you saw from the serologies, it's very clear that the overwhelming majority of new H3N2 strains are poorly inhibited by antisera from people who have been immunized with the current vaccines that do contain A/Wyoming/3/2003.

High growth reassortants, however, for the A/California/7/2004-like strains are not yet

available, but on the plus side, there are a large number of egg isolates that have been recovered, and they're being evaluated and work is ongoing in many laboratories to prepare high growth reassortants that could be suitable for manufacturing.

So for the H3N2, the first option, of course, is to retain A/Wyoming/3/2003. In favor of that would be the manufacturing has been very well worked out. Yields are predictable, and that could all be accomplished easily.

Not in favor of that, however, is that, as mentioned, the HAs or most of the H3N2 viruses and certainly the great majority of the viruses in the last several weeks are antigenically distinguishable from the current vaccine strain.

And in addition to that serologic results from the current vaccines indicate poor responses against the more recently circulating viruses, and we also know that H3N2 influenza viruses are often responsible for significant morbidity and mortality, and so this choice should be made very carefully.

The second option is to change to use a

more recent H3N2 virus, and here in favor of that, a more recent strain is likely to provide a closer match with the contemporary strains, and the ones that would be expected to be going forward.

The serologic results with the current vaccines do indicate, again, that most of the current strains are not well inhibited by current vaccine, and, again, the morbidity and mortality of H3N2 viruses is often quite significant.

Not in favor of this, however, is the fact that we don't at the moment have a high growth reassortant for an A/California-like virus in hand, and so yield potential for this, if that would be a choice is really there's no information to go on at all on this.

The third option is to defer the recommendation, and in favor of this, the choice does need to be made carefully because of the significance of the morbidity and the morality, and a more recent strain might be likely to provide a closer match for the HA and the NA.

But against this is that we already have

a great deal of information from a number of sources about their current H3N2 viruses, and we don't really expect that there's going to be anything that we acquire that's going to change, significantly change or enhance our understanding of that in the next few weeks.

And then moving on to Influenza B, as has been pointed out and as has been continuing for some time, the Influenza B viruses and the two known HA lineages are co-circulating. Strains that are like the vaccine HA have continued to circulate, and they seem to be predominant everywhere, including in the United States.

However, there are strains that are more like the non-vaccine HA lineage, and they're making up approximately 20 to 30 percent of Influenza B viruses in the United States. Influenza B viruses haven't been predominant most places, but where they have been found, the majority of the strains have been B/Shanghai-like, and as was mentioned, in Japan so far with their influenza season, those are the only Influenza B viruses that are being recovered. It

doesn't mean that that would be true in the future, but that's certainly true at the moment.

We didn't dwell on, but there does seem to be some antigenic drift in the non-vaccine HA lineage Influenza B viruses, and for the most part, the B/Shanghai-like viruses, B/Shanghai/361/2002 vaccine-like viruses seem to be pretty well inhibited by antisera from people who have gotten the current vaccine. It's not as clear cut for young children where responses may be less robust, and whereas we have information that suggests that although responses may be reduced against the non-vaccine lineage in adults and elderly, it's pretty clear cut that for very young children who haven't been immunologically primed and/or boosted with both of the different HA lineages that we can expect that immunization with one lineage is not going to produce antibodies that cross-react with the other lineage.

At this point no other vaccine strains have really been evaluated for potential for vaccine production, but there are some egg isolates that are available.

So having said all of that, the options here, again, would be the first option would be to retain the current vaccine strain, which is B/Shanghai/361/2002-like. In favor of that, manufacturing is very well defined. It's predictable now. The predominant strains continue to be in the same HA lineage, and they have been found in many parts of the world.

Against this would be that Influenza B viruses not in the HA lineage in the vaccine have been increasing in frequency a little bit in some places, and it's clear that they're not as well inhibited by either post infection or post immunization antisera, and in particular, in relation to the immunologically naive young children.

That brings me to the second option which would be to change to use a more recent B virus, and in favor of that we might get a better coverage for Influenza B viruses.

Against that, we don't really know that a new strain would provide superior immunogenicity and efficacy compared to the current strain. It's not

clear that non-vaccine strains will increase any further infrequency, and again, they're not found in all areas of the world.

And adding another Influenza B strain may causae difficulties in manufacturing. As you heard, the B viruses are often the rate limiting ones these days and particularly if a wild-type virus needs to be used.

So the third option, again, is to defer the recommendation. In favor of that, there may be some additional information that comes out about what strains might be closer matches with the hemagglutinins and neuraminidases of the contemporary strains.

But against that, there's not any way really to know whether a new strain of either HA lineage would prove to be superior either in immunogenicity or efficacy compared to the current one overall, and it seems at this point, although there are still strains being collected, it's not clear that there will be any additional significant information to help to inform the recommendation.

So this is the question for the committee, just to put that up there. I'll leave that up there during the discussions. Again, the question for the committee would be: what strains should be recommended for the antigenic composition of the 2005-2006 influenza virus vaccine? And I would ask that that recommendation be based on consideration of the epidemiology and antigenic characteristics, serologic responses, and availability of candidate strains.

And I'll stop there.

CHAIRPERSON OVERTURF: Roland, usually it's intuitive in your recommendations what you're recommending, but I didn't catch it for the H3N2 strain. Could you be a little more precise there?

DR. LEVANDOWSKI: I'm sorry. I'm not sure I understand the question.

(Laughter.)

CHAIRPERSON OVERTURF: Did you have a specific recommendation for the H3N2 direction? You gave the pros and cons of three different decision pathways.

DR. LEVANDOWSKI: Right.

CHAIRPERSON OVERTURF: Did you have a preference for one of those pathways?

DR. LEVANDOWSKI: Oh, you're asking my preference.

CHAIRPERSON OVERTURF: Yes.

DR. LEVANDOWSKI: Well, I think what is very clear is that the current H3N2 viruses are antigenically distinguishable from what's in the vaccine, and furthermore, the current vaccines do not seem to produce antibodies that cross react with those viruses very well.

There is the difficulty of being able to prepare vaccine, but as compared to some previous years, we're in much better condition because CDC has been able to get some egg isolates very quickly for a lot of these strains, and it puts us in the position of being able to respond.

And as you heard from the manufacturers, they have some ability to wait to get the third strain. If there's a change in a strain, they have some ability to accommodate that in their manufacturing, although obviously, it would be ideal

for them not to have any down time at all.

But there is the possibility of responding with a new antigen for the H3N2, and I would say that the data that's available to us points to that direction.

CHAIRPERSON OVERTURF: Yeah, I think I just want to clarify for the committee. I think the options actually include recommending a lineage reference for the H3N2 strain but could still defer, if we wanted, the final selection until we have more information about that.

DR. LEVANDOWSKI: Okay. So I really didn't understand the question. Yes, if you make a recommendation for a like strain, if it would be a California-like strain, for example, we would expect that it would be possible for us to meet that recommendation with whatever strains that we find that seemed to be appropriate.

And as the manufacturers indicated, we've done this in the past where the recommendation could be met by more than one strain if that's necessary.

CHAIRPERSON OVERTURF: Are there

additional questions or comments from the floor? Dr. Schwartz.

DR. SCHWARTZ: The California-like seems to be the strain that's emerging, but if it were to stop emerging and the strains that we saw circulating were more like the Wyoming or the Wellington strains that had been used in the past, I think that the data that Nancy presented suggested that at least based on the ferret studies that the California-like strain would probably provide good coverage.

Can you go into anymore detail on that? Does that seem like a reasonable assumption based on the data? And are there any other data that you could share with us that might provide an indication that a California-like strain would still be effective against some of those Fujian-like?

DR. LEVANDOWSKI: I think that's actually a question more for Nancy than it is for me. I don't have the tables of data in front of me to look at, nor do I have an immediate response to that.

MS. COX: I think there are a couple of points I'd like to make. One is that that serologic

data that we have from ferrets would indicate that California antiserum does cover a variety of viruses really quite well.

But the second point I'd like to make is that we really haven't in the past seen a situation where you have a new group of evolutionarily successful viruses which the California viruses really do appear to be now sort of falling off the radar screen and then going backwards to a previous strain. It might be that something even more successful and advanced comes along that we haven't seen yet, but we wouldn't expect to go backward.

But if we did, we would expect reasonable coverage, yes.

CHAIRPERSON OVERTURF: Any further discussion, questions?

(No response.)

CHAIRPERSON OVERTURF: What I would entertain then, I suppose, is a motion from somebody on the committee regarding perhaps the H1N1 strain, and then we can proceed with further discussions about the next discussions.

Dr. LaRussa?

DR. LaRUSSA: I make a motion that we retain the current H1N1 strain.

CHAIRPERSON OVERTURF: Okay.

DR. MONTO: Second.

CHAIRPERSON OVERTURF: We'll start with Dr. Wharton, and please vote yes or no.

DR. WHARTON: Yes.

CHAIRPERSON OVERTURF: Now, the motion actually, just to restate that, was that the current H1N1 strain would be retained.

Dr. Monto.

DR. MONTO: Yes.

DR. MARKOVITZ: Yes.

DR. ROYAL: Yes.

DR. FARLEY: Yes.

DR. McINNES: Yes.

DR. PROVINCE: Yes.

COL. PHILLIPS: Yes.

DR. COUCH: Yes.

CHAIRPERSON OVERTURF: I also vote yes.

DR. LaRUSSA: Yes.

DR. SCHWARTZ: Yes.

DR. WORD: Yes.

DR. DOWDLE: Yes.

DR. EICKHOFF: Yes.

DR. SELF: Yes.

DR. KARRON: Yes.

CHAIRPERSON OVERTURF: That was unanimous to retain the current H1N1 strain.

So I think we should proceed next to a discussion about what the committee's wishes would be for the H3N2 strain or the B strain for this year. Is there any discussion or suggestions?

DR. COUCH: I'd just like to make a comment that I think is important for us to keep in mind with our actions, and that is that we already have recommendations that are very specific from the World Health Organization. You see, we used to do this, and then they met after us. Now they meet, and we meet after them.

And harmonizing is a strong criteria for selection. If we don't agree with that, I would say that we're in the of having to need very strong

evidence. We've got manufacturers who are already underway, and that is what they're doing, and their primary manufacturing sites are in Europe, not in this country.

If we want more vaccine in this country, harmonization, I think, has to be a part of our consideration.

Now, having said that, I would say that, you know, all of the data points to needing to change the H3N2, and they have selected A/California, and we've heard data all about A/California. So we vote for A/California, for H3N2.

DR. MONTO: Second.

(Laughter.)

CHAIRPERSON OVERTURF: I would agree. I think the clarification that was necessary was to know that all we're really doing is voting for a lineage. We're not really the ones. Obviously the virologists have to decide how to do that, and I think that's all we really are voting for at this point.

Yes, Dr. Eickhoff.

DR. EICKHOFF: A question for the maker of

the motion. Is your motion to be construed as including A/California or an A/California-like virus?

DR. COUCH: A/California is never a specific recommendation. Any time you say that it will always be an A/California-like virus. I think that's implied. Oh, sorry.

It's always an A/California-like virus, never a single specific virus.

CHAIRPERSON OVERTURF: So there's been a motion for a change in the H3N2 virus to an A/California-like virus. I guess at this point we can start on the other end of the room and ask Dr. Karron to vote.

DR. KARRON: Yes.

CHAIRPERSON OVERTURF: You can make any comments you wanted to when you vote.

DR. SELF: Yes.

DR. EICKHOFF: Yes.

DR. DOWDLE: Yes.

DR. WORD: Yes.

DR. SCHWARTZ: Yes.

DR. LaRUSSA: Yes.

DR. COUCH: Yes.

CHAIRPERSON OVERTURF: That's right. Yes.

COL. PHILLIPS: Yes.

DR. PROVINCE: Yes.

DR. McINNES: Yes.

DR. FARLEY: Yes, and my only comment, and it's really a question that we can discuss after we finish, but the idea of coordinating this with WHO's decision making process and the timing of such meetings comes to mind here. I mean, we don't want to just be rubber stamping another organization, but if we're all doing the same thing, is there some benefit of working together in some way more directly?

So my vote is yes.

DR. ROYAL: My vote is yes.

DR. MARKOVITZ: Yes.

DR. MONTO: Yes.

DR. WHARTON: Yes, and a comment. My compliments especially to I guess my colleagues at CDC for having had the foresight to assure the availability of a number of egg isolates so that we're in a good position this year to move forward to

development of a high yield reassortant.

CHAIRPERSON OVERTURF: Yes, Dr. Markovitz?

DR. MARKOVITZ: Yes. I'd also like to make the same or to second that thought, that really I was very impressed with the preparation this year, and I think that's very nice.

CHAIRPERSON OVERTURF: Well, sometimes I think we are endowed with good luck in terms of having isolates, and I think this year that seemed to be the problem, and I think actually deferring most of the recommendations at this point would probably have little influence.

And having been through this process now this is the fourth year for me, that rarely results in any major change. Two to three weeks more data just doesn't usually provide us with enough information. It has on occasion.

So the next issue the B viral strain for this year, and the suggestions and options for the B viral strains included retaining the B/Shanghai/361/2002-like viruses or to consider using a more recent B virus or to, again, defer that

recommendation to another point in time.

So I open it up to the committee's discussion as to whether or not they would like to see more data or whether they think we should vote on the B strain now.

CHAIRPERSON OVERTURF: Dr. LaRussa.

DR. LARUSSA: Well, it seems to me that since most of the strains are still Shanghai and we're not going to get a whole lot more information and we're not in any position right now to recommend putting two B strains into the vaccine, but I think at least for now it would be wise to recommend retaining the strain, but moving towards the future to potentially providing a pediatric vaccine with the two Bs where it's most needed.

So my recommendation would be to retain.

CHAIRPERSON OVERTURF: Any other discussion? Yes, Dr. Farley.

DR. FARLEY: Well, I guess I'm wondering what would put us in the position of making such a recommendation. I mean, what do we need to come together for that recommendation to make more sense?

DR. LaRUSSA: You mean of having two strains? Well, I think the studies need to be done that you can actually get a good immune response in young children to two strains and that you could actually provide enough viral antigen to actually make that response.

Once that data is available, then it becomes a logistics problem of whether it's physically possible, but at least you'll know that if it works immunologically that you're going to have a constant need for it every year, and you'd feel much more comfortable about doing it, and then you could go ahead and do whatever you want for the adults.

CHAIRPERSON OVERTURF: Actually, this particular issue has been discussed almost every year that I've been on this committee, and I think there has been always a great desire on the committee's part to expand the B strains.

What is unique now is that we have a pediatric option, which we did not, and that may be a unique way to enter the problem and begin to accumulate the data.

Yes, Dr. Dowdle.

DR. DOWDLE: I think this issue about two circulating B strains or at least some concern about there being two types that are essentially two groups that seem to be around at different times and changing and prominent and so on is not new. This has been going on for a long time, and it seems that looking back, it seems that we've been more in this quandary than we have not had this quandary. I mean it has been more of a usual thing.

It would be very useful if I think next meeting that we could have a little paper on Influenza B and some of the issues over the years about how this, number one, has been dealt with, what are the issues in the past, and what are the advantages and disadvantages of going with two strains?

I mean, it would be nice to have some data for a change, and I think we've been faced with a lot of opinions and a lot of memories, but my memory could be completely wrong. It's just certainly what I remember in the past, and we've had this discussion, many, many times.

CHAIRPERSON OVERTURF: Dr. Farley.

DR. FARLEY: I fully agree, but I wonder what will motivate. Who will do? Who would produce the data and who's motivated to produce that data? Is that the manufacturer of the pediatric vaccine or is that FDA? You know, I guess I'm wondering about the process so that we won't be in the same place each year without some new data.

CHAIRPERSON OVERTURF: Yes, Dr. Eickhoff.

DR. EICKHOFF: I think the process or the discussion here has gone maybe a step beyond in what Walter commented on, namely, it's now at a level where are we going to talk about a whole separate pediatric product.

That raises a host of issues, and we would need manufacturer input on it, but a pediatric use of influenza vaccine we kind of anticipate is going to grow almost logarithmicly for the next several years. It's an issue that needs to be considered very carefully, but maybe not in this immediate framework of strain selection.

But, again, I think manufacturers will

have lots to say about that.

CHAIRPERSON OVERTURF: The assumption I had from Dr. LaRussa was that he actually is talking about expansion of the or exploring the use of two B strains in young children, the current population in whom routine annual immunization is now recommended, the six to 23 month old children; is that correct?

For this year. We still have the difficulty of deciding which of the three options the committee would like to proceed with in terms of the option. My personal feeling is that I don't see it. From the data that Dr. Cox presented this morning, it's clear that the B/Shanghai lineage was about 80 percent of the isolates in the United States so that there seems very little reason right now to change that, although there are these disturbing data -- there always are -- of isolated settings where there is perhaps a 50-50 breakdown in certain settings.

PARTICIPANT: Dr. LaRussa made the recommendation to keep (speaking from an unmicked location).

CHAIRPERSON OVERTURF: Did you make that

recommendation?

DR. LaRUSSA: Yes.

CHAIRPERSON OVERTURF: Do you want to make it as a motion?

DR. LaRUSSA: I'll turn it into a motion.

CHAIRPERSON OVERTURF: Okay, fine.

DR. LaRUSSA: I make a motion that we keep Shanghai this year.

CHAIRPERSON OVERTURF: Would somebody like to second that motion?

DR. WHARTON: (Show of hand.)

CHAIRPERSON OVERTURF: Dr. Wharton. Okay.

Well, we will start with you for the first vote. So the motion on the floor is to retain the B/Shanghai isolate for the current vaccine.

DR. WHARTON: Yes.

DR. MONTO: Yes.

DR. MARKOVITZ: Yes.

DR. ROYAL: Yes.

DR. FARLEY: Yes.

DR. McINNES: Yes.

DR. PROVINCE: Yes.

COL. PHILLIPS: Yes.

DR. COUCH: Yes.

CHAIRPERSON OVERTURF: Yes.

DR. LaRUSSA: Yes.

DR. SCHWARTZ: Yes.

DR. WORD: Yes.

DR. DOWDLE: (Speaking from an unmicked location) Yes.

DR. EICKHOFF: Yes.

DR. DOWDLE: Yes.

DR. SELF: Yes.

DR. KARRON: Yes.

CHAIRPERSON OVERTURF: This may have been done in record time this time.

(Laughter.)

CHAIRPERSON OVERTURF: Is there any further discussion or clarification? Does anybody want to speak? Dr. Eickhoff.

DR. EICKHOFF: Now that we have voted and we're not slavishly following WHO recommendation, the WHO recommendation for the Southern Hemisphere was just a little bit different than that for the Northern

Hemisphere and the B component, and a question for Roland or Nancy, I guess: do you have any insight into why this recommendation changed slightly?

DR. LEVANDOWSKI: Actually, maybe I misled people. The serologies were done with an older Southern Hemisphere vaccine. The current vaccine is recommended by WHO for Southern Hemisphere includes a B/Shanghai/361/2002-like vaccine virus. The previous vaccine that was used in the Southern Hemisphere had B/Brisbane/32/2002, and that's the serum that was available for doing serologies because the new vaccine for the Southern Hemisphere, according to the current recommendations is only just now being produced and used. So it was not available at the time the sera were collected for the studies.

So maybe I confused people with that, but the recommendation, the current recommendation for the Southern Hemisphere is B/Shanghai/361/2002-like.

CHAIRPERSON OVERTURF: Dr. Schwartz.

DR. SCHWARTZ: I'd just like to briefly raise three issues. Just to get a sense, and this is the first time I've been at this committee meeting.

So I don't know how the committee deals with these types of recommendations, but I think Monica mentioned the possibility of changing the timing of this meeting to perhaps more closely coincide with the WHO meeting or at least to have maybe better communications between the two groups.

I was wondering if that's a recommendation that the committee could make and how the committee would handle that particular idea.

It has also been discussed that we believe that a pediatric vaccine containing the two different B lineages should be studied, and I don't know if there is additional force if there's a vote and if that becomes an official recommendation of the committee.

Also I don't know if the manufacturers have candidate vaccines that include the B/Victoria lineage and whether there is material right now that could be used or whether new pilot lots would have to be produced and, therefore, there would be substantially increased time and costs involved with doing that.

The third issue that I just wanted to very briefly mention has to do with H5N1, and Pam earlier talked about some clinical studies that NIH is doing of investigation of lots of H5N1 vaccine, and I think it would be useful for this committee in some future meeting to discuss under what circumstances it might be considered to have H5N1 as a component of the influenza vaccine which would provide priming to those folks who were vaccinated in case H5N1 or H5 emerged as a pandemic strain.

That's certainly not something to talk about now, but I think it would be an interesting discussion to have in the future.

CHAIRPERSON OVERTURF: To me the pride -- and somebody from the FDA can correct me -- I would think that if there's a process that we really want to devote an entire meeting or a day to expansion of the B types, which would include presentation of data, and then an official recommendation and a vote, I think it would require me to -- I don't think we can do that here. I think this has come up over and over and over and over again, and perhaps it's something that the

FDA needs to take into hand and perhaps plan a meeting for the VRBPAC specifically to address that single issue some time with some inclusion of data.

I think that's the process that has usually been used; is that correct?

Yes, Dr. Dowdle.

DR. DOWDLE: I'm going to change the subject. Go ahead, Nancy, please. I'm going to change the subject.

DR. COX: Yes. Well, I was going to change the subject as well.

(Laughter.)

DR. COX: And for those of you who haven't been involved in the vaccine strain selection process as long as I have, it may seem to you as if this meeting could be a rubber stamp and that may feel uncomfortable to you.

We used to have the U.S. meeting first. This caused a great deal of discomfort on the part of the rest of the world which felt that the U.S. was preempting the vaccine. It also put the U.S. at a disadvantage because our meeting was first. We didn't

have access to the global data.

We had our WHO vaccine meeting in Geneva. It finished on Friday at about noontime on Friday, the 11th. We're here only a few days later really if you take the weekend into account. We were able to bring back all of those data, the global data, and compile them. And so some of the charts that I showed you really had incorporated the data from the other four WHO collaborating labs as well as data from some other national influenza centers.

And, of course, Roland was able to include the serologic data from the other four WHO collaborating centers in his presentation. So from the perspective of completeness, I think it is an advantage for the committee to actually see all of the data that's available globally, and so I think I just wanted to clarify that and make sure that you understand that there is extremely close coordination between CDC and FDA and WHO and the NIH and WHO as well, even if you don't see that specifically as a committee member.

DR. FARLEY: That's very helpful. Thank

you.

CHAIRPERSON OVERTURF: Dr. Markovitz.

DR. MARKOVITZ: If I could just add to what Nancy said, from what I've seen -- I think this is my fourth year on the committee -- is that having the meeting earlier would not be good because we seem to get like a lot of our best data within the last few weeks right before the meeting actually takes place. So I'm less concerned about appearance of rubber stamp and more concerned that we have everything together to make the best decision.

CHAIRPERSON OVERTURF: I think the only thing I would add is that at the time the presentation is made about what the options are, I really think we should -- it was in the very first presentation that I think Dr. Levandowski made this morning, what the recommendations for the Northern and the Southern Hemispheres were, but it probably needs to reappear at the time just prior to the vote again because I think Dr. Couch --

DR. COUCH: I think Nancy and Roland could confirm it. The technical comment, as I understand

it, the WHO is a global recommendation, and then it is up to each individual country and organization who deals with these decisions to then consider and make their own independent decisions.

But that doesn't negate the comment I made earlier. It's important for us to harmonize unless there's a strong reason not to.

CHAIRPERSON OVERTURF: Norman.

DR. BAYLOR: I just wanted to comment on the comment made about in a sense the vaccine development, like the H5N1, incorporating that into the current vaccine and whether this body would be the one to discuss that and make recommendations.

I think that process starts with the manufacturers and sponsors of INDs, and we have that discussion with FDA, and there's a process to have those type of meetings. And as those discussions expand and we start moving into clinical studies, that may be something that we would bring back to the VRBPAC, but the process will start with a discussion between the manufacturers, sponsors, and the FDA.

CHAIRPERSON OVERTURF: Any other

discussion, questions? Dr. Markovitz.

DR. DOWDLE: If I understand your question, Ben, it really is how would an avian flu vaccine interdigitate with this one, right? So that's, I think, your question. What would be the answer to that? I'm curious, too.

No takers.

CHAIRPERSON OVERTURF: Dr. Levandowski.

DR. LEVANDOWSKI: Well, I think there are many precedents for going all different directions with influenza vaccines. Historically people have been telling me all day how we've had five and six antigens in the vaccine in very early days. In early times it would be something like PR/8 plus another H1 and B/Lee plus another B, and some of those uses, I guess we wouldn't go back to doing it exactly that way.

But we've had monovalent vaccines. We've had monovalent supplemental vaccines. Most recently the one that comes to mind was in 1986, the A/Taiwan/186 supplemental vaccine. It's possible to have a monovalent vaccine. I mean we're used to

thinking about trivalent vaccine, and that's a convenient way to administer the product, but in reality that's just one way to do it, and monovalent is always available for us.

And this may be a consideration not only for an H5N1 vaccine, if it comes to that, but it could be a consideration for priming and boosting young children as well. If we need an additional component for a specific population that might be an alternative way to go.

But, again, thinking about how we get the different valencies of vaccines, before H1N1 reappeared it was an AB. It was a bivalent vaccine and nota trivalent vaccine.

So there are ways to get there, and I don't think there's anything that's so set in stone that it couldn't be evaluated and worked out

CHAIRPERSON OVERTURF: Dr. LaRussa.

DR. LaRUSSA: Just two quick comments. Can we work on some way to get some updates on what's going on with the California light strains once you see how the reassortments work out?

And then the second thing is I'm not sure how we left things with the discussion about the pediatric vaccine. Is that something you're going to go get back to us about, whether we could discuss that at a future time?

DR. MIDTHUN: Karen Midthun, FDA.

I think with regard to trying to explore bivalent B vaccines in a pediatric population that's certainly an excellent suggestion. I think what's needed though, and I think Dr. Baylor was alluding to this in the context of H5N1 is that you need to have a sponsor working in conjunction with a manufacturer who is willing to undertake such studied, and certainly we as FDA are there to work with them as they put these particular products into clinical trials to evaluate them.

So I think the question really is, you know, there has to be identification of an entity who is willing to make such a product, and then there has to be a sponsor who's willing to take that product into an IND. And obviously we're there to work with whoever would want to do this and think that would be

very good information to be able to have for everyone's consideration.

But you know, we, FDA, don't have the ability to make let's say a candidate vaccine and then conduct a clinical trial. We're there to provide oversight as this goes forward, and I think that's certainly hearing the discussions that have been made here. You know, we can get together with the rest of the other agencies and Health and Human Services and discuss, you know, are there some ways that one could facilitate moving into that direction.

CHAIRPERSON OVERTURF: I think it's a problem a little bit of agency overlap. I think there's issues that a lot of who makes recommendations about research and what needs to go forward. Obviously the NIH is involved. NVAC and other advisory committees really have to make a decision about whether this is a viable alternative.

I don't know whether this committee can do anything more than get it on the table, and I think that's what we've done, but I still think that it could be carried as a topic, even as a portion of a

meeting some time in the future so that we give it a little more airing.

Dr. Dowdle, did you have a question?

DR. DOWDLE: No, no, no, no, no. The point I was going to make was exactly the same point Nancy made about a plea not to change this meeting in relation to the WHO meeting, and just to point out that as Bob said, if there's a good reason to change, we certainly could change. And I would add that it wouldn't be the first time that we went against U.N. advice.

CHAIRPERSON OVERTURF: My experience has been the same. This is my fourth year on this committee, is that the data that are available from all sources seem to come together for this meeting, and usually it's very close to the WHO meeting. It would seem unlikely that it would be helpful to move it back much further. We would have even less data to try to develop our own policies and recommendations.

DR. COUCH: I have one more comment. I need to point out to this audience my name is not Ed Kilbourne, but we continue not to give the kind of

emphasis that many of us think we should to the neuraminidase.

You see, we've gotten it from when Roland talked about selections, he didn't just say the hemagglutinin. He said the hemagglutinin and the neuraminidase, and when Dr. Cox presented her virus isolates, she gave us the evolutionary development of the neuraminidase.

It's an important antibody most of us think. I'm a strong believer. We really want the hemagglutinin as the primary antigen, but the neuraminidase is an important second antibody. I think that was one of Walter's terms one time, and we've never really come to grips with what kind of standards or that we could adopt to include the neuraminidase.

It does contribute and it is desirable, and we do know from some of the tests that have been done on vaccine marketed preparations that the quantity of neuraminidase activity varies all over the map, and presumably some of them lack immunogenicity for the neuraminidase at all, and others are probably

pretty good.

This is not to anything other than make that as a point of record, that I think this committee needs to continue to think and to try and make attempts to how to address the neuraminidase in some sort of standards, and that's not easy in itself, for those of you who are worried about what would you say is your standard for the neuraminidase in each vaccine. I have my own ideas. That's a different discussion.

But I don't think we should lose sight of that antigen as an important one that we all recognize is a part of the vaccine immune response that we'd like to have and somehow get it in with not hopefully in the too distant future some criteria for its presence and appropriateness of immunogenicity.

CHAIRPERSON OVERTURF: Dr. Schwartz.

DR. SCHWARTZ: Let me just ask you a question about that. So we're talking about a number of potential California-like strains that we're developing reassortants for, and so let's say that there are reassortants for five different California-

like strains that go to the manufacturers.

Some of them may produce more neuraminidase than others and some of them may grow better in eggs than others. Are you suggesting that their neuraminidase production be a criterion for which is the best California-like strain that could be selected?

DR. COUCH: No. I think it's a manufacturing product decision, not an antigenic seed. I think that what CDC would contribute to that and the FDA would be that if there are neuraminidase differences among the A/California-like strains, then they would select one that is more characteristic and more changed perhaps than A/Wellington or an A/Fujian, just for that hope that that gets the appropriate neuraminidase.

So far I don't think there have been any examples in which that's been necessary, but that would be the seed control on that. No, we're talking about manufacturing control on the presence and immunogenicity.

CHAIRPERSON OVERTURF: Any further

comments?

Are there any further comments from the floor or the manufacturers?

(No response.)

CHAIRPERSON OVERTURF: Christine Walsh has an announcement.

MS. WALSH: I'd just like to ask all of the committee members to please take your red folders with you tonight. They do contain confidential FDA material that's in them, and we cannot leave them in the room overnight.

Thank you.

CHAIRPERSON OVERTURF: The meeting is adjourned.

(Whereupon, at 3:51 p.m., the meeting in the above-entitled matter was adjourned, to reconvene at 8:30 a.m., Thursday, February 17, 2005.)

CERTIFICATE

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

Before: DHHS/FDA/CBER

Date: February 16, 2005

Place: Bethesda, Maryland

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