the strains that are there.

MS. CANAS: Right, and that's one of the things we would like to try and find out. We do track whether they're active duty, but we cannot tell whether they're retired or active duty. So it's hard to tell when they were vaccinated.

DR. GOLDBERG: So you really don't know --

MS. CANAS: It's a work in progress. That's something that we want to know as much as anyone. It is a population where we should be able to study that.

DR. GOLDBERG: That's the confusion in the presentation because you would expect it to be low if they truly were vaccinated.

MS. CANAS: This is very heavy. I try and watch it each day on the children and the dependents so we don't know any of their vaccination status.

DR. GOLDBERG: Are they required to be vaccinated, the children?

MS. CANAS: No.

DR. GOLDBERG: So it's just the recruits themselves. Okay, thanks.

DR. DAUM: I must add that those data would be incredibly valuable.

MS. CANAS: Yes.

DR. DAUM: Dr. Diaz.

DR. DIAZ: Actually, just in follow-up to the same kinds of discussion, I was -- when you were describing surveillance system I was wondering if the surveillance system is integrated into the DMSS, the Defense Medical Surveillance System because all that data should be in those interrelationship data bases.

MS. CANAS: Right, making sure it's up to date. There are efforts to match that and to try and --

DR. DIAZ: So this doesn't automatically dump into that system then?

MS. CANAS: No.

DR. DIAZ: What are your triggers for doing, trying to do isolate recovery from cases? Is it voluntary or is there a certain threshold from the Sentinel Sites that you look for before you start swabbing?

MS. CANAS: Basically, it's October 1st when they're asked to start sending samples. And this is part of the military culture, especially in the Air Force. It's been part of what's been done for a long time. When we first hit the problems with the vaccine a couple years ago there was considerable interest on what it was going to mean. There's a history in the

military of what happens when influenza hits. So probably more than in any other single population, this is very important, so it is something that's mandated, that it be followed and there's an interest on every level. I get calls from people who say I'm not a Sentinel Site, but I want to be part of this. Okay. But these are the ones -- we try and get a representative geographical population and it is for the health of our people too. So if they're going to be deployed, we want to know what's going on with them, if it's flu or if it's something that can be treated, if we can get amantadine in there or not. This is of interest to the DOD.

DR. DAUM: Dr. Manley?

DR. MANLEY: Yes, would you clarify again what you said about the vaccination status of the recruits on the information that you get? And if they are vaccinated, is there a particular time in the annual cycle at which the Air Force would be vaccinating?

MS. CANAS: It's my understanding they're vaccinated soon after they arrive at the recruit centers. I believe that's all year round, but I'm not sure in the summer about that. Someone might be able to clarify that.

DR. DINIEGA: This is Ben Diniega from Health Affairs. We do have a policy for year round vaccination of recruits on entry to the installation.

DR. DAUM: Now sir, do you wish to ask a question of the speaker? Tell us who you are.

DR. FREAS: For the transcriber, sir, will you come to this microphone here?

DR. DAUM: Could you begin by telling us who you are and --

MR. BRADSHAW: Yes. My name is Dana Bradshaw. I'm currently with DOD Global Emerging Infections Surveillance and Response System here located at Walter Reed Army Institute of Research. I was formerly Chief of Preventive Medicine in the Air Force, Surgeon General's Office, so was involved with a lot of this stuff. I was just going to try and help clarify some of the questions that were asked.

We do kind of a hybrid kind of surveillance in terms of influenza surveillance and respiratory disease surveillance. There's a program at the Naval Health Research Center which she mentioned which is population-based surveillance where they have a denominator, clear denominator at all the recruit centers. They have them with the Army, the Navy and the Air Force and they collect respiratory

disease surveillance information on those recruit populations, so they specifically look at recruit populations. They have a web site. If you're interested in this, the questions, for instance, earlier about adenovirus 4 and 7, they have that information on their website.

The Sentinel Sites that we use for influenza surveillance, we pick the sites looking, trying to look at portals of entry, places where historically we've seen influenza start and spread, etcetera. And so those are the sites that you saw. Most of these bases do have dependents with them. The policy in the military and the Air Force is to vaccinate all of our active duty, but we have -- we follow ACIP recommendations on dependents. So as you can imagine, we have variable uptake in our populations just as the rest of the U.S. and the world does in terms of uptake of influenza vaccination. But the Air Force has a policy and we do do immunization tracking. We've done this for our population's active duty since 1998 and since 2000 for all of our dependents. So we can get influenza vaccination information and Linda was mentioning that we are looking at doing some efficacy studies, trying to look at vaccines, diagnosis of influenza and

correlate with some of our laboratory data, so hopefully maybe that helps clarify.

DR. DAUM: It does. Thank you very kindly for those comments.

Are there other questions for Ms. Canas? Thank you very much for an insightful presentation.

We'll move on to Dr. Levandowski and he will put before us a plethora of vaccine responses.

DR. LEVANDOWSKI: Well, I sometimes feel plethoric.

Okay, my task is to give some information about the vaccine studies that have been done in anticipation of this meeting. And I have to tell you that looking at the tables, my eyes start to cross. I'm sure yours do too. So what I'm going to try to do here is to summarize all of that data into some form that is more readily digestible. I don't know whether I'll succeed, but I'm going to try.

What I'd like to say is background information is the data that we're presenting and actually you have tables from both the Center for Biologics and from CDC in the handouts that you received. I'm not going to follow those directly, but the information I'm going to present comes from that. There is an on-going international collaborative

effort to look at immune responses or the antibody responses for current vaccines and that's largely possible because of the commitment that there is from the World Health Organization and its influenza centers and this overhead that's up here now shows the different serum panels that were provided for doing the testing that we're looking at today. These have come from adults and elderly from Australia, Europe, Japan and the United States. The vaccines that have been used for immunizing the people in these studies are shown and I really would just call your attention to just a couple of items here. The Influenza B strains that have been used, as has been mentioned, there have been several different ones. Really, there are three different strains that are currently in use around the world and they're considered to be equivalent and B/Sichuan/37/99-like. The three strains that have been used are B/Johannesburg/5/99 which are -- Australia and Japan and I'm not really clear. They might also be using B/Guangdong/120/2000 in Australia now.

And the B/Guangdong/120/2000 strain has been used predominantly in Europe and for the studies that was the vaccine strain, but they have also been using B/Johannesburg/5/99 as their vaccine strain.

And the strain that's been used predominantly in the United States is B/Victoria/504/2000, but we also have B/Guangdong/120/2000 containing vaccines in the United States. So these are the components that were in the vaccines that were used in the clinical trials I'll be talking about, but just to make -- I'm trying to make it clear that there's a mix of vaccines being used around the world for, at least for Influenza B.

So the laboratories that are participating here include WHO Influenza Center in Melbourne, Australia, the National Institute for Biological Standardization and Control in London, CDC in Atlanta. More recently, the National Institute for Infectious Diseases in Tokyo is involved in these studies and we at the Center for Biologics have been involved also. And the five labs are sharing the sets of sera that shown and this represents about 200 individuals who have been immunized for the studies and I should say that there still is testing that's going on. You have been used to seeing, I think, in previous years information from Europe and from Australia, but we have not had access to that yet. So what I'm showing is current to Monday of this week and on the next overhead these are the H1N1 antigens that have been used for serological testing for the studies that

you'll be looking at. Not every one of these antigens was used in all the laboratories, so that a wide variety of new antigens could be examined, but there's a core of antigens that can be tested in each of the laboratories and that gives us an opportunity to compare what the results are between labs and we do know that there are technical differences between the laboratories and you'll see that reflected in some differences in the level, the absolute titers for specific serum panels and for the same strain.

These studies were performed, that I'm going to show were performed actually in two different go's. Some were done as part of the preparation for the Southern Hemisphere, WHO Southern Hemisphere recommendations in September last year and some of these were done during the last few weeks. The antigens that are shown here for H1N1 are representative of the different strains that are circulating and all of these are in the A/New Caledonia/2099 group. None of these represent the BAYERN or Johannesburg strain that Sasha and Nancy were talking about.

On the next overhead these are some typical results. If you push that up towards the top, there's an opportunity for people to see it -- it will

be a little bit hard from the back. But these are sera from adults in the United States and this table and the others like it that I'm going to show will include data that has the geometric mean titer, the percent that are greater than 32 or 40 and the percent of 4 fold rises.

What I've attempted to do is to underline what represents the vaccine strain and also I think the organization for all of these is that results from the CDC will be at the top and from the Center for Biologics at the bottom.

So the vaccine strain here was the IVR-116 reassortant virus for A/New Caledonia/2099 and it was also used as the test antigen in these serologic results. Generally what I can say is that the vaccine used was immunogenic and it produced good, homologous antibody responses. Although the New Caledonia-like strains were mostly well inhibited by the antisera in response to this vaccine antigen, there were some strains that were less well inhibited and in testing done at the CDC, for example, you can see that the geometric mean post-immunization titer for the Auckland/65/2001 strain was 50 percent of what the result was for the vaccine strain. And I believe that Auckland/65/2001 is one of those strains that was

pointed out as being one of the low reactors.

Similarly, in testing that was done at the Center for Biologics, the results for the -- I guess it's the Hawaii/15 strain here was more than 50 percent reduced compared to the vaccine strain.

Next overhead, this overhead shows the results that were obtained from sera that were from elderly in Australia. And again, the vaccine that was used seemed to elicit pretty reasonable responses to the vaccine antigen and in general, the inhibition of the other H1N1 viruses was very similar to the vaccine strain. In testing that was done at CDC, I think you can see there's some minor reductions here to the Bangkok/255/2001 strain and the Hawaii/15/2001 strain, but not to the extent of being 50 percent or a 2 fold difference. And in testing done at the Center for Biologics, there was also again a minor sort of reduction for the Hawaii/15/2001 strain.

Other serum panels that were tested gave somewhat similar results and I'll try to cover that in a summary form in some later tables. So now moving on on the next overhead what I'll be showing you are some results for the H3N2 viruses or I guess I'll be showing you the H3N2 viruses that were used for the testing. Again, these are strains that are

representative of many of the strains that have been circulating over the past year in both the Northern and the Southern Hemisphere. And on the next overhead I'll show results for one of the serum panels.

This table is for adults who were immunized in Europe and what it shows, generally, is that the current vaccine strain, the A/Panama/2007/99 was reasonably immunogenic in terms of the response to the vaccine strain and again, this particular vaccine strain was a reassortant virus, the rest are 17 reassortant. However, in this table, I think you'll see that there are geometric mean titers that are reduced for some of the other strains that were tested. Neither the A/Chile/6416/2001 strain or the A/Singapore/15/2001 strain seem to be well inhibited in the tests that were done at CDC and for both of those, the geometric mean titers were reduced by more than 50 percent and similarly data from testing done at Center for Biologics shows 50 percent or greater reductions for both the Darwin/3/2000 strain and again for the Chile/6416 strain. So for other strains, I guess I could say generally the antibody responses seem to be pretty much similar to those for the vaccine and the next overhead will show some results for some elderly in the United States.

These data, I think, again demonstrate that the current vaccine produces antibodies that cross react reasonably well with many of the new H3N2 viruses such as the Argentina/37/59 strain and also the Alaska/14 strain.

In tests that were done at the Center for Biologics, there was more than 50 percent reduction in the responses for the Philippines/78890 strain, but that was not seen in testing at CDC. And again, I'm going to cover other serologic results in more of a summary form a little bit later.

So moving on now, this overhead shows a list of the Influenza B viruses that were used for serological testing and you'll recall that there are two hemagglutinin lineages that are present in circulating viruses. The antigens that were chosen here represent, I think, as best we could both of those lineages as they're circulating and those at the top here are related to the current vaccine strains and they're all in the B/Sichuan/379/99 lineage, generally, or maybe I should qualify that some and say this B/Johannesburg/69 strain here is in that sort of -- can I call it a splinter group? I'm not sure it's a lineage, but there's a divergence, antigenic divergence developing and it's more like the

B/Harbin/794 strain. And then at the bottom I'm showing the B/Victoria lineage or as it's sometimes being called, the B/Beijing/243/97-like strains.

Unless I say otherwise, all of this serologic testing that I'm going to present here was done with B antigens that had been ether extracted for use in the serology.

In the next overhead there should be results from a panel of adults in the United States again and I think this gives a pretty reasonable overview of recent isolates from a number of locations around the world and in general, the antibody responses seem to be pretty good to the vaccine strain and also to most of the newer strains that are circulating. However, there were some reductions in geometric mean titers for some of the antigens that were tested and in particular I'll just call your attention at the CDC testing with the Johannesburg/69/2001 strain was more than 50 percent reduced compared to the vaccine strain. And in testing that was done -- or as I mentioned, that particular strain is in that Harbin/794 lineage.

In testing that was done at the Center for Biologics, there were reductions of 50 percent or more for a couple of strains, both the B/Hong Kong/332/2001

which is not in the same lineage, HA lineage as the current vaccine and also for the B/Hong Kong/692 AND B/Sichuan/317 viruses.

Now I will point that that result does not seem to be typical of results from either the Center for Biologics or from CDC, but it is one of the variations in the antibody responses that we sometimes note.

In the next overhead, these are some results that were obtained from a panel of sera from elderly in Australia again and what they demonstrate are again reductions, predominantly reductions in antibody responses to the B/Victoria/287 lineage strains represented here by B/Hong Kong/330/2001 and B/Hawaii/10/2001 and what you can see is what we have come to expect with current vaccines of the B/Yamagata lineage in terms of producing antibody responses for the other lineage and I will not have any data from any pediatric populations, but what I could say is that in earlier years when the B/Victoria strains were not circulating so widely, but were still present, what we had found was that adults and elderly tended to have, although reduced titers, somewhat higher. So I think we're starting to see for adults and elderly over the last couple of years, in fact, continually

decreasing responses in the face of the current vaccine strain.

So now moving on to sort of a summary, in this table and the following tables, what I'm going to be showing are how we've tried to handle these data which are complex and coming from different laboratories in the past few years and what we'll have here is a table that shows the frequency with which we found new test antigens that gave a 50 percent or greater reduction compared to the current vaccine strain.

We picked 50 percent arbitrarily, but it represents a 2 fold reduction in geometric mean titer and that's fairly marked in terms of GMTs. The data that are included in the table are as much as we can for antigens that have been tested in more than one laboratory and I should note that we haven't really had access to information outside the United States at this point, partly because the WHO meeting for strain recommendations will occur next week and others are getting ready for that.

In this table for H1N1 viruses, all these viruses again are New Caledonia-like and if you just more or less look at the line for the total results, generally there are really two instances in which

multiple tests detected differences compared to the vaccine strain and that would be for the A/Hawaii/15/2001 strain and also for the Auckland/65/2001 strain.

The majority of the tests performed resulted in a 50 percent or greater reduction in titers as compared to the vaccine for both of those. For the Hawaii strain on average, the reduction was about 60 percent with a range from 31 to 82, depending on which of the serum panels were picked. And for the Auckland/65 strain, that difference was somewhat less than 50 percent, just less than 50 percent and it ranged from no change to 93 percent reduction. So there was quite a broad range there.

However, I'd say overall, the data don't indicate that there is a generalized substantial lack of inhibition of the current strains by the current vaccines. So the next overhead should show summary data for the H3N2 viruses.

And what you'll see here, I think is that many of the more recent strains were very well inhibited by sera from persons who were immunized with the current vaccines, but here again, there are also some strains that appear to be somewhat less well inhibited in comparison to the vaccine.

And those that are less well inhibited include the A/Chile/6416 strain, the Philippines/78890 strain, the Singapore/15/2001 strain, and possibly the South Australia/102 strain.

Although there was reduced inhibition for the Chile/6416 strain in the majority of the tests, on average for all these tests there was only, there was somewhat less than a 50 percent reduction, and again the range for the difference here was wide, from nothing to about 75 percent.

For the A/Philippines strain, the reductions were only seen in one laboratory and so you have to factor that into thinking about this particular one and on average for all these tests it was really very moderate and there was a very, again a very wide range of responses that were seen in the tests that were done.

I think here with the Singapore/15 strain, I believe, both the Singapore/15 and the Australia/102, South Australia/102 strains again represent those that were low responders. Is that correct? I think I got that right. And so I would suggest again factoring that in and sort of considerations about what these responses are showing. But for the Singapore strain, in particular, it was

consistent in all the tests that were done, it was really a very narrow type range of reductions here, so there may be something more to that particular strain.

The overall picture though, I'd say is somewhat similar to what we're seeing for the H1N1 viruses and that the results don't suggest a generalized lack of inhibition of currently circulating strains. And also, similar to the results for the H1N1 viruses, the results for the mean percent reductions shown in the last column are somewhat variable with some tests where there really is no reduction at all.

Okay, so moving on to Influenza B, this overhead should show the summary data for Influenza B viruses and just again as a reminder, the B/Hawaii/10/2001 and the B/Hong Kong -- where's B/Hong Kong, B/Hawaii/10 and B/Hong Kong/330/2001 are strains that are in the B/Beijing/243/97 or B/Victoria/287 lineage, hemagglutinin lineage. All the rest are in the B/Yamagata lineage and the B/Johannesburg/69 is in that B/Yamagata lineage, but it's representative of the divergent, the strains that are diverging more like the B/Harbin/799/794 strain.

Although most of the strains that are in this B/Yamagata group seem to be very well inhibited

by the current vaccines, the only notable exception to that is the B/Johannesburg/6901 strain where about half of the tests done indicated a reduction and on average that reduction was just shy of 50 percent with a somewhat broad range, but again, there were reductions seen in -- some reductions seen in each of the tests that were done.

I think it's no surprise that the recent B/Beijing or the recent B/Victoria/287-like strains were poorly inhibited and I don't think I need to really dwell on that since that information is very consistent with what we've been seeing in the past couple of years.

So you can take the overhead off and I'd say in summary the vaccines that were used for the clinical studies appeared to be very immunogenic in the populations that they were tested in and for all three of the vaccine component strains, we can see some evidence of antigenic drift. The results, I think, are the most obvious for the Influenza B strain, where only the strains that are in the same HA lineage are well inhibited by sera from the current vaccine studies and any even there there's some evidence that antigenic drift is continuing. And so I'll stop there and take any questions, if there are

any, that I can answer.

DR. DAUM: Thank you very much. Are there questions?

Ms. Fisher, then Dr. Poland.

MS. FISHER: Dr. Levandowski, every year when new flu vaccine candidates are tested for efficacy, do those tests usually involve about 200 individuals? I think you mentioned that was true for this year. Is there any reactivity data gathered and are children or pregnant women included?

DR. LEVANDOWSKI: These aren't for efficacy. They're really looking for immunogenecity and the real purpose behind is to have some -- we're trying to emphasize a comparison between the current vaccine strain and the newly circulating strain, but the number of 200. There are no pediatric patients that are being immunized at this point. And we're not including pregnant women and I don't know whether in all of these serologies that are done in other places and I don't know the answer to the question about whether reactogenecity data are being collected from those 200 people. It's not the specific reason for the study.

MS. FISHER: Right.

DR. LEVANDOWSKI: It might be done

elsewhere, but in the United States I don't believe we're doing that.

MS. FISHER: But these immunogenicity studies are the only ones conducted, correct, every year on the new flu vaccine candidates, or am I wrong on that?

DR. LEVANDOWSKI: Well, it might not be the only ones, but these are the ones that we have access to the antisera. We get these antisera specifically for this purpose that I mentioned, to try to get information to compare responses about the current vaccines with the newly circulating strains.

MS. FISHER: Right, but I think it's really important for the public to understand, is there more testing done on the flu vaccines other than this immunogenicity testing?

DR. LEVANDOWSKI: If you're asking is the Public Health Service doing some specific testing --

MS. FISHER: No, is there any other testing besides this testing done on new flu vaccine candidates? Is anyone aware of any other testing?

DR. LEVANDOWSKI: Okay, well, specifically related to the influenza vaccine candidate strains, I think the answer is probably not.

MS. FISHER: Okay, that's all.

DR. LEVANDOWSKI: But are there studies being done to look at current vaccines, in a number of ways I think the answer is yes, but I don't know that I can give you a categorical response to that.

MS. FISHER: Thank you.

DR. DAUM: Dr. Poland, please.

DR. POLAND: Just a point of information, Roland. Are the laboratory protocols that CDC and CBER are using identical? Because it appears almost systematically that CBER's results are in some cases significantly lower than CDC's.

DR. LEVANDOWSKI: Right. I understand that and we do, although we follow very much the same procedure, there are some technical differences that we know about and that we have perpetuated purposely, I think. One difference is that serologic studies that are done in CDC are done using Turkey red blood cells which tend to be less different in their response to hemagglutination inhibition than chick cells. Chickens, individual chickens tend to be either good or poor responders in terms of hemagglutination and at the Center for Biologics, we have continued to use chick cells. It's pooled chick cells, but I believe that may have something to do with the technical differences. And then possibly

another area that could result in differences that we see in any of the serologic testing is what you exactly call the end point because telling exactly where hemagglutination has been inhibited is sometimes a little bit tricky and there can be interferences within the sera with the red cells themselves. The serum can have nonspecific glutinins that we try to remove with neuraminidase, but we see those kind of things and then just being able to decipher exactly what you're going to say is the end point, there may be some difference there.

DR. POLAND: In terms of looking at the data and trying to make a decision is do we really understand what the statistical significance is of these findings and which one do you believe, sort of. I know that overall we're looking at kind of the preponderance of evidence to make a decision, but in the specific case of the HAI titers --

DR. LEVANDOWSKI: Right, well, there's a logistical issue here too in trying to get the information for recent strains and how many serologies you can do and that's the reason we have multiple laboratories involved in this that we don't -- we think that if more laboratories are saying the same thing, maybe not the absolute titers are the same, but

the same direction seems to be true, that that is confirmatory and I think that's what we've been trying to do all these years with multiple labs being involved as to -- I don't think we can do statistics in a real sense because of the small numbers that we're looking at here generally, but I think we can get a pretty good idea about the trend and get confirmation from multiple views of the same data.

DR. DAUM: Before I call on Dr. Kohl and then Dr. Couch and then Dr. Goldberg, I wanted to just follow up on this particular point. I was also struck by the discrepancy sometimes between the two labs and then at the end, I believe you showed some summary data, where results done in each laboratory were sort of added up and then summed, so that we get a sense of how many low responders there were, how many high responders there were. And if two labs differ in their results markedly, so that one was low and one was high for a given virus, were they then summed into that total and if so, is that statistical double dipping or do I not understand statistics very well?

DR. LEVANDOWSKI: Well, I'm not going to answer the statistical question, but the answer to the first part is yes, we're not making any differentiation between whether we had high antibody

titers or lower ones. We're looking there mostly at a ratio between the pre and the post -- not the pre and the post -- we're looking at a ratio between the vaccine strain and the new influenza viruses that are circulating and we're hoping that whatever technical differences there are, affect everything equally, proportionally between the vaccine strain and the other strains. What I would say as another way of trying to control for that, when these serologies are done, when you see one of those serum panels, everything would have been done on the same day with the same red cells, the same reader doing the -- reading the end points and so on. So as much as possible, there's a control over that part where we're trying to get the comparison between the vaccine strain and the newly circulating strains.

DR. COUCH: Could I get my comment in now? It relates to that. I just wanted to say that if you had a third lab, you would get a third set of data. That's the reproducibility of the HI between laboratories and between tests to some extent as well.

DR. DAUM: Okay, Dr. Goldberg wants to speak to this very point.

GOLDBERG: Could I ask a question of clarification about your design really? Are you

testing sera from the same 24 individuals in both labs?

DR. LEVANDOWSKI: Yes.

DR. GOLDBERG: In which case what you really need to be doing is thinking about comparing the results individual for individual in the labs and then looking at what you have because the real issue is some individuals were low in one lab, high in another, and that would speak to the assay variability. It may be that low is low, but the range is different and it's a systematic lab bias which would have to do with what you talked about about the kind of -- the way the assay is done.

So I think you need to relook at how you present the data and pair up the data so that you're looking at individual by individual and then summing up differences or whatever the appropriate measure is. I'd be happy to discuss it with you outside.

DR. DAUM: Thank you, Dr. Goldberg. Now we'll go to Dr. Kohl. You've been patient.

DR. KOHL: Roland, thank you again for your usual lovely annual report. I get to take my plaque home today because it's four years of serving on the Committee, but I have the same frustrating question that I've asked for four years which has

previously been reflected, I think, by Bob Couch's question and by Barbara Loe Fisher, where are the children? We're thinking about using a new antigen this year, I guess, with the B/Vic and I'd love to see some data on children.

What can we do to help whoever needs to be helped so we can get some children data because those are a critical group to be considered?

DR. LEVANDOWSKI: Pardon me, well, I guess we can't disagree with what you're suggesting and it is something that we would like to see done and again, it's I believe predominantly a resource issue. The pediatric population, of course, is a protected one and we want it to stay that way, but in terms of being able to do studies, there needs to be some way to access an appropriate population which requires both time, investigators and money, all three of the key issues for doing anything successfully.

DR. KOHL: It's an unprotected population, unfortunately, not a protected one in terms of the influenza virus and there's more and more data showing that children have quite a high burden of disease. We need to do something about this.

Bob, I don't know if there's something, a sense of the Committee that can carry this forward a

little bit, because it really has been a major frustration over these years on my part and I think other members of the Committee.

DR. DAUM: Well, I think that making comments like you make put it into the record. There are many people here who pour over every word that you and everyone else says and I think that it comes up this afternoon when the Committee is deliberating and casting their votes as an issue again that we'd be heard. We have said it before. You've spoken about it before and so have others and I think it's a crucial issue. And FDA, audience, industry people, please hear us.

Dr. Cox, you had your hand up.

DR. COX: Yes. I just wanted to say that unfortunately this year, as Roland mentioned, we don't have access to data that has been generated or is being generated in London, in Tokyo and in Melbourne and it really helps when you have more than two sets of serologic data. So when you have five sets you do begin to see patterns and it falls out a little bit more clearly.

DR. DAUM: Thank you. Okay, I think Levandowski, you're off the hot seat. Thank you very much for your input.

Dr. Ye is here. There he is.

DR. YE: And I'm going to present the status of candidate vaccine strains and the related potency reagents.

Next slide, please. Inactivate trivalent influenza vaccine contains the antigen of two type A strains which are H1N1 and H3N2 and one type of B strain.

The current vaccine for Influenza A, H1N1 strain is A/New Caledonia/20/99, reassortant between New Caledonia and PR8 is VIR-116 which has lower to higher growth curve characteristics in eggs.

At this point we do not have a new candidate for H1N1 virus.

Next slide, please.

The current vaccine for Influenza A, H3N2 is Panama/2007/99 which is A/Moscow/10/99-like viruses.

Resvir-17 a reassortant between Panama/2007/99 and PR-8 which has moderate to high growth characteristics. Again, at this point we do not have a new candidate for this strain.

Next slide, please.

Now we will move on to Influenza B strains. The current vaccine strain for B Influenza

viruses is B/Sichuan/379/99-like viruses which belong to Yamagata/1688 lineage. There are three current vaccine candidates. One is B/Johannesburg/599 which has lower growth characteristics in eggs. The second one is B/Victoria/504/2000 which has moderate growth characteristics in eggs. The last one is B/Guangdong/120/2000 which has moderately growth characteristics.

Next slide, please.

The candidate strain for B Influenza viruses are shown on this slide. There are two lineages for Influenza B viruses. One is B/Yamagata/1688-like virus. There are two possible candidates for B. One is B/Shizuoka/15/2001 which gives a lower to moderate growth characteristic in eggs. B/Sichuan/117/2001 which has moderate growth characteristic in eggs. The second lineage represented by B/Beijing/243/97 and this also belongs to B/Victoria as mentioned earlier.

There are three candidates to be considered. One is B/Hong Kong/330/2001 which has lower growth characteristics in eggs. B/Hawaii/22/2001 also has a lower growth characteristic in eggs. B/Shangdong/797 which has moderately growth characteristics previously used for

vaccines in Asia in 1999 and the year 2000.

Now we are moving to the potency reagents. The antisera and antigen for H1N1 New Caledonia/2099 and 83 N2B Panama/2007/99 are available now from CBER. If new strains are choosing new reagents, need to be made and will be made available at the earliest.

Next slide.

In reagents currently available for B Influenza viruses as follows, the antisera and antigen for B/Victoria/504/2000 now available from CBER for manufacturer usage. Antisera for B/Guandong/120/2000 available from CBER, but antigen for this virus can be required from NIBSC. NIBSC also produced both antigen and antibody for B/Johannesburg/599.

Now we will move on to single lineage which is represented by B/Beijing/243/97 which is also Victoria-like lineage. The antiserum and antigen for B/Guangdong/797 are also available now in CBER for manufacture usage. Next slide, please.

The candidate strain for B viruses, if the new strains are choosing and again reagents needed to be made from CBER and will be available May at the earliest.

Thank you.

DR. DAUM: Thank you very much, Dr. Ye.

Are there Committee questions or input? Dr. Decker.

DR. DECKER: Is there a handout available that has those information -- those data?

DR. YE: Pardon?

DR. DECKER: Is there a handout available that has those data? The Committee would be interested in having them.

DR. YE: Not now but I think we can make it after meeting.

DR. DECKER: So after we decide, we can get the data.

(Laughter.)

DR. YE: I think we can get this from Web site.

DR. DAUM: I think what Dr. Decker is hinting at is that it would be nice to have them for this afternoon's discussion. If there's any way this could be accomplished during lunch, we'd be grateful. Dr. Griffin, then Dr. Levandowski.

DR. GRIFFIN: Could you just remind which of the strains in the current vaccine, we've had production problems over the last couple of years which has been due to slow growth. Is that due to the B, the current B strain or which of the three strains in the current vaccine?

DR. YE: B strains is always the problem because compared B to A, B always grows lower, never can see the HI titer higher than 1,000 compared to A. And the second thing is to B, we do not have the reassortant available for like A to generate a high growth viruses.

DR. GRIFFIN: And from what you know about the strains, if we went to the Victoria-like strain, there's no reason to think those would be better than the current strains that we're dealing with in the Yamagata lineage?

DR. YE: If I understand your question, we have one, it's a Shangdong/797 which previous to use of vaccine, commercially has been used in Asia. So we had quite an experience for that strain.

Another one is Beijing/243/97 and as mentioned by Nancy as being experimentally started in Europe. So I think we have the information for that strain, but compared to Guangdong --

DR. GRIFFIN: The Victoria/504 is what's currently in the vaccine?

DR. YE: I would defer to Roland.

DR. LEVANDOWSKI: Yes. In the United States, both B/Victoria/504/2000 and B/Guangdong/120/2000 have been used in vaccines that

are currently in use here in the United States.

DR. GRIFFIN: Right, and their growth characteristics you would say in general are sort of comparable to what we're looking at for the B/SHANDONG?

DR. YE: It is the best that we have right now.

DR. GRIFFIN: Okay.

DR. DAUM: Dr. Levandowski, did you want to make any other comments? You had your hand up.

DR. LEVANDOWSKI: I'll just follow up on that last bit, the Shangdong/797 strain was a reasonably good growing strain when it was used for commercial purposes a few years ago. And as Zhiping has mentioned most of the B strains, they usually are the great limiting step I think for most manufacturers because we don't have high growth -- the capability currently of making high growth reassortants although that's something that's on the table and there are other ways to get to that.

DR. DAUM: Thank you. Oh, one more. Dr. Eickhoff and then --

DR. EICKHOFF: A question for Dr. Levandowski. Was the B/Shangdong strain used by U.S. manufacturers and have they had experience with it?

DR. LEVANDOWSKI: Yes, the answer is at least one U.S. manufacturer has had experience, but that strain was distributed widely to many manufacturers, for examination and feedback from them suggested that that strain would be a reasonable grower as Influenza B viruses go.

DR. EICKHOFF: Thank you.

DR. DAUM: Okay, at this moment we have adjourned our morning session. Thank you, Dr. Ye, and we will now go to lunch. I think we can safely take a one hour break. It will be quarter of one in the Eastern Time Zone now and we'll reassemble promptly at quarter to 2.

(Whereupon, at 12:48 p.m., the meeting was recessed, to reconvene at 1:45 p.m.)

A F T E R N O O N S E S S I O N

1:56 P.M.

DR. DAUM: Okay, could we come to some degree of order, please?

(Pause.)

Everybody sort of finish their conversations and have a seat.

Dr. Slusaw at hand, here he is. Get ready, Dr. Slusaw.

With the departure of Nancy I don't have the little bell that I didn't realize it was she that furnished. The bell is gone, but we still need to get moving quickly because it's an airplane day and we're going to call on Dr. Slusaw, please, to give the comments from manufacturers.

DR. SLUSAW: Thank you. It's my pleasure to address the Committee once again this year on behalf of the manufacturers and just give a little bit of insight and share some of our concerns on the practical aspects of manufacturing flu vaccine.

The Committee is once again faced with the challenge of recommending strains for the 2002-2003 vaccine formula and I see this as kind of a dual challenge. One is, of course, you're trying to find the best antigenic match for the circulating viruses,

but of particular concern to us is that you also make a timely selection and you choose strains that are practical for vaccine manufacturing.

I think it's safe to say that the manufacturers feel fairly comfortable that we know how to make the current strains and turn them into vaccines, but each time we adjust the vaccine composition or fine tune the formula, we're introducing some uncertainty and some risk into the process that we may have difficulty growing the viruses or purifying the viruses to make the final vaccine.

Just to give an overview of the process and the components that have to fall into place each year in order to successfully produce vaccine, the first slide lists the key ingredients that are required. Of course, the most important raw material is the supply of embryonated eggs that are used each year to grow the virus. Second, the activity that we're doing today is looking for candidate strains and seed viruses and in particular, not just any seed virus, but where possible, it's extremely important that we have high growth reassortant viruses available for production.

Those ingredients allow us to start

manufacturing the monovalent components for the vaccine, but we can't test or measure the quantity that we've produced or we can't formulate the trivalent vaccine until we have the potency test reagents and homologous reagents that are created specifically for each new vaccine component.

I'd like to give a brief overview of the process and just hit some of the highlights that are perhaps most critical to us today. This time line demonstrates from start, from obtaining a vaccine manufacturing seed through distribution of final container the process of making flu vaccine. And for the new strains we're considering today we're right here somewhere where we're talking about potential new strains in some cases, potential A strains, even the H3 which we don't have candidates in hand yet. And of course, it takes about 6 to 8 weeks to prepare a high growth reassortant of an A strain and then another month or so to prepare working seed and begin using that to make the vaccine components. So just to caution that anything new we're talking about considering as a candidate strain today that the manufacturers do not have in hand and have not had a chance to work with, we're perhaps 3 to 4 months away from being able to produce the vaccine components with

a new strain.

The B strain, since we're currently not using high growth reassortants has a somewhat shorter time line and isn't as critical in that regard.

Next slide, please.

And briefly, an overview of the annual manufacturing cycle, the entire process of manufacturing actually begins about a year in advance when the egg suppliers order their birds in order to be able to supply the embryonated chicken eggs that we use each year. And that typically happens in January for use the following year that they'll order those birds.

This time of year we're somewhere in here where we're receiving some candidate strains and also hope today to definitely at least get the recommendation for the first strain in the vaccine formula. And the model of annual production has worked out fairly well for us, recently, as to have the first strain in January and then following with the second strain about a month later and the third strain about a month after that.

I think in summary, we could do worse than following last year's scheduled strain selection as a model. I think it went rather well, at least from a

manufacturing standpoint for most of the manufacturers in that the data was analyzed and considered thoughtfully at this meeting and then with the kind of pragmatic outlook, the strain selection proceeded rather quickly and we had received the third strain selection by March, which actually made for a fairly smooth and efficient manufacturing cycle.

Any questions from the Committee or any comments?

DR. DAUM: We do have some. Dr. Faggett, please?

DR. FAGGETT: Yes, thank you for that very clear presentation. You mentioned from this point it would take 4 or 7 months to have vaccine ready for use? What was the time line from now to having it on line?

DR. SLUSAW: Actually, if you could go back one slide? If we're talking about the A strains in particular, again, adding on the time line of the high growth reassortant, it's about from the identification of the initial wild type candidate strain to having a final container, it's about a 6 month period.

DR. FAGGETT: Six month, okay. Thank you.

DR. SLUSAW: Of some interest, perhaps, in

that is the actual manufacturing time of the vaccine components is less than 2 weeks and all the rest of the time is various testing and release process for the intermediates and vaccine components.

DR. DAUM: Dr. Kohl and then Dr. Eickhoff.

DR. KOHL: How big a problem would a quadravalent vaccine be in terms of time and also if there are any other licensure problems, if you have to do four strains?

DR. SLUSAW: Well, I think it's safe to say that it would reduce the total quantity of doses that would be available this year and/or delay the timing of the availability of the doses. Just simply having to produce more antigen. I think most of the manufacturers are currently running, essentially, at full capacity insofar as the number of eggs they're producing or consuming per day to use in their manufacturing process. So producing additional vaccine components would mean less doses or more time.

DR. KOHL: But I'm asking you to try to quantify that. How much more time, for instance?

DR. SLUSAW: For a fourth component I would say that that would add or reduce the total doses by about a third or add that one third on additional manufacturing time.

DR. DAUM: Dr. Eickhoff and then Dr. Couch.

DR. EICKHOFF: We may be in the position this year of having the most slowly growing problematic strain being the last one to be selected. Does this introduce another element of delay?

DR. SLUSAW: Well, that's actually about the worse combination of events that can happen and kind of reflective of the events that occurred several years ago where the supply was a little later than expected. But really, the critical factor in the timing of the availability of the vaccine is the characteristics of that third strain and when the third strain is announced exceptionally late or if it's a particularly slow grower, the results are very serious and reduce the number of doses that are available.

DR. DAUM: Dr. Couch.

DR. COUCH: To follow up on Steve's question, when you're talking about a quadravalent vaccine, you were talking about the time delay. That was the assumption that all components would be 15 micrograms because you were talking about the total vaccine produced, isn't that correct at that level?

So if you split one of them to 7.5 and

7.5, then there would be some delay there, but not to the level that you had suggested. Is that correct?

DR. SLUSAW: Right, as far as the total quantity there would be less impact because of that, but handling a fourth vaccine component --

DR. COUCH: Fourth vaccine --

DR. SLUSAW: Our systems are generally set up to handle three would be a bit of a change that's difficult to make on the fly in a short period.

DR. COUCH: And you're manufacturing time line in which you say start the third strain, that's actually start the production line, correct?

DR. SLUSAW: Right.

DR. COUCH: Everything has got to be right for the production line?

DR. SLUSAW: That's right.

DR. DAUM: Can I ask a question about how the process occurs by which industry or people who manufacture flu vaccines help you prepare for these comments and how you take what you hear here back to industry? Can you give us some sense of how that back and forth works?

DR. SLUSAW: Representatives of the manufacturers and the FDA and CDC meet in December of each year where we essentially do a post-mortem and

analysis of the previous year's manufacturing cycle and distribution, testing, release, all the aspects of vaccine production and that's a fairly open forum where we raise a lot of the issues, where we had difficulties that we'd like to correct the following year and if we also have any suggestions for streamlining or improving some of the systems, we generally identify them at that time. It's also an early update for us on surveillance information and also sharing some feedback on growth characteristics of any candidate strains that have been distributed up to that time.

So that's the forum where a lot of the background information is discussed before this meting.

DR. DAUM: But companies that make the vaccine are aware that through you, I guess, they have representation today and input into this process?

DR. SLUSAW: That's right, and again, I mentioned the December meeting, but we also have additional telephone and e-mail contacts where we share concerns that we would like to emphasize and bring up at this meeting.

DR. DAUM: Thank you.

MR. YORK: This is Richard York from Wyeth

Laboratories and I'd just like to reaffirm what Greg has just told you. He's actually sent the slides out to us ahead of time to review and it's pretty much an industry situation, the time lines that he described is the same for us. I'd just also like to emphasize that if you throw a fourth strain in and it takes -- sometimes it takes 6 months before we can play with that to get the yield up if it's a low yielder and that would certainly delay our time line and that's part of what happened with A/Panama a few years ago. That was a very poor grower to begin with and now we all love it. It's a great growing strain because we've had time to work with it.

DR. DAUM: Thank you very much. I think we'll move on now to hear the options for strain selection from Dr. Levandowski and then we will begin Committee discussion and recommendations.

DR. LEVANDOWSKI: Okay, thank you. I'll try to be to the point and brief. I'll start out with a little bit of review. You can take that down. I'll start out with a little bit of review about each of the strains and then go over what I think we see as reasonable options here.

First of all, I'm going to go in the order that the presentations were previously with H1N1, H3N2

and then B viruses.

So just to summarize, I think what we heard this morning, so far there have been relatively few influenza A/H1N1 viruses isolated in North America and Europe. However, there's some recent isolates from China that CDC has, but hasn't had a chance to really analyze fully at this point.

What we know from what's been done the HAs of most of the strains are antigenically are very similar to the current vaccine strain which is A/New Caledonia/2099 and H1N1 viruses generally seem to be well inhibited by the antisera from people who have been immunized with the current vaccines that contain A/New Caledonia/2099.

The high growth reassortant of A/New Caledonia/2099 is already available, obviously. It grows well and the manufacturing for that has been very well worked out. So the first option that we would have, I think, if you want to put the first overhead up, please, would be to maintain the current vaccine strain as A/New Caledonia/2099. And in favor of that, the manufacturing is worked out. The yield is very predictable. Most of the viruses this year are A/New Caledonia-like by antigenic characterization. On the negative side for that,

however, there have been relatively few recent strains for analysis and so that leaves a little bit of a blank in terms of where things are really headed. And some of the recent H1N1 isolates have not yet been completely analyzed. So a second option would be on the next overhead would be to change the current vaccine strain to a strain that is more representative of currently -- the few currently circulating viruses that are out there and a reason to do this in favor of that would be that a more recent strain might provide a closer match with the hemagglutinins and the neuraminidases of contemporary strains although I think we heard that in that respect it doesn't seem like there's too much that's changing from the strains that have been analyzed.

I guess that would be that a new strain might not provide any superior immunogenicity or efficacy compared to the current vaccine strain. And furthermore, we heard that there aren't any new strains suitable for manufacturing that have been identified, therefore any manufacturing issues that there could be haven't been investigated. And then a third option for the H1N1 and I'm going to repeat this so this will be the sort of order I go through things, the third option would be to defer the decision to

accumulate more data and in favor of this, I'd say that possibly there could be some additional analysis of contemporary strains that might identify some change that would lead to suggesting a change in the vaccine, but I guess that is there's really very little new information that appears to be forthcoming, not only because there's -- although there's some work to do in the laboratory, there just aren't really many strains out there. So you can take that off. I don't need a slide yet.

So moving to the influenza A/H3N2 viruses, again to summarize, predominantly there have been influenza A/H3N2 viruses isolated during the recent past and there have been quite a number of them. The HAs, most of the strains that have been investigated seem to be similar to the A/Moscow/1099-like viruses and that includes the current vaccine strain A/Panama/2007/99. However, at this point, it looks like the influenza season, not only in the United States, but in other parts of the Northern Hemisphere, is really still just developing and we don't really know what is likely to turn up at a later point.

Furthermore, Nancy Cox mentioned that analysis of some new H3N2 viruses from outbreaks in China are just in progress and we've seen in the past

a lot of the N3N2 strains that are really different have come from China to begin with.

The A/Panama-like H3N2 viruses tested to date are generally well inhibited by antisera from people who have been immunized, but as I pointed out earlier in the serologic data, there are some exceptions to that, mostly in terms of those viruses that have been identified as low reactors with ferret sera. And finally, the current high growth reassortant of A/Panama/2007/99 grows well and the manufacturing is very well worked out.

So the options for the H3N2, the first option again would be to maintain the current vaccine strain which is A/Panama/2007/99. And in favor of that again, the manufacturing has worked out and the yield is very predictable. And also, most of the viruses this year are Panama/2007/99-like by their antigenic characterization.

Against that would be the analysis of some newer strains really hasn't been completed and just to reiterate what's been stated before, the H3N2 viruses often are responsible for the most significant morbidity and mortality. This is not to say that the other influenza viruses don't cause that, but H3N2 in many occasions in the past seem to have been

associated with some significant morbidity and mortality.

So the next option would be to change the current vaccine strain to one that's more representative of the other strains that are out there. And the reason to do that would be that the more recent strain might provide a closer match for the hemagglutinins and neuraminidases and again, a reason to do it would be because the H3N2 viruses often are responsible for significant morbidity and mortality, but against that option of changing at this point at least would be that the analysis of the newest strains really isn't completed and a new strain might -- we don't actually know, there might be other strains that pop up, a new strain may not provide superior immunogenicity or efficacy compared to the current vaccine strain. And finally at this point there aren't any new strains that have been identified as being suitable for manufacturing, so that manufacturing issues have not really been investigated.

So now that brings me to the third option here and again, it's to defer the decision to accumulate more data and in favor of that, this would provide some additional time to complete analysis of

the strains that have been recently received from Asia. A more recent strain might provide a closer match with the HA and NA of the contemporary strains and again, just to reiterate the H3N2 viruses are viewed as being responsible for morbidity and mortality.

On the negative side, however, again, we don't know whether a new strain would provide anything superior in terms of immunogenicity and efficacy, compared to the current vaccine strain and again, we don't really, at this point have anything identified that seems to be suitable for manufacturing. And in manufacturing, the practical issues have not been addressed. So you can take that overhead off.

And now I'll move to influenza B viruses which I think is a lot more complex. What seems to be happening is that there's antigenic drift continuing and influenza B viruses in both of the two known HA lineages continue to circulate. Some of the strains that are in the vaccine HA lineage are antigenically distinguishable from the current vaccine strains and all of those vaccine strains are similar to the B/Sichuan/379/99-like strain.

There's evidence that some influenza B viruses in the vaccine HA lineage are less well

inhibited by antisera from people who have been immunized with current vaccines.

The viruses that are in the B/Victoria/287HA lineage also seem to be undergoing antigenic drift and strains in that lineage have been only recently, really, within the last couple of weeks, identified in a number of regions where they had not previously been found. So there's evidence for recent spread of those strains where they had been mainly in Asia over the last several years.

Strains in the B/Victoria lineage seem to be poorly inhibited by antisera from people who are immunized with current vaccines and as I pointed out earlier today, again, we've been seen developing not only for children, but for adults who are immunologically prime. We've been seeing much reduced responses to the current B/Victoria-like strains.

The current vaccine strains, the Johannesburg/5, the Victoria/504/2000, and Guandong/120/2000 all seem to be pretty well worked out in terms of their manufacturing status and vaccines with all three of those strains, actually, are being manufactured, have been manufactured this year.

A B/Victoria/287-like strain, actually two

of them have been used in producing experimental vaccines, both the B/Beijing/243/97 and the Shangdong/797 have been used for experimental vaccines in Europe. And furthermore, the B/Shangdong/797 strain is one that has been used for producing commercial vaccines for parts of Asia a couple of years ago, so that there is some information on manufacture there as well.

And finally, there are strains in both of these influen: a B lineages that have been distributed to manufactur(rs and there is some development that's on-going. It's not complete, but there's development of information as to how these strains might perform in terms of manufacturing. So I'll just go on to the options now.

Next overhead. One option would be, of course, to just retain the current vaccine strains which for the United States are really predominantly B/Victoria/504/2000 and B/GUONGDONG/120/2000. And in favor of that, of course, the manufacturing is well defined and it's predictable, but against that is that there have been new variant strains that have been identified in the vaccine HA lineage and in addition to that, B/Victoria-like strains, B/Beijing/243/97 HA lineage strains are appearing in increasing numbers

and in new regions. And some of the influenza B strains, particularly those in the B/Beijing/243/97 HA lineage are not really well inhibited by post-infection or by post-immunization antisera.

So this brings me to the second option and of course this one is to change the current vaccine strain to some other influenza B strain. In favor of that, of course, our hope would be that the vaccines would provide broader coverage for the current influenza B viruses and also in favor of that, I think from a practical point of view, several candidate strains have been identified and they're being examined for their suitability in terms of manufacturing. But against that, again, we don't know whether a new strain is going to be any more useful than the current strain in terms of its immunogenicity and efficacy, although we might expect that for the B/Victoria lineage and it's always possible that a new influenza B strain, and in particular, could cause some difficulties in manufacturing.

And so the third option here would be again to defer the decision to accumulate some additional information and in favor of this, I think it would provide some additional time to look into the

antigenic properties of influenza B isolates of both lineages that are out there. It would provide some, more time to evaluate the candidate vaccine strains and see how they're likely to perform and it would also -- a more recent strain might again I think we would hope that that would be true would provide a better match for the hemagglutinin and neuraminidase. Against, this option, again, a new strain might not be any superior. I think that's all I have to say there and I'll stop and see if there are any questions or comments.

DR. DAUM: I'm sure we have some. Dr. Katz, first and then Dr. Dowdle.

DR. KATZ: The one contraindication you didn't list in your three options was the price of deferring, as far as time is concerned. As we listen to the schedule of how vaccine is prepared, with the new strain, the necessity to be able to replicate to high enough titer to produce enough vaccine, it seems to me that the threat lies in again having a delay in availability if you hold the manufacturer to waiting until you have additional information.

Can you comment on that at all, Roland?

DR. LEVANDOWSKI: I think that's the tradeoff. I think we're always concerned. As I

mentioned at the very outset, the understanding about how inactivated influenza vaccines work, it's based on antibodies to hemagglutinin and the match of the hemagglutinin to the vaccine has a lot to determining how well the vaccines are going to perform. I think that's been seen since the very first influenza vaccines have been used. So it's always a tradeoff, I think between making sure that there's the best match we can get for the vaccine and understanding that it's a huge stress on manufacturers to try to put together more and more vaccine every year and have uncertainties about what's going to be coming to them. Obviously, we have a lot of faith in their capabilities and I think they have shown time again what resourcefulness they have in manufacturing to overcome some of these obstacles, but obviously there is a point in time in which it becomes too late to do anything and I guess I would argue at the moment, I don't think we're at that point where it's too late to do anything. I think the additional information that could be accumulated could help, for example, just the practical end of it, knowing which strains do not perform so well and which strains the manufacturers are not interested in pursuing any further. That sort of feedback is helpful to us. So I think we

understand why you're asking that question and I think it's a concern that we all have to try to balance those two needs to have a good vaccine match and still permit manufacturer's to do what we're asking them to do.

D R . K A T Z :

Well, you know, it's February now and I'd love to hear from the gentleman who preceded you as to what he sees as the deadline beyond which it's just not possible to meet time commitments if you were to give them a new strain on March 1st, is that too late or is that still possible?

DR. DAUM: Dr. Slusaw and perhaps Dr. Decker want to comment on these things?

DR. SLUSAW: It's really two different questions whether the final decision is made March 1st or if March 1st were considering a new candidate strain isolate that has just arrived and thinking maybe we should include that in the vaccine formula. I think the key is some time in March, preferably by mid-month to have the third strain identified and ready to use in manufacturing.

DR. DAUM: Thank you. Mike, do you want to say anything?

DR. DECKER: Yeah, I'd like to comment

because Dr. Slusaw and I approached this from different viewpoints. He's got to make the stuff. I approach it from the viewpoint of a public health physician.

First thing, Sam, is there's no specific deadline in the sense that what's going to be handed over on March, a strain that grows easily and well or a strain that takes three months to labor over. No one knows until you hand it over. So there are risks in every element of our decision making here, trying to enhance the public health. If we go for a quick answer and we pick the strains badly, bad for the public health. But if we wait too long and pick well, bad for the public health. We don't know where the cutoff for sure is.

I can tell you this, that I know from being there that the manufacturing plant from the moment it can go, runs at full capacity basically 24/7 until production is shut down which happens when we reach the end of the production season. We go as long as we can. We make every bit we can. That was -- this year, for example, and the ability to do that enabled us to put some more doses out there in the marketplace, most of which, got bought, but not all.

If -- let me comment on the potential

impact of adding a fourth dose which -- a fourth in the strain which looks attractive for some reason. We're not sure. Is this Victoria going to resurge and be the problem and the public is not well protected against them? But you're adding a risk. So if, for example, the two best B strains both look -- the two that look the best are both strains with which the manufacturers don't have familiarity, you've doubled the risk of having year before last recur. If you hand them one strain they haven't seen before, that's one unit risk. B is the hardest to grow. It's the most problematic. It's the one that's obviously going to get handed to them last. You've already stacked the deck a little bit against timely delivery of vaccine.

If the Committee ends up going for two B strains, what I would say is a public health doc, I would immediately turn to my friends at CDC and I would say you have to redouble your already excellent efforts from last year to make sure that the practitioner community is ready to immunize late and they don't like that and they're a little bit better, but not good enough, and the press will understand why the vaccine is showing up late again, that it's a deliberate thing. So this is all intertwined and the

public health decisions aren't easy.

DR. DAUM: Thank you, Michael. Dr. Dowdle and then Dr. Kohl.

DR. DOWDLE: Thank you. My question was the same as Sam's.

DR. DAUM: Okay. Then Dr. Kohl.

DR. KOHL: Roland, can you address CBER's view on the possibility of a four component vaccine?

DR. LEVANDOWSKI: I'm sorry, I didn't hear all of that.

DR. KOHL: Can you comment on the possibility of a four component vaccine?

DR. DAUM: From CBER's perspective was the question.

DR. LEVANDOWSKI: Okay, you guys really want to put me on the spot, don't you?

(Laughter.)

DR. DAUM: We sure do.

DR. LEVANDOWSKI: What I could say is that in the United States, there have been all sorts of valencies of vaccines at one time or another. Through a large part of the 50s and 60s we had pentavalent vaccines and of course, in the 70s it was mostly a bivalent vaccine and it's only -- it was only when the H1N1 strain came back and persisted unexpectedly,

along with the H3N2 influenza A, that we developed a trivalent vaccine. So if you're asking is it something that could be done, I think the answer is yes. And in more recent times, there have been quadravalent vaccines produced with 2B strains. In Europe, in the mid-1990s, in the Netherlands there was a quadravalent vaccine that was used. Commercially, it was the vaccine that went out which had 60 micrograms total of HA, so 15 micrograms of each component. It was not large scale manufacturing, but from the study that was published from use of that vaccine or from the experience from that vaccine, it sounded like that there was not an increase in acute adverse reactions, meaning local pain, fever, febrile responses and so on, but it was, I believe the studies were directed mainly toward adults so it would not necessarily cover pediatric.

In the immunogenicity part of the study, both of the B strains that were included seemed to be immunogenic. So in terms of the performance of more valent vaccine, I think our expectation is that it would be somewhat similar and in terms of the total amount of hemagglutinin that goes in, there does seem to be some relation to at least acute adverse reactigenicity, particularly in young people, children

and those who haven't been infected or immunized previously. But that we don't exactly know where that point is.

DR. DAUM: Thank you. Dr. Couch, please.

DR. COUCH: Did you call on me?

DR. DAUM: Dr. Couch.

DR. COUCH: I'm pursuing the same thing because Steve keeps doing the quadravalent and that was the option that you did not have up there was the four component vaccine.

I don't know how long it's been, but as you say, there have been bivalent B components in vaccines in the past and in the past that total dose for B has been split between the two components. That was the reason for my question. If you had two components, but only half the quantity, what does that do to manufacturing? Well, you know it would lengthen it a little bit, so the question is since you already have both strains that are moderate growers, one with experience here and one with experience in another country. The two strains that you would want to consider for the bivalent B are in hand with experience now. If you split it, 7.5 and 7.5, you don't have the 60 microgram reactigenicity risk. That's more of a risk, I think, than it is a reality

of concern as well. That was an option I thought you ought to have up there.

DR. DAUM: Dr. Levandowski, do you want to respond to that before we call on Dr. Snider?

DR. LEVANDOWSKI: Well, I'd actually like to hear from manufacturing on that issue.

DR. DAUM: Okay, punt over, Dr. Slusaw, do you want to comment on that?

DR. SLUSAW: I'd like some of my other colleagues in the audience to chime in with their individual reactions to the question.

Clearly, if we're including two B components, but reducing the amount of antigen, it's not as big a problem related to our capacity to produce vaccine. Clearly, all our systems have been evolved and geared around producing a trivalent vaccine, the last decade plus and it would introduce additional testing, perhaps release delays. Handling another vaccine component which we wouldn't normally have to include in the vaccine. So it would introduce complications, not as much impact on capacity.

DR. DAUM: Dr. Levandowski. Don't go away Dr. Snider, we've got you. Dr. Katz and Diaz next.

DR. LEVANDOWSKI: So just as another reminder about history, from 1978 to 1981, the

vaccines used in the United States had 7 micrograms of each hemagglutinin present. That was changed in 1981 because there was some recognition from clinical studies that were done that antibody responses were higher against the vaccine strain and also they seemed to be substantially higher against heterologous viruses that weren't exactly the same as the vaccine strain. That's actually how we got to 15 micrograms, HA, of each of the three components. So those vaccines were trivalent with seven micrograms of each component. The immunogenicity at that time, I guess, was thought to be not as optimal as it could be with -- by increasing the dose twofold. I don't know if others have comments along those lines, or thoughts. Maybe Dr. Dowdle. No.

DR. DAUM: Let's go on to Dr. Snider and then Dr. Katz and Diaz.

DR. SNIDER: I just want to bring up the point which I'm sure everybody is aware of. There's another variable that needs to be put into this discussion when we think about what are we going to include in the vaccine and how many doses are going to be available. Another piece of this, of course, is who is the target audience for receiving this vaccine? As many of you know, we have targeted the over-65 and

those under 65 who have certain medical conditions and I'm sure many of you know we have not done a very good job, particularly with the latter group and there has been a great deal of interest in lowing the age of eligibility and the population at large to 50 and to recommending everybody 50 years of age and over, receiving influenza vaccine.

And then recently there also have been discussions about immunizing infants and young children because of publications, I'm sure many people have seen addressing not only the morbidity issues in children, but the role they play in the epidemiology of the disease in bringing the influenza to older family members who may have medical conditions and may suffer from influenza or die from it. So at the same time we're talking about this, we also need to keep in mind that we're talking about the potential for expanding the target population for influenza vaccine in order to achieve optimal public health outcomes and so I'm just saying that we consider all of this, we not forget about on the other end that there is a desire to vaccinate more people this coming year or more people in the near future than we have been able to reach in the past.

DR. DAUM: Thank you. Dr. Katz.

DR. KATZ: I think Dr. Diaz and I had the same question which Roland alluded to indirectly and that is if you halve the dose of antigen in B by having two different strains, what do you anticipate as far as immunogenicity is concerned?

DR. LEVANDOWSKI: Okay, so let me use the analogy from 1981 again. At that point there was both an H3N2 and an H1N1 component to the vaccine and they were both at 7. The two didn't seem to result in increased immunogenicity for the other, I guess I would say at the end. I think the situation with the influenza B viruses might be similar. They're not different subtypes, but certainly antigenically they seem to be about as far apart or closer to about as far apart as the H1N1 and the H3N2 strains are.

Maybe I'm exaggerating that a little bit, but I think that's a reasonable analogy.

DR. DAUM: Thank you, Dr. Diaz --

DR. DIAZ: That was my question too.

DR. DAUM: Okay, good. Dr. Decker.

DR. DECKER: A question. Maybe it will turn into a series of questions for Roland and possibly the manufacturing representatives. If there were two B strains included this year, would one of them -- would you recommend that one of them be the

strain that was included last year or would you favor changing the strain that's covering that lineage to an alternate as well as introducing one to cover the new Victoria lineage?

DR. LEVANDOWSKI: Well, now you're asking me to make the recommendation, I think.

DR. DECKER: Well, I'm trying to simplify --

DR. LEVANDOWSKI: I will answer it though. I think the concern is that there are differences in the current influenza B HA lineage as well as what we're seeing as a new geographic spread of the B/Victoria lineage, so I think those are two slightly different directions, but I think the answer is that I don't know that I have enough information to answer strongly that if even the current HA lineage were the one to be in the vaccine, whether the current strains would be ideal.

DR. DECKER: The reason I asked because based on what I knew and absent of reassurance on the manufacturing specialists here, I would think that changing both B strains would represent an unreasonable risk to the vaccine supply for the year. Whereas changing, adding a half strength one and retaining the one they already know how to make is a

safer gamble and so I think if there's an interest by the Committee in pursuing two, we'll have to get quite precisely into what two, and the choice will alter the risk.

DR. DAUM: Fair enough. Dr. Couch?

DR. COUCH: Just a couple more comments along that same line. If we look at the information from Asia, most of the lineages have co-circulated for more than one year, you see, and it locks as though we're getting the Victoria here, will Sichuan disappear? I doubt if anybody can answer that. If they can answer that, then your question can be clearly answered.

And the other is I would differ with Roland a little bit to take the 7 microgram analogy as to what we would do to immune responses if we had two Vs in. We've looked at the immune response data here to B/Sichuan and it does cross react with the B/Victoria lineage viruses. We don't have the other half of that equation. I didn't know until today that maybe it's available in Europe, that if you give B/Victoria, do you cross react and if so, in what age group against the Sichuan, but I would at it as two B drift viruses with some relationship and something to be gained in the direction of that 15 micrograms as

opposed to an isolated 7 ½ of unique antigens.

Now the problem with 7 ½, if you should do something like that is that the cleanest separation of that would probably be in the young children. Where they would get one they won't get the other antibodies. But if you've got both of them, you got a little bit of something maybe for both of them. You can tell where I'm leading it's fairly obviously.

DR. DAUM: Dr. Dowdle and Dr. Myers have their hands up before. Dr. Palese was ahead of you. So we're going to do Dr. Palese, Dr. Dowdle, Dr. Myers and then I'm going to ask people to really and try to bring this to a close so we can start polling the Committee and seeing what people sort of think. Dr. Palese, please?

DR. PALESE: I just wonder whether we get sort of carried away in terms of the re-emergence of the B/Victoria, because if you look at the handout of the CDC on page 44, there is in the time period of October of 2001 until January 2002, there are very few isolates, really, from which we try to make a conclusion. And particularly we are sort of disturbed by the 25 isolates from Asia which make up 66 percent of the A/Victoria-like viruses. So I think there's a sort of a very, very small number and also I would

like to note from what geographic distributions do those 25 isolates come from? If they all come from the same city, then I think we might be very much misled here, particularly if you talk about small numbers. All the four isolates we have from the United States are all from the current vaccine strains.

So I just wonder whether we are -- are those all the data we have? Twenty-five isolates from Asia and we're getting all worried? How sure are we that this is really a representative sampling?

DR. DAUM: Maybe that question goes to CDC folks first?

DR. COX: Right. Peter, I think that what you're looking at here is the viruses that we've tested at CDC, but you have to remember that there are additional viruses that have been testified by the other WHO Centers. And we did have a call yesterday morning from Alan Hay in London and he called specifically to tell us that four out of seven Italian viruses that they had received were B/Victoria-like, and furthermore, three out of four of the viruses that they received from Genoa were Victoria-like. We --

DR. PALESE: It is still a very small number.

DR. COX: It is small numbers, but when we've seen -- you have to take this within the context of not having seen Victoria-like viruses at all for the past 10 years in North America and Europe and South America and so on. And that when we have seen this pattern where viruses were confined to distinct geographic areas, once they move out they tend to move quickly. We've seen that before with the Yamagata, B/Yamagata strain which emerged from Asia and subsequently supplanted the Victoria-like viruses. We saw it with a sublineage of B viruses represented by the B/Beijing/184-like strains and then we saw it again with the Beijing/262-like strains. So it's a pattern that we have seen before for other groups of viruses, either A viruses or B viruses and it's a red flag to us, certainly.

DR. DAUM: Thank you. Dr. Dowdle now. You've been patient.

DR. DOWDLE: Well, two issues and basically two questions is that I think adding an additional B strain on the surface sounds like a very good idea, but I think that we -- the question is can we make assumptions here and by splitting the dosage in two different strains would we have to undergo a certain, at least a limited field trial in order to

see what serologic responses may occur and indeed if there was a difference and whether that would add to the additional time period.

The second question is that I think one of the options that were listed here was a broader B strain and it wasn't clear to me that which B strain might give broader coverage, is there a candidate strain that's available? Or is that one which you're waiting for that might show up and would take additional time for surveillance?

DR. DAUM: Dr. Levandowski do you want to comment?

DR. LEVANDOWSKI: Well, I don't think I can answer all the surveillance end of it, so Nancy Cox may want to answer also, but I think or the sense that maybe I would convey comes from looking at the data from the study in which a B/Victoria-like strain was used to immunize people who had been previously primed with a B/Yamagata-like strain and there, the antibody responses were recently good, were they not? There's a -- I'm blocking on the word. It's the original sin concept, where the antigens of first contact are also increased with contact with another strain if it's similar enough or even in the right ballpark. So I think what we saw with those studies

was that the B/Victoria-like strain induced antibodies, as long as there was immunologic priming. Without immunologic priming, however, there was not antibodies produced against that second lineage. So I guess the question would become similar to what was being raised about populations in which population would you be aiming to protect that way, if you knew the population was immunologically primed and had some reasonable expectation that you'd get antibody responses that were protective to both lineages and that might be one direction. If, on the other hand, you think that there will be no response say someone who is immunologically not primed, then you have to weigh what the risks and benefits are for which strain is going to win the contest the following year.

I would maybe follow up on something that Nancy said about the B/Yamagata strains. I believe the year that that was chosen for the vaccine here, there were none of those strains identified in North America. I believe they were only from Japan at the time. In fact, I think -- and I don't think there were very many. I wasn't here, so I may be completely wrong, but my sense from what was happening at the time was was that was not a strain that was present in the United States and then the next year, the next

influenza Bs and those were the only strains. We did not see the B/Victoria-like strains at all here, although in Europe, it was 50-50 for a couple of years. They had about half B/Victoria and half B/Yamagata-like strains, so those I don't think that we know how to predict whether that -- which of those scenarios might be likely to play out.

DR. DAUM: Thank you very much. Dr. Myers, you're on my list here.

DR. MYERS: Well, I guess considering the third option of waiting. Keiji showed that only 21 of 1278 isolates were B and looking at the graph that Nancy showed, this is very few of the isolates around the world are B strain, so I guess the question would be if we waited until March to make a decision, would we actually gain any sufficiently more information to have a more informed -- be able to make a more informed decision or will we be basically working with what we have now and maybe a couple more strains?

Does it really matter if we wait for the amount of data we'll have?

DR. LEVANDOWSKI: I'll take a stab at that. The influenza season is very early. I think we're still in the early phases of it as I think Keiji was trying to point out. I don't think we've seen the

end of the year and we have had experiences in the past where the year starts out with one type of influenza virus and ends up with a second one and I can remember several years where it's been combined influenza A and B. I believe there was a relatively significant amount of influenza B activity last year, so maybe that wouldn't be true this year, but I don't actually know. So the fact that we're hearing about strains from Italy and this is information in just the last couple of days, I don't know exactly when the strains were isolated, but the fact that we're hearing about B/Victoria-like strains in a part of Europe where it hasn't been reported is a little bit-- I don't know how much activity there's going to be and whether that will give guidance in terms of epidemiology.

DR. DAUM: Okay, thank you. I'd like to, unless there are issues which haven't been touched on, haven't been thought about, haven't been raised, what I'd like to do is begin the process of asking each Committee Member, consultant and guest to reflect on each of the three viral components or if you wish, four viral components, but reflect on each of the serologies that were involved and addressing sort of the way Roland has set things up with what is your

opinion about what should be done about next year's vaccine composition, with the choices being to keep, to change or to defer. And once we get that process going we'll appreciate hearing from everybody on it and we'll call on everybody to speak to it.

So Dr. Kohl, did you have one last burning thing to say?

DR. KOHL: One last burning thing. I strongly want to reiterate what I believe most of my colleagues agree with, my colleagues on the Committee, that we desperately need pediatric immunogenicity data, especially as we move to new vaccine strains and potentially new doses of vaccine.

DR. DAUM: I think that this is something that everybody at the table seems to be in favor of doing and I think the message is very clear and I think that it should be clearly part of our record today that this group is strongly supporting the notion that Dr. Kohl is advancing.

Okay, so let's go. Dr. Manley, this is truly the last comment.

DR. MANLEY: Well, it's a question really. Do we need to hear from FDA about that statement and if there's anything other than making the statement that this Committee should do to assure that there

will be some action on this item?

DR. DAUM: That's a fair question. We'll ask Dr. Levandowski or Dr. Midthun or whoever from the Agency wants to comment, whether something else should be done or whether you've heard us.

DR. MIDTHUN: I think we've heard you and it's very important here that you feel so strongly about that and we will take it under advisement.

DR. DAUM: There you have it. I think that was actually well put.

So Dr. Stephens, you're up there. I can see you. Would you begin our discussion please and we'll hear from each person and we really want you to address each component of the vaccine and we're recording your opinions.

DR. STEPHENS: From this end of the table, things appear reasonably clear, moderately clear and murky regarding the three components of the vaccine.

(Laughter.)

I think that the data from my perspective suggests that for the H1N1 component, the A/New Caledonia/120/99 strain is I would think that that will be the strain for the vaccine. I think that for the H3N2 component that it's moderately clear. I'm a little concerned about some of the Chinese strain

information that we are still waiting on, that the A/Panama/2007/99 strain appears to be the component.

I'm really unclear about the B component. My sense of the discussion is that covering both the Victoria strains and the Yamagata lineage strain would be appropriate and I think a strong consideration should be made in that arena, based again upon the information presented today.

I will say that overall, I think we may be a bit premature in making some of these recommendations in the sense that the influenza season, I think it's already been emphasized, is early. There is an upcoming WHO meeting where additional data from additional laboratories will be available. Other world-wide data will be available. More information, for example, about the Chinese strains, so I think additional information in the next few weeks would really help crystalize some of our thought process, especially about the B strains and I think that's a summary, at least from this end.

DR. DAUM: I need, we need a little more from you. Sorry. I'd like you to sort to say with respect to H1N1 that you would keep the present component?

DR. STEPHENS: Yes.

DR. DAUM: And H3N2?

DR. STEPHENS: Keep.

DR. DAUM: And B?

DR. STEPHENS: Defer.

DR. DAUM: Thank you very kindly. We now have what we need.

Dr. Kim? Perhaps your swan song.

DR. KIM: Steve, I think he elaborated on the issues that I think, that I concur. I guess in addition to that, again, I think it's as we discussed, again including the manufacturing logistical issues and providing broad coverage and then lastly, we talked about perhaps having a consideration for different target populations such as immunologically naive for the antibodies that perhaps also may change the composition or target vaccines.

But based on the information that is available or presented today, I again, I agree the H1N1 will stay with the same and H3N2 more likely stay with the same, although I think additional data will be useful from China strains and B's concern, I think if there is such a thing, defer, because there are too many questions on the table that we are not clear at this juncture how to reach all those issues, resolved at this time.

DR. DAUM: Thank you very much, Kwang Sik. Dr. Kohl?

DR. KOHL: I basically concur with my colleagues which would be to roll now on the current H1N1, go ahead with that; to probably point toward continuing using the current H3N2, but to wait for the analysis of the Chinese strains in case there are any big surprises and to defer B, but expect that we'll need two different Bs and a quadravalent vaccine.

DR. DAUM: Steve, could you just run through that bottom line one more time for us? H1N1 keep or defer?

DR. KOHL: Keep H1N1.

DR. DAUM: H3N2?

DR. KOHL: Probably keep H3N2, but wait for the Chinese, the recent Chinese isolates to be defined better by Nancy and her group.

DR. DAUM: But that's defer?

DR. KOHL: Yes, that's defer. And to defer the Bs, but expect to have two Bs.

DR. DAUM: We got it. Thank you very much. Dr. Snider?

DR. SNIDER: I'll try, Bill, to get this in your categories clearly.

DR. DAUM: Well, please don't feel

constrained. You can make comments on any issues you like, but we do need those three things for Bill's sake and we'll read out the tally at the end.

DR. SNIDER: Well, I think we had a good discussion around a lot of these issues. I won't belabor the point. And I think I agree with my colleagues who have spoken before me, basically, but today I would retain A/New Caledonia/2099, the H1N1. I see no reason to change that and there are not that many strains around and not likely to be any additional information to make us want to change H1N1.

I agree that H3N2 is likely to wind up in the column of retain, but since we have a little time for your purposes, put it in the defer box, Bill.

DR. FREAS: Thank you.

DR. SNIDER: Because I would like to see the additional data at the WHO meeting. So that's that one. With the B, I think we all are struggling quite a bit. I definitely put it in the defer box, put it in the defer box. But I mean it seems to me that it's highly likely that we are not going to retain at least in my view, that we are going to have to change and the question is going to be what do we change to and it would be nice to have as much information as we can. We'll have to take it up to

that point, Sam, where we guess is the optimal point, make the best decision, have the most information, but not be too late to get the manufacturers in business to produce the optimal amount of vaccine and that can't be much after the beginning of March. So we don't have much time, but we can get much more information and make a decision about B.

DR. DAUM: Thank you, sir. Dr. Griffin?

DR. GRIFFIN: Well, I think for H1N1, that's quite straight forward, we should retain the New Caledonia strain.

I disagree a little bit about the H3N2 in that I think we should agree now to retain the Panama strain as well. There are several problems with suggesting deferral of that strain, a choice of that strain. Admittedly, it will be interesting to get more information from these new isolates from China, but we have to recognize we have no candidate strains for vaccine manufacturers. We don't have any reagents for changing that strain. We would then be talking about deferring two of the strains to very late in the manufacturing process and I think that since we have so little information that there is any need to change the H3N2 strain that I think we should decide today that that should be retained. Obviously, if some huge

epidemic occurs next week, you know, we would have -- we would still revisit that, I guess. But I would think that retain.

For the B strains, I think that there's personally good evidence that we should have a Victoria lineage strain in next year's vaccine and I think that -- I do agree that we'll probably have more information that points in that direction presumably, although possibly it would become dramatically different if we wa.ted, even another few weeks. And so I certainly wou..dn't disagree with deferring that decision. I think the big decision is whether we also need to have a new also Yamagata lineage strain. I'm not as convinced of that. What I am convinced of is that we do need to include this new -- the new Victoria lineage strain and the Shangdong looks like that that's a reasonable virus that manufacturers already have experience with and so therefore we would be able to produce a timely vaccine.

And the need for changing then and/or adding a new Yamagata lineage strain I think is a lot less clear. Whether that will be clear with more data, I'm not sure. What I think will become clear with more data is whether there's the sort of accelerating appearance of Victoria strains. And two

of these strains are from Hawaii, isn't that right? It's not just Europe, of the Victoria lineage strains? Were they from Hawaii?

DR. COX: There were a number of isolates from Hawaii during the summer and early autumn.

DR. GRIFFIN: Right, so it's not that it's not already in the United States. It's going to be here. I mean we can feel confident of that. So therefore I think personally we should make the decision that that's going to need to be included and to defer the decision whether we should also have this three or four component decision is the one that I personally would hope that we could go with just a three component vaccine.

DR. DAUM: So Dr. Griffin your bottom line today is to -- is what on the B?

DR. GRIFFIN: Defer.

DR. DAUM: Thank you. Dr. Katz, would you mind waiting for just a moment. I want to put Dr. Couch up next because air planes are starting to call.

DR. COUCH: Later flight out of Houston has been canceled. So I appreciate that and I'm not changing, differing a whole lot from here, but New Caledonia is an obvious. That one we retain. The H1N1. That's the easy one. It's the other two that

are not so easy.

Take them in the order that we had them up here. I would defer H3N2. And my reason for deferring H3N2 is that's the one, our biggest concern for hospitalizations, mortality. We've had Panama out there now. We've got it again this year. It's ripe for the change ,you see, and we might have had nothing and if we're getting it, it's just now emerging out of Northern China and the tracings are just beginning and so that one is so important and because we may be emerging into a need and an obvious change, why that one I would defer for those reasons alone.

The next one, I would have either a deferral or a vote for half and half. I cannot -- we must have B/Victoria, I think, and so the question is do we have B/Victoria only and take a risk that Sichuan was not needed at all? Well, if we defer, then the information may emerge there when everything comes in that well, that Sichuan is gone, you know. It's now B/Victoria and that decision could be made. So that would be my deferral. But I would be perfectly comfortable today with taking that 15 micrograms and splitting it half and half between Sichuan and a B/Victoria derivative.

So if the majority vote continues to go

for deferral, I think that would be the question, does B/Sichuan -- it's not B/Victoria has emerged. The question is did B/Sichuan disappear.

DR. DAUM: Thank you very much, Dr. Couch. Go safely.

Dr. Katz, now we'll come back.

DR. KATZ: I don't think I have anything new to add. I would retain A/New Caledonia as H1N1. I would agree very much with Dr. Couch on if we're going to defer, let's defer both H3N2 and B. I don't know again from the comments of the manufacturer how long we can wait when you give the roosters their Viagara and what the schedule is to produce eggs that don't age out too rapidly. But if we can, I would defer both H3N2 and B and I would retain H1N1.

DR. DAUM: Thank you very much. Dr. Diaz, looks like she stepped away from the desk, so maybe we'll go on with Ms. Fisher and we'll come back to Dr. Diaz if she does.

MS. FISHER: I will abstain and defer to the expert judgment of the other Members of the Committee and the FDA staff as to which strains should be included in next year's flu vaccine. However, in general, I do think there needs to be more data on immunogenicity and safety of new flu vaccine

candidates in children and pregnant women, if the flu vaccine is going to be recommended for them.

DR. DAUM: So I need to press you a little bit because I didn't quite understand. You said I'm going to abstain and defer.

MS. FISHER: I'm going to defer to the judgment to the rest of the Members of the Committee and the FDA staff to making the selection of the new --

DR. DAUM: So we're going to record you as abstaining?

MS. FISHER: That's correct.

DR. DAUM: Okay. I understand. Thank you very much.

Dr. Manley?

DR. MANLEY: Thank you. I concur in general with my colleagues, not all, but some, who have spoken already. I think that A/New Caledonia is very clear that we should stay with that and will vote to defer on the H3N2 and defer on the influenza B. And I'm not clear as to how we should go on that, but right now I think we should wait if we have the time and I'm getting the general impression that we have probably until about mid-March to get new information to make the decision on both of these.

DR. DAUM: March 6th might not be called mid by some.

DR. MANLEY: March 6th.

DR. DAUM: I think that's what we're getting is a follow-up. Is that correct, Dr. Levandowski?

DR. FREAS: All Committee Members should have a little orange sheet saying that March 6th we're scheduling a teleconference to follow up by phone on the results of this meeting.

DR. MANLEY: I see.

DR. DAUM: Defer comes back like a boomerang.

Dr. Griffin?

DR. GRIFFIN: I guess I want a clarification because -- and so the manufacturing time line was to have one that they could start in January, okay, they've got one day to do that. So in January we'll probably make one decision at least. Another one that needs to start in February and the third one to start in March in order to be able to produce a vaccine on time and so is there a mechanism by which a decision could be -- some kind of a decision could be made in February on one of these deferrals or is everything going to -- when we say defer, everything

waits until March 6 is my question.

DR. DAUM: We'll ask the Agency for clarification, but that's my understanding.

DR. LEVANDOWSKI: Well, I guess the basic answer is yes, that everything in the sense of looking like something on the outside is happening would be deferred until March, but the fact is that information would be collected and any pieces that would be useful to the manufacturers would certainly be sent on to them, including any strains that seem to be helpful to them, any reassortants that might be in the process of being made. We don't actually know -- because I haven't been in touch with anybody to know if there are some other reassortants that are available at this point. We might hear something like that from WHO next week. I mean any information that comes along and any useful tools for the manufacturers would be sent to them immediately. We would not be waiting to start to share information and materials for the next meeting.

DR. DAUM: But basically, we will reflect next on this issue March 6th. Isn't that correct, not before?

DR. MANLEY: Yes, but that is the basis of my deferral. Thank you.

DR. DAUM: Dr. Palese?

DR. PALESE: Yes. I am concerned that if we defer that there will not be enough time to really get enough vaccine doses and this is important for me that one will get the benefit of vaccine to as many people as possible. So therefore I would retain the H1N1 clearly at this point, also the H3N2 and with the information we have today, if the question is today what decision should we make, I would also go for retaining the B component because I'm not convinced of the data that the Victoria has reared its head at this point. So clearly, one can always change his mind, but if I'm asked today, to me the evidence is weighing towards retaining all three components, to allow enough vaccine doses to go out.

DR. DAUM: Well, I think it's fair to say we are asking you today.

DR. PALESE: Then I would retain, retain, retain.

Can I make just one other point?

DR. DAUM: Please.

DR. PALESE: And that has to do with the statistical analysis in terms of percent of all deaths due to pneumonia and influenza. I can't believe that suddenly we have, in effect, two different numbers

from what we had over the last 10 or 20 years and then there's a new sort of tweaking of the data and then it's only 30 percent of. Why don't we know how many people die of pneumonia and influenza? I mean this is somewhat disturbing. I can't believe that we can't get sort of really straight numbers. And also, that someone tries to help us to compare earlier data with the new data if there's really a compelling reason to do this. So I feel very uncomfortable with numbers changing by 100 percent suddenly because the statistical parameter gets changed.

DR. DAUM: Thank you, Dr. Palese. Dr. Diaz, you were out when it was your turn. Would you now like to step up?

DR. DIAZ: Thank you, I will. I had to answer a page. I wasn't in the restroom.

DR. DAUM: We didn't ask.

(Laughter.)

DR. DIAZ: Well, knowing how the Oscars go these days, I thought I would clarify. In regards to the strains that we have to pick today, I would agree with most of the colleagues that I've heard speak which is the H1N1 is fairly clear in my mind that we stay with the current strain.

The H3N2, I was prepared to consider

deferring more out of the concern of the severity of that particular strain and wanting to get the data from China as has been brought up and yet Dr. Griffin reminded me in her comments that we don't really have much on the horizon in terms of alternate strains available from a manufacturing standpoint. With that in mind and knowing that at least for that particular strain we probably have the most data at this point, I would vote to continue this coming year with the same H3N2 component.

The B strain, in particular though, I would likewise defer. I agree. I'm not sure deferring another month will give us a tremendous amount more data and yet it's the paucity of data completely that worries me about that B strain. And so I would probably defer and I agree that we probably will end up with a picking a B/Victoria-like strain for that component ultimately. I would have to have more discussion or be convinced about how effect a quadravalent vaccine would be and yet would defer those kinds of discussion for more data.

DR. DAUM: Thank you, Pam. Rich, Dr. Whitley?

DR. WHITLEY: Yes, I'll preface my vote by saying that from a public health perspective I think

the worse thing in the world would be to have the vaccine appear in the public domain late, especially after the events of the last six months in this country and the concern about bioterrorism. If that happened, it would be horrible.

So I do think decisions needs to be made as quickly and as appropriately as possible, based upon the soundest medical information that's available. So my vote for H1N1 is to keep it. My vote for H3N2 is keep it. I see no alternative strain that's immediately available and I don't see a change in the epidemiology which would alter that position and for B, I would defer two weeks, three weeks, but you can't defer past March 1, if the industry is going to be able to produce these vaccines and make them available to the public by the fall. And I would just point out one other opportunity that CBER and its colleague at the NIH, namely, the Division of Microbiology Infectious Diseases has and it goes back to looking at the behavior of these vaccines in children, there is the opportunity to collaborate with vaccine treatment and evaluation units and that should be capitalized on as an inter-agency collaboration for children.

DR. DAUM: Thank you very much. Dr.

Faggett?

DR. FAGGETT: Thank you. Again, I go on record as applauding increased involvement in children as well. In coming out of the DC experience immunizing of school kids, I am really concerned about the urgency of the matter and I vote to keep New Caledonia/2099, H1N1. For the H3N2, based on that sense of urgency as well as unavailability of a new candidate strain, I think we should keep H3N2. Again, we still have the opportunity in our March 6 meeting, if something comes up at that point, we could possibly comment again, but I think at this point we should keep H3N2 and for the influenza B candidate, I would defer at this time.

DR. DAUM: Thank you very much. Dr. Goldberg.

DR. GOLDBERG: I would retain the New Caledonia for the H1N1 for all the reasons that my colleagues have given. I would retain the H3N2 since I don't really see any viable alternatives in the short run. And for the B, I think we have to defer it, but I don't know how much more we're really going to have. I mean my gut from the data that we're seeing today is that we do need to consider the Victoria strain very seriously and then we're into the

quadravalent issue which I think we'll have to discuss at length, pending, hopefully the new data will clarify this.

DR. DAUM: Thank you very much. Dr. Eickhoff?

DR. EICKHOFF: I came down just about where Dr. Griffin came down. H1N1 retain, H3N2 retain, B defer. Now having said that I'd like to make just a few comments about the B issue. One, I am not one of those in favor of a quadravalent vaccine. I think we sacrifice immunogenicity to the point of being on the marginal side if we do that, unless we go to 15 mics each and then we affect timely delivery of vaccine and we affect the total number of doses that are likely to be made.

Two, I think we will be moving to a B/Victoria strain rather than one of the current strains.

Three, the consequences of making a wrong decision with an influenza B candidate are really nowhere near as grave with influenza B as they are with influenza A, particularly H3N2. Influenza B is not a huge cause of mortality in the elderly, not a huge cause of morbidity in adults. I think the target population to use Dixie's argument earlier, the target

population for whom B is in the vaccine in the first place is really high risk children. That's the group we're most trying to protect with the influence of B component.

I think that's all.

DR. DAUM: Thank you. Dr. Dowdle?

DR. DOWDLE: Well, we seem to be on a trend here. I would vote to retain H1 and retain the current H3. I would support deferring on the B, however, I would like to join Ted in urging caution about considering a quadravalent vaccine. I think we have to be very careful about doing that and if that's being considered, then I think the pros and cons have to be very carefully laid out in the scientific data supporting that decision, because it is precedent setting. It's been done before, but it certainly is precedent setting from the last two years of vaccine decisions. So it's not something that should be made lightly.

DR. DAUM: Thank you. Dr. Poland had to leave, so Dr. Myers, I think you're our last person up there with a vote.

DR. MYERS: For the H1N1, I would retain the New Caledonia, the H3N2, the A/Panama, but I concur with comments of several people made that we

ought to watch that very closely.

DR. DAUM: Marty, can you speak into the mike?

DR. MYERS: I'm sorry, we can always reevaluate later, but I think you need a vote today, so I would vote to retain the H3N2 as the A/Panama.

On the B, I think the data that we've seen today, particularly what Nancy showed us suggests that we need to include a B/Victoria strain, but I thirk the -- I mean we need to include a B/Victoria strain and I guess the point I'd make on deferral would be I think the only decision that I would recommend that we defer on is whether we need to consider a fourth strain or not. But I would go with the B/Victoria now.

DR. DAUM: So is your B issue a --

DR. MYERS: A B/Victoria strain.

DR. DAUM: B/Victoria now.

DR. DAUM: Okay, good. So there are three things left to do. One of them --

DR. FREAS: Could we get the industry opinion and your opinion before we change the topic?

DR. DAUM: I wasn't going to change the topic, but we certainly have industry representatives' opinion.

Dr. Decker?

DR. DECKER: Had I a vote it would have been keep, keep, defer. Not even having a vote, I still offer the comment that I'm delighted to see that the vote has ended up being 11 to 5 if I counted right on the H3N2 keeping because every deferral is a risk, every change is a risk and there's only a certain number of risks that we ought to take in a year if we can help it.

I would think that if we were changing H3N2 that that would then constrain our options with respect to B. And I think it's much more clearly important to retain options on B. But we're deferring on B is the question of which strains, how many strains and if we have two strains, how many of those strains will be new strains which is more than enough to defer to create headaches for production.

So I think it's doing the right thing to defer and is the right thing to defer only that one.

DR. DAUM: Bringing things on home, what we will have now is I will vote and Bill will announce the results of the vote. Then Bill Egan will make a comment from FDA's perspective orienting us toward a March discussion, then we will have an open public hearing and then we will adjourn.

So with that last four items in mind, I vote to keep the H1N1. I think there's unanimity on the Committee on that issue. H3N2, I would love to hear more data in March, however, I'm very persuaded by Dr. Griffin and the many others who made the point that the candidates aren't there and the need to give as close signal today as we can is there. So I vote to keep H3N2 the way it is, but I sure would like to hear more data in March if there is some. And the B issue, I think is a heavy one and I think it's very clear from the discussion and the learned points of view that were exchanged today that the B/Victoria needs to be part of this, but whether to have two B components or just go with one is the difficult question and I'm hoping that we're not compromising industry by waiting until March and I'm hoping that Roland and Nancy and their colleagues will have some light to shed on this topic by March. So I'm going to defer on the B issue.

I also would like to encourage Department of Defense presenters and others, CDC, perhaps NIH, BTEUs, although I hadn't thought carefully about them in that role, to gain more information for us about how these vaccines are performing. I feel like a bit of a broken record saying this over and over again,