to year, a supplement to each manufacturer's biological license must be submitted to and approved by the FDA each year. The license supplement includes changes to the vaccine product labeling, such as updating the trivalent formulation with the new strains. Large scale packaging of the influenza vaccine does not typically begin until this approval is received in the early-July time frame.

This next slide depicts a typical time line for trivalent influenza vaccine manufacturing. There is an arrow listed here signifying the time frame of today's meeting, the strain selection meeting.

The overall time line, as I mentioned previously, for influenza vaccine is based on the requirements to produce, and release, and distribute vaccine in time to support immunizations for the upcoming influenza season.

The desired time frame to begin distribution of vaccine is beginning in early-

August with completion in early-November, as depicted by the yellow bar on the time line.

The past several seasons have been an exception to the typical timing in that distribution of vaccine has extended late into November, actually even into December in several years.

In late-December to early-January of the preceding year, time frame today, manufacturers typically begin production of the first monovalent strain at risk. This risk that the monovalent strain that is under production may not ultimately be selected in the upcoming formulation. Production at risk is necessary because the time to produce the monovalent component lots are limited. Again, as limited at the beginning at the time of strain selection and limited at the end by the need to be able to distribute and administer the vaccine prior to the onset of the influenza season.

Thus, at the time of the mid-

February VRBPAC strain selection meeting, manufacturers are looking to begin production of the second monovalent string. Assuming the availability of an appropriate production seed, manufacturing of the second strain typically begins immediately following the strain selection meeting.

Due to the later scheduling of the VRBPAC strain selection meeting this year, several manufacturers may have already started the at-risk production of the second strain or risk over-production of the first strain that they had underway.

This time line depicted here is based on the fact that there would be one strain change, which is listed as strain 3. Prior to beginning the production of the third strain, the high growth reassortant would first need to be developed, and then manufacturing working seeds would be developed form that reassortant.

Please keep in mind that the

development of a working seed for manufacturing typically requires four weeks from receipt of the reassortant at the manufacturer.

The final stage of production of the monovalent lots involves strain balancing, in which manufacturers are targeting the production of an equal number of dose equivalents of each monovalent string to support trivalent formulation. Balancing is required due to the difference in yield, per lot, of each of the monovalent strings.

There are about 30 weeks available from the beginning of the year until the early to mid-August time frame when the monovalent production would need to cease. The time that manufacturers produce at risk is typically six weeks, the timing from the beginning of the year until the typical timing of the mid-February selection meeting. So the at-risk production time is 20 percent of the overall time that is available to manufacturer the

monovalent components.

If manufacturers were not able to utilize this at-risk time, this 20 percent, the overall vaccine manufacturing capacity would drop by 20 percent. So, for example, assuming an industry capable of producing 125 million doses, that would be a 25 million dose reduction from overall capacity if this at-risk time were not able to be utilized.

In parallel with the production of the monovalent component lots are the activities related to trivalent vaccine formulation, filling, packing, and release. The most critical element involved in this timing is the preparation and standardization of the potency test reagents for a new strain.

The preparation of the potency test reagents again typically requires between 8 and 12 weeks and begins once a seed is available for the new strain. Formulation of the trivalent vaccine begins following standardization of the potency test reagents,

which is then filling of the vaccine into vials and syringes. Typically, a target for beginning trivalent formulations is early-June.

Following approval of the Biological License Supplement, packaging of the vaccine begins, and typically in early-July. And following final release of the vaccine, distribution of the vaccine would begin in early-August.

The greatest challenge that manufacturers have had is achieving this time line. Specifically in the past several years it's been related to when trivalent formulation can begin. The last year which manufacturers were able to begin trivalent formulation in this desired early-June time frame was 2003. Due to numbers of strain changes, availability of test reagents, or low yield, this has been delayed to the mid-June to actually early-July in some years, which has pushed out the time frame for vaccine

distribution.

And please keep in mind this is a typical or desired time line. The time line again for each individual year will depend on the number of strain changes, the yield of each strain, as well as the timing for preparation of potency reagents.

The next slide provides an update of current manufacturing status. As previously mentioned, due to the limited time frame that is available for production of the monovalent components, manufacturers have chosen to begin at-risk production as soon as or at the beginning of this year.

Again, by manufacturing at-risk, prior to strain selection, manufacturers gain additional time to produce the monovalent component lots. In past years, manufacturers have chosen to produce the A H1N1 New Caledonia strain at risk. But with the greater potential of this strain changing in this year's formulation, manufacturers have

had to select a different strain.

Based on the surveillance data available at the beginning of this year, the manufacturers of the inactivated influenza vaccine have chosen to produce the A Wisconsin strain at risk. MedImmune has recently begun production of the B Malaysia strain at risk.

And again, based upon the timing of this years strain selection meeting, several manufacturers may have also had to begin the production of the second strain at-risk, or risk overproduction of the first strain.

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

A tangible example of these results are the increased availability of egg-isolates and high growth reassortants, which manufacturers are able to evaluate for potential growth characteristics of strains that might be antigenically similar but do have significantly different growth characteristics in large scale manufacturing. And I believe Dr. Cox had presented some of that, some of the data listing the increased number of isolates that have been available in recent years.

Another very tangible example of this was during last year, when the initial yield of the A Wisconsin strain was perceived to be very low. And obviously that would have an impact on vaccine supply. New York Medical College very quickly developed an approved reassortant. That reassortant was reviewed and ultimately approved, and it was able to be phased into manufacturing. And a whole new set of reagents were produced in a record time

to ensure the nation's supply of influenza vaccine in 2006.

So, in summary, it is necessary to consider the various factors, such as the appropriate selection of strain, based on antigenic and genetic match, as well as the availability of C-candidates and high growth reassortants in order to best ensure the supply of the influenza vaccines.

And once again, I would like to thank the Committee for the opportunity to present the comments from manufacturers at today's meeting.

DR. KARRON: Thank you, Mr. Thomas.

Questions?

DR. JACKSON: I wondered if you could comment on how production of thimerosal free or reduced product interacts with your time line that you showed us?

MR. THOMAS: Sure. This may be different for each specific manufacturer, but

particularly the example of no preservative formulation for Sanofi Pasteur is essentially the same time line, however we are not adding the preservative. The biggest constraint for the no preservative formulations are that they are filled into unit dose vials and syringes. So it's primarily a filling constraint, both from the capacity point of view as well as the timing. For example, filling multi-dose, 10-dose vials, you could essentially fill the equivalent of 10 times the number of doses in a given time than you would for unit dose.

So the time frame is similar, however you are limited on how quickly you can fill and package the product because it's in a unit dose or single dose presentation.

DR. KARRON: Thank you, Mr. Thomas.

MR. THOMAS: Thank you.

DR. KARRON: Next, Dr. Pandey will present the strain selection options.

Excuse me, Dr. Pandey, I

apologize.

There is, next on the agenda is an open public hearing.

Christine?

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

I have not received any requests at this time.

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

I see no response.

Dr. Karron, I turn the meeting back over to you.

DR. KARRON: Okay, Dr. Pandey, now it's your turn.

DR. PANDEY: Thank you.

Now, I will be presenting the

options for strain selection for 2007-2008 season influenza vaccine.

As the Committee has heard before, there are implications of strain selection, both in terms of vaccine efficacy and availability. If the recommendations match the strains that will likely circulate in the given season, then there will be a great benefit to the public health. However, if the recommended strain well for the manufacturers, we may not have enough vaccine available for use or there might be delays.

So, as you can see on this slide, despite two strain changes last year, the vaccine production went pretty well and the vaccines were available almost on schedule.

The supply of the vaccine, despite these two changes has, as in the previous presentation you heard, that we had a record 110 million doses available. And it shows that it definitely met or exceeded the demand.

So we must applaud the

manufacturers for a job well done considering all the problems one can face when there are more than one strain changes.

And now coming to the options for the vaccine composition, for Influenza A H1N1, we can retain the current vaccine strain recommendation, which is in New Caledonia 2999 like virus.

Or the other option could be to replace the current strain with the Solomon Island/3/2006 like virus, as the WHO has recommended.

Or the option could be to replace the current vaccine strain with something else, another alternative H1 isolate.

Now, of all these three possible options there are pros and cons.

The advantage of keeping the current strain, obviously, is that manufacturers have worked with this strain for years. They have the reagents available. But then the disadvantages of keeping the current

strain, obviously, we have heard that it is a poor match.

So then the option for A Solomon Islands, if we were to switch to that, the reagents are going to be available in May. The manufacturers have already gotten some experience with this vaccine, and based on what I have heard, that it is reasonably, it goes reasonably well.

And we don't have another option at this time, I guess, for if we were to change to a different strain.

Now, the option for Influenza A H3N2. Again, we have the similar options. You know, either we can retain the current strain, which is A Wisconsin/67/2005 like virus, replace with an alternative H3N2 isolate, or another option that manufacturers definitely don't like is to defer the decision to a later date, in case there is more data going to be available in helping make that decision.

So, if the recommendation again, as I said, is to retain the strain, we have the reagents available and we have the manufacturing experience.

But if we were to change the recommendation to another strain, the availability of reagents is an issue that won't be, as Galina mentioned before, it won't be available before May.

For Influenza B, either we can retain the current B/Malaysia/25/06/2004 like virus, which is of B Victoria 287 lineage, or our other option could be to replace it with an alternative virus from B/Yamagata/16/88 or B/Victoria/2/87 like lineages.

Now, if you were to retain the B/Malaysia like virus, which was in last years recommendation as well, and also has been recommended to be retained by WHO, we have the experience with this strain and the reagents are available.

But if we were to change, then

currently there are no better strains available and the availability of reagents could also become an issue, and also how it would out for the manufacturers.

So, finally I come to my last slide, which is basically the question every year for the Advisory Committee is that what strains should be recommended for the antigenic composition of the 2008, 2007-2008 influenza virus vaccine based on the epidemiology and antigenic characteristics of the influenza virus strains circulating in the human population that the committee has heard, the serological responses to circulating influenza viruses of persons immunized with the current influenza virus vaccines, which was presented earlier, and also the availability of suitable vaccine candidate strains, which also the Committee has heard.

So I'll turn it over to Dr. Karron.

DR. KARRON: Thank you, Dr.

Pandey. At this point I'll open it up for discussion.

But I actually want to ask one, can I ask you one specific question, which is, if you go back to your H3N2 slide and you talked about the possibilities being A/Wisconsin or something else, would you, based on the data you've heard, if there were a something else, would you think, for example, it would be a Nepal-like strain?

DR. PANDEY: Well, that definitely came up as a possible, you know, option. But I don't know at this time and I think that's for the Committee to discuss if that could be a good option.

DR. KARRON: Thank you.

So at this point I'd like to open the strain selection up to discussion, questions, and if there are additional questions for Dr. Pandey or the manufacturers.

Everything is very -- oh yes, I'm sorry.

Dr. Wharton?

DR. WHARTON: Given that we now have a number of, we've got the wonderful privilege in the United States now of having multiple influence of vaccine manufacturers producing for the U.S. market, but some of them do not exclusively produce for the U.S. market. A couple of them do have major production facilities outside this country. And presumably those production facilities are not only, will be having to deal with recommendations from other national authorities. What is the impact of that on realistically if this Committee were to make a recommendation different from the WHO recommendations on how we would get vaccine from those facilities that have to deal with potentially two different sets of recommendations?

DR. KARRON: So this is a question for the manufacturers?

MR. THOMAS: Maybe I can sort of

answer and maybe some of the other manufacturers would also like to participate. But a selection of two, for example, H3N2 strains, different one say for the U.S. and possibly a different one for the WHO recommendation would be extremely difficult. Manufacturers who produce vaccine for several markets would have to produce four strains. So there are inherent inefficiencies in doing that. The overall number of doses of vaccines would be reduces, as well as the additional complications of preparing another set of reagents and having to test the different strains. So that would have a significant negative impact on vaccine supply.

And I'd also like to point out with the discussion here of the H3N2 that there is currently no other production seed currently available other than the A/Wisconsin/67. I know there was a potential there for evaluating another strain, but currently no other seed exists today.

DR. KARRON: Thank you. Yes?

DR. MCINNES: So, I think I heard that it would be very difficult but not impossible. And I'd like to probe a little bit more about what would be the feasibility of actually getting a high growth, or using a high growth reassortant for H3N2 that could be used for production. And I don't know who wants to comment on that.

DR. COX: As soon as we realized that the so called Nepal Canada group of viruses was increasing, we went back and looked and found that we had a Nepal egg isolate, which didn't grow particularly well during initial passaging. However, on subsequent passage it seemed to pick up a little bit. That virus has been distributed to a number of individuals, including to Doris Boucher at New York Medical College. And I know that she's been working on making a high growth reassortant for that particular virus. Of course we have no idea how it will grow or

what its antigenic properties will be because, of course, after going through a number of passages to select for high growth in eggs, we often do see changes. So I think there are a number of unknowns. But maybe Doris would be willing to make some comments about when the high growth reassortant might possibly be available to distribute to manufacturers.

DR. BOUCHER: I can only say it's under development. So far everything is proceeding according to plan, but we don't have it as of now. We are trying, we would like to ship it off to the CDC for them to begin analysis next Wednesday, a week from today. But we don't know what will happen with the testing. And as Nancy said, we don't know how it's going to grow.

DR. KARRON: Nancy, I wonder if I could ask you to comment on some of the ferret antisera data, Nepal, and the Wisconsin strains, and the differences that you see. And some of these are the tables that we

looked at, in trying to discriminate between the Nepal strain and the Wisconsin strain.

DR. COX: Yes, I think that the H3 table in the CDC package is actually fairly instructive. We were hoping to see a different pattern. That's on page 19.

What you see here is the Nepal antiserum on the right, which has been made to an egg grown virus. So that was the virus that was sent to Doris to make a high growth reassortant. As well as antiserum made to the Canada/1212, which is a cell isolate. So we tried to control for the fact that, you know, sometimes you see a little bit different results for cell and egg-grown isolates that are genetically similar, or at least in the same general and genetic group.

And what we see, if you look down the rows, if you compare the Wisconsin/67 wild type titers, as you look down the table, and then the Nepal, the titers against the Nepal and Canada/1212, you will see that you have

the same viruses being low reactors for all three antisera.

So you may get a two-fold higher titer for the Nepal and Canada antiserum, but you still get the same low reactors. And so that has been the real issue.

And as I mentioned in my talk, there have been some studies done that indicate that the receptor binding pocket of the H3 viruses has evolved. And of course the shape of the receptor binding pocket can have an impact on what you see in an HI test. So antibody could still be binding to the hemagglutinin, but not inhibiting the, if the pocket is lighter, not inhibiting the ability of the virus to agglutinate to red blood cells.

So I think that what we are going to be doing in the future with the H3 viruses is to look at virus neutralization tests for a small number of viruses. It's a very labor intensive test, but I think it might really

help us to discriminate exactly what is going on here.

DR. KARRON: Right, so I guess also to summarize what you're saying, we don't really see a difference in, or much of a difference, more than a two-fold difference when we look at the HI test, Wisconsin and either the Nepal or the Canada strain?

DR. COX: That's correct. So we were hoping to see that the Nepal and Canada antisera would cover the viruses that are in the same genetic group better than the Wisconsin virus does. But really there doesn't seem to be that much difference.

DR. KARRON: Right. And there's certainly, going back to some of the human data, there's certainly a difference when you look at the human sera. But I would think that the problem is really that we don't have the reverse experiment in humans. We don't know what would happen if you immunize a person with A/Nepal or A/Canada strain. We

don't, we of course don't have that information because that's not what we do. We can only look at responses once you vaccine.

Yes?

DR. FARLEY: As a follow-up to that, is there a way of, because I guess if I'm reading this correctly, the Canada and Nepal cross-protect for each other that they seem to have, am I reading that correctly if you go down further? Now, I guess the question is, is there a way of knowing among these low-reactors what proportion the burden of disease that is taken up by Canada and Nepal isolates as opposed to these various others that are listed here, with mostly U.S. designations?

DR. COX: We, because we really can't discriminate between viruses that are in the Nepal group and in the Brisbane group using the antisera that we have, we've done a lot of sequencing. And so, what we're seeing, I think I mentioned, so for the 91 H3N2

viruses that have been sequenced, and those are viruses collected since October of 2006, we found that 48 percent were in the Brisbane group and 45 percent in the Nepal group.

So we're seeing an almost equal distribution of viruses in those two groups. And it doesn't seem, it, I would say that the Asian viruses are predominating in the Nepal group. But that, for example, there was a fairly, the National Influenza Center in Seoul, Korea had sent us quite a number of H3N2 viruses from an outbreak that occurred in November and December. And those viruses were distributed in the two groups. So even if you look at a particular country you can see that viruses fall into both the Brisbane and the Nepal Canada groups.

DR. KARRON: Dr. Couch?

DR. COUCH: I would, if you permit, I think it's probably worth pursuing H3 because that's the one that's bothering us. We started there and Dr. McInnes indicated

that we've already heard that follow-up too. If you look at the ferret sera and the H3 strains, you know, there's no big differences there anywhere, as Dr. Cox has pointed out. If you pick all these various isolates now, you can say well, you know, it looks like there's maybe a little shift toward the right side over there of which Nepal can just be one example.

So I make my little chart each time on this one, so antigenic change I ended up saying well, probably zero here. No big antigenic changes we can hang our head on, you see, as part of the decision making. Epidemiology always comes with a question mark and wait to see what Dr. Couch tells us. And we had no major problems with H3 anywhere in the world so we don't have the benefit of viruses that dominate in an outbreak that would help us decide that one is about to move there.

And then the final one I always

look at is the human sera. And the human sera results for H3 is quite bothersome because some of those strains that are out on that side there's not very much in the way of cross-reactivity. And Dr. Ye pointed out, you know, that the reduction that you deal with GMT's for the H3s, with these various laboratories, is comparable to the H1, which is a little bit of a discussion item, but less so maybe than this one, you see.

And the final statement to make at H3, around this table and every time we do this, you know, that is the most important decision we make because that still is clearly the most common epidemic virus with the most, the most serious impact against humans, with attack rates and in hospitalizations and disease.

And so I came around here bothered about the Wisconsin decision that we were told had been made by WHO, but we all accept the fact, the position that was pointed out to us

by the industry representative. If we talk about doing something different, we are really tampering with vaccine supply and perhaps significantly. So I feel like we're in a bind here this year on H3. And some other people may want to comment on that as well. That one is my tough one.

DR. KARRON: I'll say that I am particularly bothered by this sort of discordance, if you will, between the ferret sera and the human sera. And I was wondering do you want to comment on that, Bob? Does that bother you too?

DR. COUCH: The differences between the two? Yes, that bothers me. I mean I think a ferret, you know, if I want to try and biologically do something with this, I say well let's look at, and you've expressed here, let's start seeing more pediatrics here. Because if we say those ferrets are helping us differentiate these, then the most comparable individual for humans, which is our primary

interest not the ferrets, is going to be how those children do. And the children, what we have this year, their Wisconsin antibody didn't like the strain either. So the ferrets maybe didn't agree with the children very well here. Now, so what data do you like for your decisions? I like to see them all fall into place, but maybe that represents what I do and my strongest interests. I want to be sure those antibody responses to that antigen cover the ones that may be coming out in the future in humans. I'm a little more concerned there than I am whether the ferrets manage to pick up a difference or not. But we'd like to see both of them.

DR. KARRON: John?

DR. MODLIN: Right. Ruth, I don't think I got an answer to my question earlier, and that is the age range for the pediatric sera. I mean it's a big difference whether they are two-year-olds or whether they are nine-year-olds.

And it may be that is the entire range, but Dr. Ye, do you know what the age range for those panels?

DR. YE: Yes, the age range is 6 months to 36 months. So they are quite young.

DR. MODLIN: Indeed, as Bob said, they could be very useful, particularly if we had larger numbers. So I think the recommendation might be, you know, in future years if we could look at a larger number of pediatric panels that would help, at least with this particular conundrum.

DR. YE: Yes, I think this year, normally we send this to CDC ourselves, so probably we should send it to different centers to give, you know, more confirmative data from it. We're limited to the limits of this sera sample, so sometimes it's harder to share with other centers.

DR. KARRON: Pamela?

MS. MCINNES: We started a little bit of this discussion at the break, but I

need to, I'd like to look at page 23 in the CDC. And I need to just have somebody explain this to me. So the A/Wisconsin was our vaccine strain, right? And the A/, wasn't A/Hiroshima an alternative?

DR. COX: Yes.

DR. MCINNES: So I'm confused about the data.

DR. COX: Oh, this is a different Hiroshima.

Thank you.

DR. COUCH: I'm with you. I looked at it on the chart. It's right next to Wisconsin, Hiroshima/33, so I assumed that was the same one we were talking about last year. But I had the same problem with that that Pamela is talking about.

DR. COX: It's a 2006 strain. And in the old one was a 2005, so there's something wrong with it.

DR. COUCH: Something wrong with it?

DR. COX: Yes.

DR. COUCH: I see, okay.

DR. COX: Yes.

DR. COUCH: If you look at table 21, I think Sasha has got it. Hiroshima may not be 33, but down at the bottom lists the, should've been 2005. It's a different Hiroshima.

DR. COX: It's an old, the one in the vaccine is an older strain.

DR. MCINNES: So I can be just a little less worried.

DR. COUCH: I hate to tell you how long I spent worrying about that particular one.

DR. COX: I apologize.

DR. KARRON: Is there more discussion? Are we ready to select our strains, as ready as we're going to be?

(No response.)

Okay, I'm going --

DR. MODLIN: Ruth, I'm sorry.

Just maybe a little bit more discussion about the H1 strain and then the recommendation for a WHO. I mean it sounds like to me that the experience here in the U.S. is a little bit discrepant from what the rest of the world has been this past year and so it's easy to see why the WHO made their recommendation. I guess we haven't had any discussion about what this really means for us for next year. My assumption would be that it would be presumptuous to think that we were going to experience the same H1 activity as the rest of the world is over a period of time, at least that one could predict, they would be more likely to predict that. But we haven't had that discussion and I would just be interested to what other people think of that.

DR. KARRON: Nancy?

DR. COX: I think what we have to take into consideration is we've had a predominantly H1N1 year this year. So that, generally speaking, brings up the antibody

levels in the population. And so, we hadn't had so much H1N1 activity before, so just in looking at what might come next, I think it's more likely to be something different next time.

DR. COUCH: Do you want to talk H1? I've got my table on H1. The ferret data here said we've got different viruses. And so I was waiting for the epidemiologic data on that one, and it's a U.S. epidemic. It's, you know, scattered around a little bit in Asia, but presumably it's different and the antibody results are erratic. Instead of a yes and a no that New Caledonia was the highest growth, and I might of gambled on keeping that one. But WHO voted to go for another one, you see, and I said well, we had a significant year and Influenza A viruses drift. And we've got pressure, as Nancy said, you know, that we have to have some drift coming up here. So H1 has got to change, if not the coming year the following year. And New Caledonia has been

there a long time.

So I rationalized my way into a week support for changing H1.

DR. KARRON: While you're at it Bob, do you want to comment on the B? There's not too much probably to say there?

DR. COUCH: B's are actually easier. Maybe if somebody wants to redo it after we have our discussion this afternoon that might be different, but no, no discussion on B, no problem.

DR. KARRON: Pamela?

DR. MCINNES: So let me return to the H3N2 dilemma and also I am very troubled by the sort of lack of concordance, the comfort that we have that the ferrets are compared with the human serum. You know, we can say well maybe the HI test is not the best way for us to do this, but in effect, the reality is we do have, I think, some troubling data here. And the question on the table would be, I'm aware of what WHO Committee

recommended, I'm going to throw out the idea of two H3N2s.

DR. KARRON: Nancy?

DR. COX: I think that it would be wise for us to have comments from the manufacturers about that.

MR. THOMAS: I guess some of the questions would be, initially, what would it replace, first of all? And again, we're into the same is this a, how different of a product is this from the licensing aspect? Does this require clinical trial, that whole aspect. So there are a lot of questions on defining what the product actually is and ultimately deciding is it the H1 strain that is removed and there are two H3s. I'm assuming it's still a trivalent formulation, based upon the question. So I think there are a lot of questions on definition of the product, licensing aspects.

Now, specifically for the manufacturing point of view, the concern that

I mentioned before about manufacturers producing the A/Wisconsin at-risk, obviously you would alleviate that because a lot of that product is already produced, but we're still introducing another H3 strain that today a production seed does not exist. There is no yield date available for that seed, nor do we have a definitive time line of when that see would be available, which could impact overall vaccine supply as well as the timing of when reagents could be prepared and when vaccine would ultimately be available for distribution.

DR. KARRON: I was just going to say sort of back in response, I'm, what's troubling me the most is I don't, is trying to understand low responders and what those viruses are, and what it means, and how we interpret the tests. I think despite all the manufacturing caveats, if I had seen that there were really good responses to the ferret, the ferrets had very good responses

and they were clearly these were very different viruses I would've said, you know, maybe we should be postponing our decision until March until we have, until we know if we can get an isolate that represents the H3N2 strains. My concern in looking at this data is I don't know that a new H3N2 strain would do better. And if you gave that to children that that would induce a better HI response, or whether there is something about these low responder viruses that's different and that we have the, you know, we need a different test to really understand this.

So that's what's, that's what I think is troubling me the most.

DR. COUCH: And I would hope that when you do those HI tests that you've got controls in there to indicate that you're not dealing with a low responder antigen. And when you run these HI, these HI batteries, see we don't have all these ferrets here in my lab.

DR. COX: We have controls.

DR. COUCH: But you're suggesting a low responder. I would think that ought not be a question of the --

DR. KARRON: But if you give a ferret A/Nepal and look for their HI titers to A/Nepal, they're relatively low. Correct? I mean there's something about this virus that induces low levels of antibody as we currently measure them in HI tests.

DR. COX: Actually, Nepal does find, there are some viruses that are, will give you a homologous titer of 80, and that really indicates to us that that's a low avid virus. But these viruses, both Nepal and the Canada/1212, when put into ferrets, elicit titers of 640 or so. So I think that we have sort of the, we really have a contradiction in the data. And I honestly have wrestled with this and have lost sleep over this data, these data.

DR. COUCH: I thought you were

talking about the humans here not the ferrets here. Because the ferrets here, I've been hearing problems with them.

One more and I quit. And you can end up, the antigens don't all agree. I mean that was part of, somebody talked about the HI yesterday. But we've got three of them for H3, Santiago, Canada, and Hiroshima and they're uniform. That's, see, if you look at the H1 data there's an erratic one in there every now and then. I can bypass erratic results, but all three of them?

DR. MODLIN: Could I ask a very basic question, and I'm embarrassed I don't know the answer to this. But for a particular antigen, if a human already has a high titer of antibody and a relatively high titer and receives an inactivated antigen, how much of a boost do we expect, or does that high titer actually inhibit a boost like it does with other inactivated antigens? And if that's the case, then it seems to me that if we have a

discrepancy between our animal sera and our human sera that perhaps the human data may be a little less reliable in terms of making these types of decisions. Am I way off base, Bob or Nancy?

DR. COUCH: One of the things you'd like to know to fully understand the data, which is maybe what you're driving at, is I would like the battery to each time say is that the same group of individuals? Were they vaccinated last year? And the industry might not prefer that, but I'd like to know which of those vaccines they received as well. Because if you look at some of the data, I don't mean to be picking on my friends, I worry about some of those antigens in the Japanese vaccines, if you just look at the comparisons of the battery of sera there. But we don't know that, you see.

And your point would be that if they're already high from Wisconsin and you re-vaccinate them and they're high, then

you're going to have less likelihood of finding a cross-reactivity to one of those other strains.

DR. MODLIN: Exactly.

DR. COUCH: I guess I think that's probably correct but I don't know that for sure.

DR. KARRON: Zhiping?

DR. YE: Dr. Couch already answered the question.

I just want to comment on that. Because of the serum in humans, especially for adults, previous years may expose them to the same antigens or different antigens, so their responses is kind of order than the children's one or the ferrets studies.

DR. COUCH: You could follow that up with saying well if that's the case and that antigen does change, we want that new antibody and we better give him that antigen to get it.

DR. KARRON: Dr. Eickhoff?

DR. EICKHOFF: A question for the manufacturers. Would, if we try to put 60 micrograms of hemagglutinin in a vaccine, wouldn't that automatically equate to a 25 percent reduction in the amount of vaccine available?

DR. HETHERINGTON: Yes, I think that is the point that there is a maximum capacity for total antigen that gets produced in the U.S. And you can cut it up anyway you want to, but a trivalent vaccine you get "x" does and quadravalent vaccine you're going to get 25 percent less. And also the increased risk of delay in production because you have yet another antigen, another seed stock you need to get up and go, so timing is at risk as well. So you're really taking two hits on going to a quadravalent vaccine.

DR. KARRON: But as maybe a follow-up question, you can answer both of these, Mr. Thomas, is what percent of the vaccine produced this year did we actually use

total, of the vaccine that was made available by manufacturers because we have increased our capacity significantly.

MR. THOMAS: So the first question regarding the increased formulation, the answer exactly would be an equivalent to a fourth strain, in terms of monovalent requirements, so you'd have that 25 percent decrease.

And I'm assuming the question for a vaccine that wasn't administered, was produced last year in this current season, the biggest impact there was the timing of the vaccine. The fundamental feeling is that the timing was available, the vaccine was available in a time frame that everyone desires, the September/October time frame into early November, then there wouldn't be, there would be much less vaccine unused.

A great deal of distribution of vaccine this past year, due to issue of yield with the A/Wisconsin, which then created a

delay in the reagent preparation shifted a great deal of vaccine supply into the late-October, November, into December time frame. So based on what we see from immunization programs, obviously the sooner we can get the vaccine as available, the success of the immunization program will increase greatly.

DR. KARRON: But actually, just to follow-up on, I understand that timing can be critical, but do you actually know what percent of the vaccine manufactured this year was actually administered?

MR. THOMAS: I don't have any data on that.

DR. KARRON: Do you know that?

DR. COUCH: I think most of us understand and appreciate that problem that would relate to an individual decision like say a decision this year to put two H3s in there, you see, and you cut the supply by 25 percent, perhaps more, depending. If we're talking about changing and having new

concepts, and we're going to talk about one this afternoon, you're talking about it evolving slowly so that the industry can adjust to that. And they've adjusted to providing, you know, I remember the time in which you were lucky if 20 million doses were made and used. Now we're talking about over 100 million, you see, so that with time and the desire to make it and sell it, the industry can adjust, but not just like that. I think that's what we're hearing in the answers.

DR. KARRON: Lisa?

DR. JACKSON: It seems like there could be costs and purchasing implications that might not be insignificant as well.

DR. COUCH: Could you say that again?

DR. JACKSON: I'm sorry, my usual clarity. It seems like -- that's even worse -- there could be costs and therefore purchasing implications if four-valent vaccine

were say more expensive than a three. And you know, as you were saying, the ability to adapt quickly to that kind of change, you know, may cause additional problems with distribution and purchase.

DR. KARRON: Pamela?

DR. MCINNES: I mean I think we're cognizant of all of these factors. The risk, I mean to just say because of all these issues we're just pragmatically going to go along with something bothers me. I mean I think the data are worrying. And this is, whether we like it or not, this is a collective effort. This is not someone is just the recipient and just marches along. It's not in anybody's interest to have a vaccine that isn't, you know, the best decision we could've made with the data that are on the table. So I am going to think about all those other factors and the balancing of them, but I first am going to wrestle with what I think is the best, what I think is the best decision based on this data.

DR. KARRON: Steve?

DR. SELF: Ultimately, it seems to me the tradeoff is one of coverage versus efficacy. So adding a component may make the vaccine a little more efficacious, it will probably reduce coverage due to timing and supply. And those tradeoffs are very hard to make even when you've got modeling results in front of you. We have none of that and, you know, I listen to this and I honestly have no sense at all about how much an improvement in efficacy we could obtain, what the impact on coverage would be, and how at the end that would balance out in the population impact. I mean this is, this is a very interesting discussion, but I find it informed by very little.

DR. COUCH: We have made, and I'm straightforwardly honest with you, as you might say the wrong decision in past years, and the outbreak that succeeded with the vaccine that did not have a good match, on

occasion, has really been severe. But that was an innocent error. We couldn't help it, you see, that was the only information we had at the time, you see, when the decision was made. So that concern is there. I guess my only point was you were suggesting well you lose a little bit. No, we've got the risk of losing a lot. That's our concern.

DR. KARRON: Monica and then Nancy?

DR. FARLEY: I wonder if those who, Dr. Ye and Dr. Cox perhaps, is there anything that we would gain, or you won't know for sure, but can you comment on whether a delay of the decision on H3 has much chance, if any, of clarification for us over the coming number of weeks. Is there anything that we can do with the current strains that we have, in terms of additional testing that we think might help us sort out the low responders, or will additional strains coming in, is there much chance that the volume of

additional input would be there that, you know, to help inform us, given the fact that we know it's a big tradeoff, a negative tradeoff, from the manufacturing perspective?

DR. YE: I think if we wanted to have more data probably the best we can do is to conduct human serology study using the Nepal strain. But I don't think that will be reality, because we'd have to send it to the different centers to do a similar study. This precedent we are doing this to give more data.

DR. COX: I can't, can't really add very much. I was just conferring with Dr. Klimov and he thinks that we probably have several dozen H3N2s that haven't yet been analyzed that are just coming in. We know they are coming in and haven't yet been analyzed.

We are able to generate sequence data very, very quickly, which will tell us which of the two groups the viruses are falling in genetically. It takes a bit longer

to generate the HI data because we have to grow the virus and do the HI test. But there would be limited additional information. There would also be limited additional information on how the high growth reassortant that Dr. Booker is producing grows. But again, in a three week period of time, the additional data would be limited.

And then there would be difficulty but a possibility of conducting microneutralization tests in the interim. So that would be, that would be difficult to do within a three week period but it could be done.

DR. KARRON: Bob?

DR. COUCH: Well, just to extend on that one because I'll be entirely straight with the Committee, I'm waffling. I don't want to say no. I'm waffling between abstain and defer. But if we defer, and that was going to be one of the questions, you asked about more strains, but if we defer and the

FDA just now is looking for the reassortant, once you have the reassortant you have to know that it works well and then you've got to make the antiserum. And then you've got to distribute that. We're probably talking about really almost May or June before you can even, the industry can even begin to work with a new H3.

DR. WEIR: I think that's correct from what Dr. Ye said that it would be probably unlikely that we could generate more serology data very fast.

But just to clarify one other thing from Dr. Cox, would you not also after the high growth reassortant is made, would you not need to generate ferret antisera to that before you test it to the isolates to see how well it would cover, to really give some useful data about whether that would be a candidate or not?

DR. COX: We always test the high growth reassortants to be sure that they have

similar antigenic properties to the wild type strain. However, it doesn't preclude our distributing it to see how it grows for the manufacturers.

DR. WEIR: But I thought the high growth reassortant for the Nepal was not available yet.

DR. COX: That's right. It's not available.

DR. WEIR: So what I'm saying is after it is available, then you would have to generate ferret antisera to that before you saw how well it would really cross-react?

DR. COX: That's correct. But that wouldn't preclude its being distributed.

DR. WEIR: Okay. But it would still take time to generate that additional data?

DR. COX: Two weeks. Two weeks. Two weeks to make the serum and then the test could be done almost immediately after that. And one other thing that I need to say that

needs to be emphasized I think every year, we are really limited by what the epidemic does, you know, what certain viruses circulate, where they circulate, and how many of them circulate. And we're also limited, to some extent, to the timing of when they get sent to us. But the season was a very mild season generally and that is true worldwide. And it really didn't takeoff terribly early, except for some of the school outbreaks that we had in the United States.

So this is one of the situations that we often face where we would like to have a lot more data, but the majority of, the concerning data that you've seen here today was generated in the last three weeks or so. So it's, we're really racing with the virus, and it is a moving target, and it's a very difficult business.

DR. KARRON: First Steven, then Bob.

DR. SELF: Yes, so that's a

perfect segway to a question about the epidemiology. So I see that within the H3, the low reacting viruses are sort of on the rise. But I don't see what the best current data is for the balance between H1 and H3. I see last year based on the plot was predominantly H1. Am I, is there current data sort of on the balance of H1 and H3 infections?

DR. COX: Are you talking about in the United States?

DR. SELF: In the U.S.

DR. COX: Tony, I think that because there are so many unsubtyped viruses that have been recently identified in the United States, it's difficult to say. But as Tony mentioned, there appears to be an increasing proportion of Influenza As that are H3s. But they were predominantly H1s this year, whereas last year that was not true.

DR. COUCH: But it is --

DR. SELF: You're right. It's on

page 4. Yes, so we're arguing about, for the H3 problem, what this year may be a pretty small fraction of the total cases. Is that correct?

DR. COX: Yes. So basically this year we've had predominantly H1s. So we wouldn't expect to have predominantly H1 next year, although influenza is not predictable. And I always have to say that over, and over, and over again.

So when H1 circulates in the United States again, we might expect to see a different virus because the New Caledonia viruses have been around for so long.

With respect to the H3s, we've had relatively less disease caused by H3s, but H3 activity appears to be picking up somewhat relative to H1 activity.

Did that make any sense?

DR. SELF: Yes, it did. I'm still trying to get a handle on just the magnitude of this subset of H3 viruses, what the likely

magnitude of that problem for next year.

DR. COX: That is totally unpredictable.

DR. SELF: Okay.

DR. COUCH: There is such a thing as the Harold-wave, which as been popularized by a group from Houston, suggesting that late phrase like that, that that was the proceeder for the epidemic the following year. And there are at least three or four clean examples of that, where that's been the case.

I'm willing to take us off dead center, if you want, unless there is more open discussion.

DR. KARRON: I do just want to ask a question and go back to the H3N2. So my sense, however, is when it comes to making a decision about that the only, the two options really are to retain the current strain or really to defer, because at this point we do not have a Nepal strain. I mean we don't have a high growth reassortant. So we couldn't, as

a Committee, make that recommendation. We could say that we would defer our decision. I just wanted to put that out.

And with that, I think it is actually, unless there is anyone else who wants to make any comment, question, I think it's time to actually talk about the individual strains.

And I am actually, first we'll start with H1N1. The three possibilities, as outlined by Dr. Pandey, are to retain the current vaccine strain, which is A/New Caledonia, to switch to A/Solomon Islands, or to replace the current vaccine strain with an alternative strain.

Dr. McInnes, I'm going to start with you?

DR. MCINNES: I was looking also at the decision from WHO, and I sort of do take a little bit the same view as Dr. Couch in this about concurrence with it or having difference or non-concurrence with that.

And looking at the H1 data, I would support changing that strain, the vaccine strain to the A/Solomon Islands, the H1N1-like virus for this upcoming season.

DR. KARRON: Thank you. Dr. Hachey?

DR. HACHEY: I would also support replacing the current vaccine strain to the A/Solomon Islands-like virus.

DR. KARRON: Dr. Stapleton?

DR. STAPLETON: I would also support changing the current to the A/Solomon Islands.

DR. KARRON: Ms. Province?

MS. PROVINCE: I too support changing the current strain to A/Solomon-like.

DR. KARRON: Dr. Jackson?

DR. JACKSON: Yes, I agree with the change as previously stated.

DR. KARRON: Dr. Word?

DR. WORD: I would agree with the changes as previously stated.

DR. KARRON: Dr. Hetherington, do you want to comment?

DR. HETHERINGTON: I agree with the comments so far.

DR. KARRON: Dr. Wharton?

DR. WHARTON: I concur with my colleagues in changing to the A/Solomon Islands.

DR. KARRON: Dr. Eickhoff?

DR. EICKHOFF: I concur with updating the H1N1 strain to A/Solomon Islands.

DR. KARRON: Dr. Self?

DR. SELF: I agree.

DR. KARRON: Dr. Farley?

DR. FARLEY: I agree.

DR. KARRON: Dr. Couch?

DR. COUCH: I already said I had a weak agreement, but I agree.

DR. KARRON: Okay. Dr. Modlin?

DR. MODLIN: Yes.

DR. KARRON: Okay. And I also agree with changing to the A/Solomon Islands.

Please Christine?

MS. WALSH: Just to summarize that vote, it was unanimous, 13 votes in favor of replacing the current vaccine strain with the A/Solomon Islands.

DR. KARRON: Can we actually go to the next slide?

So there are actually three options listed up here for H3N2, but I think we have concurrence among the panel that really there are only two options that we can realistically consider.

One is to retain the current strain, which is A/Wisconsin.

And the second is really to defer a decision to a later date, pending the potential availability of a Nepal-like high growth reassortant.

So this time, Dr. Modlin, we're going to start with you?

DR. MODLIN: Well, obviously we're in a box. I'm very much concerned about the

fact that these new strains have appeared so recently. And obviously the question is does that predict increased activity for these new strains next year. And I think virtually everybody has acknowledged that we don't know what the predictive, the likelihood is here.

I would point out that this represents obviously a major problem for the manufacturers and this would be a second new strain if we were to defer a decision, with the possibility that there would be a second new strain. That would be the reason why we would be deferring a decision in the first place. And that creates real issues with respect to concern about supply and cost, as Dr. Jackson pointed out.

I'm also, I recognize that we have this discrepancy between this data from ferrets and data from humans that bothers me a little bit. And I suppose if I had to make a choice between the two, I would probably come down on, based on the discussion we've

had and also recognizing the fact that I'm not a respiratory virologist or an expert in this area and I'm new to this sort of decision making, but it seems to make sense that maybe putting a little bit more weight on the ferret data as opposed to the human data, recognizing the pitfalls there.

So yes, I come down with a recommendation to retain the current strain based on all this, weighing all the information that we have. It seems to be, to me the better or the lesser of two evils I guess, would be a better way to state it.

DR. KARRON: Dr. Couch?

DR. COUCH: I agree. I've sort of already said my piece on this one I guess. But I had a weak support of H1. I have a very weak support, but I would vote with going with A/Wisconsin. And for two reasons, primarily one is you heard me say that I think vaccine and some antibody is better than no antibody. And that even if we miss, we'd have some

benefit there and we'd have plenty of doses of vaccine. Plus, the fact that I think if I could afford the luxury, my vote would've been to defer. But I don't think defer is likely to gain us anything in this decision.

So I guess what I say is I vote yes to go ahead, but I would like to add a qualifier to that and ask CDC and whoever else is appropriate to continue to monitor this one, and maybe these new strains you're seeing, very closely. And I don't propose this as an option, but to just at least point out that in the past when this has happened, and these new strains have appeared, we have made supplemental vaccines, the last one being A/Taiwan when we missed on the H1 decision and then we added an A/Taiwan supplemental vaccine that was given to us as a special supplemental vaccine. So I would not propose that now, but I would hold that out as an option in case we miss on this one and we still have some time.

So I do have concern about the H3

decision, but I'll vote with going with WHO recommendation. And somebody tell them we're not happy with what they did.

DR. KARRON: Thank you. Dr. Cox, would you like to offer an opinion?

DR. COX: I'd rather abstain. Thank you.

DR. KARRON: Okay. Dr. Farley?

DR. FARLEY: Well, I'm reluctant in my answer as well. I'm particularly concerned that deferring this year would be more problematic than it always is to defer. And that is that the manufacturers have almost uniformly chosen to do their at-risk production of this particular antigen, and so that not only be potentially be asking for a two component change, but we would have lost the two months of production that have already gone into it. So given all of that, but in light still of the concerns, I agree with whatever we can learn about these, this emerging issue, both from a testing standpoint

of how best to look at these things when there are questions, are there additional tests that we can do and is there way that they can be done in a timely fashion given all the constraints of how it happens, how the epidemic unfolds, which we can't control. But continuing to study them so that we will understand where it is going is very much, I think, is something I would concur with.

And, in addition, then my vote would be in favor of keeping the Wisconsin component.

DR. KARRON: Dr. Self?

DR. SELF: I vote to retain the current strain.

DR. KARRON: Dr. Eickhoff?

DR. EICKHOFF: Well, I was always taught by my mentor, Gordon Meiklejohn, to pay more attention to human data than to ferret data. And in this case the ferret data looked reassuring to retain A/Wisconsin but the human data did not, and I am puzzled by this.

If there were a likely, a good likelihood that we could come up with additional useful information not at a later date but by some date certain, call it mid-March, call it the end of March, that would favor an updating to A/Nepal. That likelihood does not seem to me to be great. And yet at the same time, I think while I'm sympathetic with Nancy's reluctance to make any predictions for next year, looking at the mortality data for the last several years makes me concerned that next year is going to be a pretty significant H3N2 year. And the question is what virus will predominate.

Given, however, that the likelihood of additional information is not good, I would vote to retain A/Wisconsin/67/2005. If something dramatic happened in the month ahead, I hope we could reconvene on sort of an emergent basis, but I don't think the odds favor that at all.

DR. KARRON: Thank you. Dr.

Wharton?

DR. WHARTON: I would concur with retaining the A/Wisconsin, but have to say that I really feel like between the at-risk production the manufacturers have already done and the WHO recommendation, which presumably will be affecting the U.S. suppliers who are located in Europe, we simply have no choice. I think those two things together would provide such a hit to supply that whatever benefits might accrue from a better match were we to wait, and all these other things that might happen do happen, that we simply would be in a very unacceptable situation regarding the influenza supply.

That is a really place to be. And I don't know what kind of signals the manufacturers look for when they make these decisions about at-risk production. I am sure good efforts are made to have those be the most informed decisions possible, and I do not know if there is any signal that could have

been detected regarding these potential issues of the H3 strain at the time those decisions were made, but I hope there can be some consideration of making sure that the at-risk decisions are the best ones possible, because at this point I feel like we don't have any choice.

DR. KARRON: Thank you. Dr. Hetherington, would you care to offer an opinion?

DR. HETHERINGTON: Well, just briefly. The Committee obviously is faced with a very difficult decision, but I think it's all about coverage and delivering the vaccine in a timely manner to get what positive benefits we know will exist out of this, as opposed to putting more, excuse me, putting more at risk because of the timing and trying to gain an additional benefit that really is not quantifiable with the data we've got, unfortunately. And hopefully that situation will improve, but you're stuck with

the pragmatic.

DR. KARRON: Dr. Word?

DR. WORD: I guess as I sit here I listen to many of my colleagues who have more experience in influenza and, you know, we keep hearing about issues with manufacturing, you know, they've started things up. Then I keep saying why are we here. Because if you are presented with the information and you're here to make a decision, I know that the WHO has made theirs, but then if because of, you know, various constraints from other areas, we're not going to be able to make the best decision that we think is best for this particular country, then I'm saying I'm not sure why I sat here and listened to all this. I mean so many people here felt uncomfortable with moving forward, yet they're saying I can't get this information quickly enough, and I guess with that I'm not as comfortable moving on with the A/Wisconsin. Even though I'm struggling and I'm still trying to figure out

the best way to phrase this because I know you're saying you may not get additional information in a timely fashion, we should get some vaccine out to people, but then I'm going to say we're going to revisit this every single year, aren't we? I mean wouldn't that be the same discussion every year if something happens?

So, I'm going to extremely reluctantly agree too. I don't know, I'm torn. I want to say no.

DR. KARRON: Are you saying retain, defer, or abstain?

DR. WORD: I don't want to abstain. I have a thought. I would defer in good faith.

DR. KARRON: Okay. Dr. Jackson?

DR. JACKSON: Well, I agree. I mean the concerns voiced are very concerning. And if we have a significant mismatch here that's obviously something we want to avoid. But I agree with Dr. Wharton that it seems

we're in a box and we don't really have much of a choice. And, you know, delays in vaccine supply really impact vaccination programs, of course, but in particular, vaccination of children which is an area of increasing emphasis. And what we find where I am is if we don't have vaccine by, at the latest, early November, we really don't get children, interest wanes, and they certainly don't get two doses. So we just really are dealing with a situation which we have really limited good options. So I would vote to retain.

DR. KARRON: Ms. Province?

MS. PROVINCE: I echo Dr. Word's sentiments. It seems that, not every year, but every year we face these same kinds of questions since I've been on the Committee. We're driven, understandably, by limitations of the manufacturer, but I don't want to be driven, I don't want my decision to be completely driven by limitations of the manufacturer. Although I know what the

realities are, I understand those, but I think we need to look at the processes that we are going through, examine those, and figure out sort of from year-to-year how can we get out of this box that we seem to be in more and more frequently, and maybe make better decisions and have data available at a time where we can act on it and still accommodate manufacturing schedules.

So reluctantly, I too vote to retain the current strain, but with those caveats.

DR. KARRON: Dr. Stapleton?

DR. STAPLETON: I think Dr. Word's comments, I would perhaps argue that this is somewhat unusual to have the difference between the human the ferret data. And the timing of the isolates coming in late and having a late epidemic in the U.S. is part of it, and contributes to a complication that we couldn't really predict.

And I have to say that being on

this Committee is fun because I hadn't though of children being more like ferrets than humans, although I'm thinking about it immunologically I understand that. But I think that getting children immunized is important, and if they're more like ferrets then I'm reassured by that.

So I vote to retain, but I echo Dr. Couch's comments that I think it's important to monitor and to keep the option of a monovalent supplement as an option if indeed we find there's a serious mismatch.

DR. KARRON: Dr. Hachey?

Dr. HACHEY: I'm going to agree that the problem is we just don't have a good fit this year, as far as the current vaccine. But I really don't see a clearly superior strain that we have an option to pick. And any delay is associated with clearly some substantial risk in regards to production, supply, and delays. More data would be nice, but that doesn't look like it's going to

happen, at least data that is substantial enough to have a high likeliness of altering the decision.

So I vote to retain the current strain.

DR. KARRON: Dr. McInnes?

DR. MCINNES: I'm not comfortable with retaining the current strain. I think there are some additional data that could come to the table. I think we would, we have a potential within the next month, 4 weeks, 3 and a half to 4 weeks to understand about this potential, this reassortant, how it's going to perform. I think CDC has indicated that they do have some additional viruses to look at and I want to acknowledge the extraordinary amount of work that they do, and that they have put on the table, and that they continue to be willing to do. And I would vote to defer.

DR. KARRON: Thank you.

I am going to vote to retain the current strain. With all of the concerns,

both voiced by I think many of the people around the table, I'd actually, two points that I'd like to make. One is I'd really like to echo what Dr. Wharton said. I think that if, for example, the B strain had been made at-risk instead of the H3N2 strain, this would've been a very different discussion. And I realize the manufacturers are working with the best data they have, but I don't know how those decisions were made and I would urge them to review them carefully each year, as I imagine they do.

The second thing is I would like to have some kind of mechanism for dissemination of the additional data that will become available in the next month or so from the CDC and from other centers to members of this Committee. Not necessarily because it will have an impact on any decision-making, but because I think all of us are concerned about this decision and we would like to be able this data as they become available.

And Christine needs to summarize the vote. And then did you have a comment John? But I'll let her summarize.

MS. WALSH: To summarize the vote on the options for H3N2, there were 11 votes to retain the current strain, A/Wisconsin, and 2 votes to defer the decision to a later date.

DR. KARRON: John, did you have a comment?

DR. MODLIN: Well, just one comment. I guess we're now in a post-hoc position of second guessing the decision to go with A/Wisconsin for the first strain, as opposed to say the B-strain. And I guess the question is when that decision needed to be made did we have anymore information at that time that we would be seeing this shift in the H3 strain compared to a similar change in the B-strain? I haven't seen that we have and so I just would question. Obviously you roll the dice and was there anymore information that would've been informative when the dice were

rolled a couple of months ago compared to what we have now. And I haven't see that we have it. So that was the only thing that I would raise.

DR. COUCH: I guess we're saying the same thing, but when the industry has told us repeatedly that they have to commit before we sit around a table and make a decision, I guess what I'd say is if your commitment is H3N2 be very thoughtful that is the one of greatest concern to us. And if you cannot make that one, we'd prefer it.

DR. KARRON: Norman?

DR. BAYLOR: I just wanted to make a comment. I guess Bob, the commitment has already been made. They have committed. They have started, many of them already. We do have the march, you know, as we follow-up VRBPAC, which we usually have sometime in March, and that is the time that we could review the data from CDC. We can arrange that meeting anytime in March if that data would

suggest that we need to have a further discussion. So that's open, although, again, the commitment, I think the manufacturers have already started, and they can correct me if I'm wrong, how far they've gotten. But if the data are so impressive that we need to make a change, we can have that discussion at the March meeting.

DR. KARRON: Did you want to make a comment, Mr. Thomas?

MR. THOMAS: Yes, I could provide a little insight into the timing or the decisions making for at-risk production. Just bear in mind the decision to produce the A/Wisconsin strain at-risk was decided over seven weeks ago. And that was based upon the best available surveillance data at the time. And if you recall, based on some information already presented here, at that time both B/Yamagata and B/Victoria strains were co-circulating. There was still data on both. So the B-strain was uncertain. There was

indications that the New Caledonia strain, which is what had been selected in years past, would be changing, based on the availability of the Solomon Islands. So there was a new egg isolate. The B-strains were co-circulating. And at that point we all realized that the H3N2 strain is the one that has the most potential changing year-to-year, but again it was the, essentially our only available production candidate. And at that time there were no additional egg isolates available, nor did the surveillance say that there was going to be a grouping of an antigenic drift that was currently identified.

But the manufacturers would completely support another method here of looking at how we would begin that decision for producing at-risk.

DR. KARRON: Thank you. Dr. Choeling?

DR. CHOELING: Kathleen Choeling for MedImmune. So I think maybe I should

explain just for transparency why we made the decision to go ahead with B, having the same information. And I think maybe the timing was a little bit different when we made our decision. It could've been. But the other thing that the Committee probably may or may not know is that we make our own reassortants. So the CDC supplies us new isolates in a very timely manner. So when we got the A/Nepal H3N2 strain, we were aware that there was a possibility that that strain could change.

So I think it's, there are a number of different reasons for that difference in our deciding to go ahead with the B/Malaysia at-risk.

DR. KARRON: Thank you. And speaking of the B, that's our one decision left to make.

Christine is going to put up that slide.

And Dr. McInnes, we're going to start with you?

DR. MCINNES: I would vote to retain the current B/Malaysia/2506/2004 like virus, B/Victoria 287 lineage.

DR. KARRON: Dr. Hachey?

DR. HACHEY: Vote to retain.

DR. KARRON: Dr. Stapleton?

DR. STAPLETON: Vote to retain.

DR. KARRON: Ms. Province?

MS. PROVINCE: I also vote to retain.

DR. KARRON: Dr. Jackson?

DR. JACKSON: I also vote to retain.

DR. KARRON: Dr. Word?

DR. WORD: I vote to retain.

DR. KARRON: Dr. Hetherington, do you have any opinion?

DR. HETHERINGTON: No other comments.

DR. KARRON: Okay, thank you. Dr. Wharton?

DR. WHARTON: Vote to retain.

DR. KARRON: Dr. Eickhoff?

DR. EICKHOFF: Vote to retain.

DR. KARRON: Dr. Self?

DR. SELF: Retain.

DR. KARRON: Dr. Farley?

DR. FARLEY: Vote to retain.

DR. KARRON: Any, no, okay. Dr. Couch?

DR. COUCH: Retain.

DR. KARRON: Dr. Modlin?

DR. MODLIN: Concur.

DR. KARRON: And I also vote to retain.

Yes, Christine, please summarize.

MS. WALSH: For the option, options on Influenza B, there were 13 votes, unanimous decision to replace -- I'm sorry, retain, retain current, the B/Malaysia virus.

DR. KARRON: Thank you.

This concludes our morning session.

It is about 12:15 and I would like

to propose that we reconvene at 1:15 instead of 1:30, unless does this pose any particular hardship for anyone?

Yes?

DR. WEIR: I thought we were getting an H5 update?

DR. KARRON: Oh, I apologize.

Nancy, an H5 update, of course.

DR. COX: Gosh, I thought I was going to be let off the hook.

This is not the right presentation.

Okay. This should be easier. This is just for information only, but I thought it would be very useful to update the Committee on what's been going on with the H5N1 viruses that are circulating.

I'll just give you a bit of history and recapitulate what's been going on since 1997. Currently there are two discreet lineages of H5HAs that have descended from the A/Goose/Guangdong virus. And the

A/Goose/Guangdong virus is really then ancestral virus of all of the H5 viruses that we have. That is that it's the nearest to the ancestor of the '97 strains that caused the 18 human cases with 6 deaths.

In '97, I should remind you that there was evidence for direct avian to human transmission with limited, very limited, and rare human-to-human transmission documented. That has remained true since then.

Then we didn't hear very much about H5N1, although we thought that it was probably continuing to circulate in South China. And then in late 2003, there was a sort of an explosion of reports of activity in Southeast Asia. And actually, that was at the end of 2003. Earlier in 2003, there had been two human cases with one death in Hong Kong that was from a family that had traveled to Fujian Province to celebrate the Chinese New Year.

And then retrospectively, it was

determined that there was a death in Beijing that was thought to be SARS at the time but it was one of those SARS-negative patients who then subsequently was tested for H5N1 and found to be H5N1 positive.

So since the end of 2003 until today, we have cases in 12 countries. The latest country to be added is Laos, and I didn't get it on this slide. I'll have it on the next slide. But Nigeria and Laos are the two latest countries, there it is, Laos and Nigeria are the two latest countries to report human cases of, and Laos reported the first human case yesterday, or WHO reported it.

So we have 275 cases, 167 deaths. It's a 60 percent case fatality ratio, and you can see where the cases are occurring. The current hotspot is really Indonesia. And then there's a lot of activity going on in birds in Africa as well. And we've heard of recurrence of H5N1 in birds in a number of a different countries, and we heard quite a bit about what

was occurring in the U.K. while we were in Geneva a couple of weeks ago. And we also have heard about bird outbreaks in Bangladesh and a number of other countries that hadn't previously reported outbreaks in birds.

So, with respect to what we're doing globally, there are some basic principles and practices that the WHO undertakes when there is a newly emerging strain.

And developing of H5N1 vaccines is one component of WHO's overall strategy for pandemic preparedness. And there are four WHO Collaborating Centers, as you know, with an additional four H5 reference laboratories. And we share the H5N1 antigenic and genetic data very frequently. It's actually put into a share compartment, which allows us to really compare what is going on. And then WHO convenes periodic teleconferences of these reference labs to discuss the data and apportion tasks require for vaccine candidate

reference virus production.

And we really have to have integration of antigenic, genetic, and epidemiologic data from both the human and veterinary health sectors in order to make the best decisions about which viruses to select as potential vaccine strains.

And consequently, the candidate reference viruses are really chosen on the basis of all of these considerations.

So, as I've mentioned the HA sequences divide into two distinct phylogenetic clades. Clade 1 viruses have circulated in Cambodia, Thailand, and Vietnam and caused human infections during 2000 and through 2005. And then subsequently caused two cases in Thailand in 2006.

In contrast, clade 2 viruses were circulating in birds in China and Indonesia during 2003 and 2004, and then spread very dramatically westward after the very well known outbreak of H5N1 at Qinghai Lake in

Western China. And it is postulated that migratory birds did assist in the spread of the virus to the Middle East, Europe, and Africa.

Clade 2 viruses have caused the majority of human infections since late 2005. And there are multiple subgroups, genetic subgroups, in the so called clade 2. And they can be distinguished both genetically and antigenically, and some of them have very discreet geographical distribution.

So the majority of the H5N1 virus detected in Africa, Asia, and Europe in birds, which have been associated with sporadic human infections are in clade 2.

Clade 2.1 viruses circulated in poultry and caused human infections in Indonesia. And as I mentioned, Indonesia is somewhat of a hotspot.

Clade 2.2 viruses have caused outbreaks in birds in Africa, Asia, and Europe. And these are the Qinghai Lake

viruses. And these were most recently associated with human infections in Egypt, Nigeria, and we're not sure yet about the virus from Laos.

Viruses in clade 2.3 cause poultry outbreaks and human cases in China.

And then there are viruses outside this classification, the 2.1, 2.2, and 2.3, which have been isolated from domestic poultry in Asia. And there are two emerging clades, which are represented by A/Goose/Guiyang/06 and A/Chicken/Shanxi/2006. And the virus A/Chicken/Shanxi/2006 is particular interest because it was mentioned at a meeting in Beijing in early December that birds that were well vaccinated with the current inactivated vaccine using the A/Goose/Guiyang strain were having breakthroughs caused by this particular virus.

So this is the way we, you can look at my next, unfortunately will not be quite oriented like this, but these are the

clade 1 viruses. And we had the vaccine candidates, Vietnam/11/94 and 12/03 about which you heard a lot about yesterday that were developed using reverse genetics to take the multi-basic cleavage site out of the HA, and then they were put on a puree backbone, safety tested extensively, and then subsequently used to manufacture the vaccines that you've heard about yesterday.

Clade 2, subclade 1, so 2.1, consists of these Indonesian viruses which have been fairly homogeneous antigenically with the exception of the viruses that were isolated from the Karo cluster. This was the large family cluster that occurred in Northern Sumatra. And those seem not to be the predominant viruses circulating in Indonesia.

And then we have Clade 2.2. I mentioned these were viruses that actually descended from the bar headed goose Qinghai Lake virus. We have a number of vaccine candidates that have been made by reverse

genetics that are in this group.

And then clade 2.3 here, which is circulating primarily in China, and the majority of the Chinese human cases fall into this group. And we have to vaccine candidates here, the Anhui/1/05, which was isolated from a human infection, and then the Japanese white-eye/Hong Kong/06 was obviously isolated from a bird.

When we look at these virus antigenically, there is also good differentiation. So we have the clade 1 viruses, which inhibit each other well but don't inhibit the clade 2 viruses, so the antisera don't to the Vietnam/11/94 virus really don't do very well in inhibiting viruses in clade 2.

These are viruses in clade 2.1. The antiserum to these viruses don't inhibit clade 1 viruses very well and tend not to inhibit viruses in clades 2.2 and 2.3, although they do better with 2.3 viruses.

Viruses in clade 2.2, likewise, in antisera inhibit to these viruses and inhibit each other pretty well but there is differentiation, good differentiation.

And the same is true for viruses in clade 2.3.

So, we can see very clearly here with color coding, clade 1, clade 2.1 in green, 2.2 in yellow, and 2.3 in blue.

If we look at the profiles of these viruses in terms of their resistence and susceptibility to anti-virals, with respect to resistence to amantadine and rymantadine, the M2 channel blockers, we see that clade 1 viruses are resistant and there's a particular amino acid change in the M2 protein that confers resistence.

Clade 2.1 viruses are a mixed bag. About 80 percent are resistant and there are two different resistence changes that are seen among those viruses.

Clade 2.2 viruses have been

sensitive.

And Clade 2.3 viruses also have been sensitive.

If we look at susceptibility to the neuraminidase inhibitors, we see that clade 1 viruses are generally sensitive but there have been several resistant mutants isolated from treated patients.

Clade 2.1 are sensitive.

2.2, again, generally sensitive but moderately resistant viruses were detected from patients from Egypt that were treated with Oseltamivir.

Clade 2.3 viruses are sensitive.

I won't bother going through that particular HI table because I think you've seen enough HI tables.

I just wanted to point out the two new subgroups here that I had mentioned before, Shanxi virus, and you can see the horizontal distance is the distance that really counts on these trees. And the Shanxi

virus is out here from the backbone, the consensus. And then also we have another group that appears to be emerging. There are a number of 2006 viruses in this group, and these are isolated mainly from Guyang. So these viruses are being sought from our Chinese colleagues to be used, possibly used to make candidate vaccine viruses. And we really haven't characterized these in terms of their antigenicity or their susceptibility to the anti-viral drugs.

So, in conclusion, I want to make it very clear, and I think everyone in this room certainly knows that H5N1 viruses remain a pandemic threat but have not yet developed the ability to be transmitted efficiently from person-to-person.

We've seen some changes in the viruses. In particular, occasional viruses around the receptor binding pocket, but those viruses have not persisted.

We're not able to predict which,

if any, H5N1 antigenic or genetic variants might acquire the ability to be transmitted efficiently. We see distinct geographical distribution of the H5N1 genetic and antigenic variants, and therefore we really find ourselves as a group, global WHO group, unable to make specific recommendations for use of one particular group or subgroup of viruses because it's not possible to predict which of the viruses in the distinct antigenic or genetic groups might acquire the ability to become officially transmissible.

Instead, we are taking the approach that we should provide potential vaccine viruses and that we should encourage the regulatory authorities to produce the reagents that would be needed to make vaccines, both for experimental purposes and for stock piling purposes.

So, as you know, the Vietnam strains have been available for some time. The Indonesia/5/05 clade 2.1 is available from

CDC. Antigen and serum should be available soon from CBER, and Dr. Ye may be able to comment on that.

The reverse genetics, modified Turkey/Turkey/1/2005 clade 2.2 is available from the NIBSC in London. And they also have the antigen and chief serum available.

The Qinghai Lake, clade 2.2 is available from St. Jude. Reagents are not yet in production. And that's true also for the Whooper Swan/Mongolia.

The A/Anhui/1/05, clade 2.3, virus is available from the CDC. This virus was made during the visit of post-stock from the National Influenza Center in China to CDC and was made together with our staff. Reagents are not yet in production.

I'd like to acknowledge all of the many, many collaborators around the world, without whom I could not have made this presentation.

Thanks very much.

DR. KARRON: Thank you, Nancy.

Questions or comments at all?

Now, it's lunch time. We will reconvene at 1:30.

(Whereupon, the above-entitled matter went off the record at 12:30 p.m. and went back on the record at 1:35 p.m.)