impressive, if you want to put it that way, but it is a more obvious difference for influenza B than it is for either the H1N1 or the H3N2 this year.

CHAIR DAUM: Dr. Griffin, and then what I think I would like to do is move on to the last two presentations. We will then have all the cards on the table, and we can continue this discussion. If you could wait, that would be great.

Let's thank Dr. Ye, very much for his presentation, and call on Dr. Greg Slusaw, I hope I'm not ruining his name. Thank you, I'm doing three for three today, from Aventis, to represent the manufacturer's point of view.

DR. SLUSAW: Thank you. First of all just an administrative note on the agenda. Today I will be representing Aventis Pasteur, not necessarily the views of PhRMA, and that is simply because all the PhRMA flu manufacturer members didn't have a chance to review the content of what I'm saying today. So we will just leave it at that.

The members of this committee are, once again, faced with a difficult challenge of analyzing today's surveillance data, and projecting that into the future, and arriving at strain recommendations for the 2001-2002 flu vaccine formula.

We sometimes euphemistically refer to this activity as fine tuning, or updating the vaccine formula. And to the casual observer it may seem that this is a trivial exercise.

But I think the manufacturer's experience, from last year, reminds us that it is not. Each time we change the vaccine composition we undertake a risk. And even though we typically change one or more of the components of the vaccine formula each year, and we are generally very successful at manufacturing vaccine, that doesn't change the fact that we are taking a bit of a gamble each time we do it.

And even looking at antigenic drift, and changing to an antigenically similar strain, the growth and purification characteristics of that virus may be much different, and may have tremendous impact on our ability to manufacture vaccine.

The first overhead, please. Really, there are a number of critical pieces that have to come together into this complex puzzle to manufacture vaccine each year.

But if I can just distill that down to some of the main components, obviously the first critical issue is our major raw material, having a reliable consistent supply embryonated eggs for

vaccine production.

This is something that we anticipate each year, though, and we can work toward, and we actually have a very robust, and reliable system in place, to ensure that we have an adequate egg supply.

Which for the 70 million doses being produced for the United States market, involves about half a million chicken eggs, per day, over about a six month period, for vaccine production.

The second critical element, strain selection, of course is the activity that we are involved with here today. And this is very important, of course, for choosing strains with the proper growth characteristics, but also achieving that balance between the best antigenic match, and having suitable growth characteristics for vaccine production.

And, of course, part of strain selection involves having high growth reassortants available for the A strains, which is very critical to being able to produce a vaccine supply.

And then the final critical piece of the puzzle is having SRID potency test reagents for any new strains that are included in the vaccine formula.

And although we have various methods for estimating the amount of antigen we are producing,

when we begin production of a new strain, it is not until we actually have those homologous SRD reagents that we know exactly how much we've manufactured, and we can begin to think about formulating the trivalent vaccine.

Next. Actually Dr. Levandowski provided a good introduction to the manufacturing timelines and constraints this morning in his presentation.

The flu vaccine manufacturing cycle actually begins about a year ahead of time, when the chickens are ordered for the following vaccine production cycle. And that usually occurs in January for the following year.

And those birds are moved into the houses and begin to lay eggs usually in the October to November time frame.

Something that is ongoing, even as we are completing the previous production cycle is we are receiving candidate seed viruses, both from the CDC and from the FDA. And this is a time of very close cooperation between the FDA, CDC, and the manufacturers, to evaluate the growth characteristics of those virus, and ensure that any candidates that are identified for the formula are acceptable for vaccine production.

And also in parallel would be the identification of new strains, the preparation of high growth reassortants occurs.

We generally plan to work on a time table beginning the first strain production in January, and followed on approximately monthly intervals with the second strain selection in February, generally perhaps after the WHO strain recommendations, and then finally, about a month later, the third strain selection in March.

And during the entire January, usually July, August, about a six or eight month time frame, monovalent concentrate production is in progress, and also in tandem with that, the potency test reagents are being prepared for any new viral strains in the vaccine formula.

Finally we attempt to target, usually the first week in June, for the first bulk vaccine preparation, and the manufacturer's license are generally issued the first week or so in July, and then immediately vaccine distribution begins, in a normal year, into the October time frame, this year, of course, was extended into November and December.

Finally we just had a lot of discussion about some of the B candidate strains, and I can

assure you that Dr. Levandowski was correct when he mentioned that we received at least 12 or 15 potential B candidates to consider for this year.

This is just a relative comparison of growth based on hemagglutination, simply chicken red blood cell hemagglutination testing. And I've just standardized them all to be Johannesburg as a growth of one, so it is just relative growth.

Also including in this graph B/Yamanashi, the previous northern hemisphere B strain. So by this slide it is giving an indication of growth of some of the candidates that we've had sufficient time to do a little evaluation on, and it is not an attempt to lobby for any particular B strain at this point.

But I think more to remind us that it is very important to consider the growth characteristics of each of these. The B/Johannesburg is something we've had experience with in full scale production for Southern hemisphere.

And actually this ratio is about correct, it appears to yield about one-third to one-half the amount of the B/Yamanashi. So based on that I would certainly consider the B/Johannesburg a low yielding strain.

Likewise something like the B/Sichuan/379

appears to be similar. Not that they are not potentially viable vaccine candidates, but there is an omen of risk there, again, because their growth characteristics may or may not improve with sufficient passages in eggs.

And certainly something like B/Alaska, or B/Canada, which so far does not even grow under conditions that are similar to production conditions, I would have grave concern even considering one of those strains for the vaccine formula.

So just to summarize, the main points are that the flu vaccine manufacturing cycle, from the manufacturer's perspective, depends on very close communication, cooperation, and I guess choreography between various agencies and the manufacturers, especially at this time of year.

And the second take home message is that changes in the vaccine formula do introduce an element of risk, and naturally one change is not as bad as considering two changes, or in years where we've had a very complex surveillance data we have considered three changes in the past.But that is an additive effect, the more changes, the more risk.

And, finally, the timing of strain selection is very critical to allow us to respond and

So rest assured there will be a lot of activity to try to maximize the growth and the vaccine availability for an strains that are selected. But there still is that element of uncertainty as far as how successful we will ultimately be.

CHAIR DAUM: Dr. Griffin, then Dr. Fagget.

DR. GRIFFIN: So my previous question was going to be, does that mean that none of these candidate strains are good if Victoria is only moderate, and the others are low?

But my reading of your graph is that Victoria is just as good as Yamanashi, which is the current vaccine strain as far as its yield. Is that correct?

MR. SLUSAW: Again, we are kind of extrapolating ability to produce vaccine from very limited data, just hemagglutination data. So it gives some indication, and there is historical precedent that it is a somewhat valid way of anticipating how well they will behave.

But it is almost like an order of magnitude guess. I wouldn't assign too much weight to it. But it does give us an indication.

And, certainly, I wouldn't select a strain that had evidence of being an extremely poor grower,

adapt to any problems with growth of the strains, and adjust our processes to be able to manufacture vaccines.

Any questions?

CHAIR DAUM: You have an opportunity for questions for Dr. Slusaw. Dr. Snider?

DR. SNIDER: Yes. You mentioned subsequent passages. But are there other things that you can do to try to improve the yield, and will be doing with these strains?

MR. SLUSAW: Influenza vaccine manufacturing licenses are for the process. And there is, generally, a lot of flexibility built into there, again acknowledging that the vaccine composition changes annually, and different strains may have different growth and purification characteristics.

So that allows us some latitude, even within our existing licenses, to fine tune the process to adapt to any peculiarities of a given vaccine strain.

And it is something that we do on an ongoing basis, in fact, whether a strain is a poor grower or not, it is something we do to optimize our process.

thinking it may get better.

CHAIR DAUM: Dr. Fagget, please.

DR. FAGGET: You were able to produce nine million doses in short order. How were you able to do that, and this year if you have another problem, will you be able to do that again? And how much did you lose?

MR. SLUSAW: I will answer the second question first, I don't know. And, again, it was a combination of a lot of hard work, and persistence, and luck, that allowed us to ultimately be able to produce A/Panama in sufficient quantities.

The downside of that was it took us many months of work, and it kind of resulted in late availability and late deliveries to finally achieve that.

But I suppose it was just as likely that we may still be working on it, and had never had some measure of success.

CHAIR DAUM: Before I call on Dr. Decker I would like to ask you, if you are not speaking on behalf of all the manufacturers today, then can you tell us how much confidence we can take from the fact that B/Victoria grows well in your hands, versus what the rest of the industry might say, or do we just not

know anything about what they might say?

MR. SLUSAW: Actually we have representatives, colleagues from some of the other vaccine manufacturers, and perhaps one of them would like to address their experience with some of the B candidate strains.

CHAIR DAUM: Before you do that I just might like to say that it would be helpful if the process of clearing had gone on, so that we could have one statement that was real clear, for the whole industry. I don't know what went wrong.

Could you identify yourself for us, please?

MR. HJORTH: This is Richard Hjorth from Wyeth laboratories. And I think one reason that we didn't fully get together in this is that some of the data just came off yesterday.

But we have been looking at slot blots, using a monoclonal antibody to B. And we thought that might be an alternative way of quantitating, with everything on a level playing field, to look at these different isolates.

And, of course, if you just pass an isolate once or twice it is hard to tell how it is ultimately going to yield. But looking at early

passage data we agree one hundred percent that Victoria is an excellent strain. We also found B/Perth to be an excellent strain.

And perhaps a third choice would be Shis loca, but I'm not sure that -- I think that was in your low category?

MR. SLUSAW: Yes, that is right.

MR. HJORTH: So at least we agree on Victoria and Perth.

CHAIR DAUM: Thank you very much, that is very helpful. Now, Dr. Decker, I'm sorry.

DR. DECKER: Actually that worked out very well because now I have the same question for both gentlemen, which is does the slide you show of the tests you reported predicting possible growth characteristics, were similar tests done at this time last year, and if so, did they predict or fail to predict the problems with Panama?

MR. SLUSAW: A/Panama was an interesting situation. And as Dr. Levandowski noted earlier this morning, I think we had five or six high growth reassortants of A/Panama to work with.

And we chose, in the U. S. and globally, the reassortant which appeared to give the highest growth. And even that, as we later found out, was not

one hundred percent assurance that we would be able to produce sufficient quantities of vaccine.

So, really, until we get into full scale production of the strain it is difficult to anticipate what production yields will be like. Many manufacturers have capability to simulate their processes on a small scale, and that may give some indication.

But it is not until we actually get into it that we know where we are going to stand with viruses yields.

CHAIR DAUM: Thank you. I have erred before, and didn't realize there is another industry representative out there. Would you like to comment? Please tell us who you are.

MR. O'BRYAN: Thank you very much. My name is John O'Bryan from Evans Vaccines in UK. I would just like to make another comment about the B strains.

Firstly, we haven't had the whole range to look at, but we have worked with B/Johannesburg, and B/Victoria. Again, obviously for the southern hemisphere.

We looked at the HA from the primary growth for sera. I think we found a similar aspect

that is being reported today. We thought Victoria was higher growth than Johannesburg.

But when we put Johannesburg through the whole of the production process, and Victoria through the whole of the production process, we actually found that at the end of the day the yield is still significantly lower than the B/Yamanashi, it is about 65 to 70 percent, in fact.

CHAIR DAUM: The yield of -- I just want to make sure I understand. Victoria was lower than --

MR. O'BRYAN: Yes.

CHAIR DAUM: Thank you. Are there other committee questions? Dr. Kilbourne.

DR. KILBOURNE: I would just like to ask Greg, and other manufacturers, whether if there is something the industry can do, by reviewing past data, to see if you have some kind of phenotypic marker that might correlate with whatever your production criteria are.

In other words, are there simple things like temperature sensitivity, susceptibility to detergent disruption, any of those things that go on during manufacturing that might allow you to, without taking each individual candidate into a pilot production, be helpful in feedback to those of us

making reassortants as to what to look for, other than high yield?

MR. SLUSAW: Well, Dr. Kilbourne, if you have an idea what that phenotypic marker is I would love to hear more of your ideas.

Actually it is something we tried to look at and many manufacturers, as I mentioned, can mimic their production process on small scale. And that is really a useful tool for evaluating.

But I'm aware of the experience with A/Panama of manufacturers who ran A/Panama through the process, even at moderate scale, tens of thousands of eggs, and thought everything looked fine at that point, only to find that when they went into full scale production the yields were disappointing.

So it would be great to identify some kind of phenotypic characteristic that could be used as a proxy for final vaccine yields. But I'm not sure what the perfect characteristic might be.

CHAIR DAUM: Thank you, Dr. Decker.

DR. DECKER: The last few answers have stimulated a conclusion in my mind that I want to articulate to give a chance to get it knocked down if it is wrong.

But it sounds as though the current state

of the art is that despite good attempts that might give clues as to which are the most promising strains, we don't really know until we are so late in the process, that it is very hard to recover from a problem.

And that is what happened in the last year. So that would seem to suggest, first, that we ought to have a clear benefit in mind when we recommend a change in strains to warrant that perhaps a reducible risk of running into production problems.

And second the one tool that we seem to have that can help to manage this is to allow as much time as possible for the detection and correction of the problems in production. So anything that can be done to move up the time table of strain selection, delivery of the validation antigens, and sera and so on, would seem to be our best safeguard as long as we are in the situation of even mini-production exercises not being able to accurately predict whether or not we will be able to produce vaccine in true industrial production scale.

CHAIR DAUM: Thank you. Other comments before we move on? Dr. Estes, then Dr. Kohl.

DR. ESTES: It is not clear to me, I heard that obviously there were problems with production of

the A/Panama. And yet in the end those were overcome.

Do we know how they were overcome? I mean, is there any information from that that gives us a hint?

MR. SLUSAW: I think, at least in our experience, there were not any tremendous mysteries with how they were overcome. We tried many of the fixes in the process that we would have tried with any other low yielding strain.

There are certain characteristics of low passage level reassortants, some morphological characteristics that might affect the purification efficiency, for example.

And, really, just through optimizing the process, and additional egg passages, which of course take time, the problem basically was corrected. But part of that is the selection process of developing new seed cultures for production.

And it is somewhat of a hit and miss kind of statistical exercise, and there is no assurance that after one week the problem can be solved. It may take months, and there would be no resolution.

So there was an element of chance involved.

CHAIR DAUM: Dr. Kohl?

DR. KOHL: I am thinking about how we make strain decisions, and typically having done this for three or four years now, we always pick the easiest one first, and say go with such and such to begin with, and then we will do the hard one as late as possible.

And this year that seems, again, like a fairly easy thing to do. I wonder if that is backwards? And if it looks like it is clear, at least, what is emerging, and that we do want to make a shift, if we can tell the -- maybe I'm putting the cart before the horse.

But if we can tell the companies we want to shift to a Sichuan-like strain and leave it at that, and let them start playing early on, although it sounds like they are already playing early on.

So we are basically doing that at this point.

DR. GRIFFIN: But I think the thing that made the changes hard, or the decisions hard, at least last year or before, because we didn't have enough data on the strains that were emerging during that year, and it was thought that another month's worth of collecting that kind of data -- I don't think we are in that situation this year.

I think we have pretty clear indications on what the strain patterns are like without a lot of, maybe except for possibly H3N2, but without a lot of questions out there.

DR. SNIDER: Dr. Kohl, do you want to make a follow-up comment?

DR. KOHL: I would hope that we can make a more rapid kind of decision, maybe even pick all three at this meeting, and at least a general idea, and let the companies take it from there.

CHAIR DAUM: Thank you, Dr. Kohl.

What I would like to do is move on and hear from Dr. Cox what the options are for strain selection. And then continue in a slightly different guise, this discussion yet again.

Thank you very much, Dr. Slusaw, and other pharmaceutical folks who commented. While Dr. Cox is getting set up you may make one more comment. Could you remind us who you are?

MR. HJORTH: Rich Hjorth, from Wyeth.

CHAIR DAUM: Thank you.

MR. HJORTH: We find in general, though, that the yield in eggs is a pretty good indicator. We knew last year that Panama was certainly going to be much worse than Sidney, but the change was made.

But I say rarely is it, for us, is it a manufacturing problem. If it is a better yielder in eggs, it usually works better through the process.

CHAIR DAUM: Thank you very much. Dr. Cox?

DR. COX: I think we can move fairly quickly, and clearly, through the options for selection of strains this year.

And for each group of viruses I'm going to start out with some bullet points, which will summarize the data, then I will go on to the three options that exist for each strain, either maintaining the same strain in the vaccine, updating the strain, and making a decision on that, or deferring the decision until a later time.

And then I will be following with another sort of more general overall summary.

For H1N1 viruses we can summarize by saying that little antigenic heterogeneity has been observed. And that most strains are antigenically very similar to the New Caledonia vaccine strain.

And in general the neuraminidase genes of current strains are also similar to the neuraminidase of the vaccine strain. There are a few low reactors, as you will recall from the tables. But they do not

fall into one clear genetic group.

And in addition to the viruses being less well inhibited by the ferret sera, we are -- we see the viruses are well inhibited by the ferret sera.

We also see that in the human serologic studies, generally these new strains are quite well inhibited by serum of individuals who have been vaccinated with the New Caledonia vaccine strain.

The current vaccine strain has been in the influenza virus vaccine for one year. So option one is to maintain the current vaccine strain. The pros are that the current vaccine strain is immunogenic, and well matched to currently circulating viruses.

Manufacturing is well defined and predictable, and we don't really have any new vaccine candidates available.

Against that position is the fact that a variant strain possibly could be identified in the next two to three weeks.

Option two is to update the current vaccine strain. I had to sort of really dig, but I could come up with one pro. We might be able to provide a closer genetic match to next year's viruses if we chose the correct sublineage, because you will recall that the HA is dividing out into two

sublineages.

But against that we can see, from our data, that there are no clear advantages based on antigenic characterization, or serologic results. And we have no superior alternate vaccine candidates.

We could defer to accumulate additional data, and we do know that there will be more data available in the next two to three weeks, including both genetic and antigenic analysis of some new Chines H1N1 viruses that have only just arrived.

Against this we realize that additional data may not alter the current considerations since, so far, the global data have consistently indicated a good vaccine match.

So in summary we can say that although influenza activity associated with H1N1 viruses has generally been low, world-wide in the past four years or so, significant H1N1 activity has occurred this season in the northern hemisphere, as well as during the southern hemisphere's season during our summer.

The majority of current viruses are antigenically similar to a New Caledonia. However, viruses similar to Johannesburg, the Johannesburg reference strain were also identified.

Human serologic responses suggest that the

current vaccine strain is immunogenic, provides a good antibody response against current viruses from both antigenic and genetic groups.

In summary for the H3N2 viruses, we see that little antigenic heterogeneity is observed. And most strains are antigenically quite similar to A/Panama.

The neuraminidase genes of many current strains fall into a different genetic group from Panama, but the low reactors, and there are a few of them, but only a few, do not fall into any particular genetic group.

And the H3N2 viruses are generally well inhibited, not only by the ferret serum, but also by human post-vaccination serum.

This current strain has also been in the vaccine for one year. So we could maintain the current vaccine strain. And the pros for this approach would be that the current vaccine strain is immunogenic, and well matched to currently circulating viruses, manufacturing is now well defined and predictable.

And we have, perhaps, only one obvious new vaccine candidate, which has been mentioned so far, and that is Ulan Ude, which was considered during the

southern hemisphere deliberations.

Against this position is the possibility that a new variant might be identified in the next two to three weeks. I should mention that we do not have any H3N2 viruses from China. Apparently their activity has been mainly H1 and B over the past few months.

Option two is to update the current vaccine strain. We might provide a closer genetic match to the HA, but especially to the neuraminidase of next year's viruses.

Against this there is no clear advantage, based on antigenic characterization, or the serologic results that we have, acknowledging that we do not have results for the -- we do not have neuraminidase inhibition tests.

The only clear vaccine candidate that we have is the Ulan Ude, which does have the correct "neuraminidase" but as I said, that was under consideration for the southern hemisphere recommendations, as well.

Option three is defer to accumulate additional data. And one of the issues in favor of this position would be that since H3N2 viruses cause the most serious morbidity, and mortality, this

particular choice should be made very carefully.

And I think we've all always given a lot of attention to this particular vaccine component. There will be a few additional pieces of data available within the next two to three weeks, but we have to recognize that at this point additional data may be insufficient to alter current considerations, since we haven't yet identified a new variant.

So, in summary for the H3N2 viruses, we can say that in contrast to most recent years, this year few H3N2 viruses have been isolated globally. Those few viruses are antigenically similar to A/Panama, the A/Panama vaccine strain.

And serologic responses suggest that the current vaccine strain is immunogenic and provides an equivalent antibody response against most current viruses, but you can find some exceptions to that.

For influenza B viruses we can see quite clearly that antigenic drift has been detected. A new variant represented by B/Sichuan/379/99 has been identified as prototype variant strain.

The neuraminidase genes of many current strains are generally similar to the vaccine strain, but are closer to the neuraminidase gene of the B/Sichuan.

There is no evidence for circulation of B/Victoria lineage strains at the present time. And B viruses are generally less well inhibited by ferret serum, and to some extent by human post-infection serum. The current vaccine strain has been in the vaccine for two years.

So we could maintain the current B vaccine strain. Once again, the current vaccine strain is immunogenic, and manufacturing is well defined and predictable.

Against this the current influenza B strains are not well inhibited by ferret serum to the vaccine strain, and so we would essentially not be able to say that we had a good match with the current vaccine.

Human serologic responses against some recent strains are somewhat reduced. And egg isolates with appropriate antigenic properties are being evaluated as candidate vaccine strain.

And I think that, as I mentioned before, there are a number of additional strains that have been sent out for examination by the manufacturers.

Option two is to update the current vaccine strain. In favor of this position would be that we would provide a better antigenic match with

the current B strains, and that vaccine candidate strains, such as B/Johannesburg/599, and B/Victoria/504/2000 have been used to manufacturer vaccines for the southern hemisphere, where smaller number of doses are produced.

Against this position would be that no data are now available on the immunogenicity of vaccines produced with any of these B/Sichuan-like candidates. And we know that many recent influenza B egg isolates grow rather poorly.

The third option, of course, is to defer in order to accumulate additional data. In favor of this we do know that more data will be available in the next two to three weeks. We have a number of viruses that are backlogged in our laboratory waiting for analysis, including some new Chinese influenza B viruses.

We will have more data available on the growth properties of the potential vaccine candidates. And I suspect this data will be developing fairly regularly over the next few weeks.

And then against deferral is that additional data may not alter current considerations.

So in summary for influenza B viruses there is antigenic drift from the vaccine strain

B/Yamanashi. And most of the viruses that are reduced in titer to the B/Yamanashi serum are antigenically and genetically similar to the prototype reference strain B/Sichuan.

Serologic responses suggest that the current vaccine strain is immunogenic, but it may provide a more limited response against some of the current B viruses.

And a great deal of work has been done since the southern hemisphere vaccine recommendations were issued to develop additional alternate vaccine candidates.

Thank you.

CHAIR DAUM: Thank you very much, that was very succinct, and very clear.

We have a moment or two for some questions. Dr. Decker?

DR. DECKER: I have two questions. The first one is, in any given year we might make a recommendation, and then events would unfold that indicate, within a month or two, that there is a serious new problem, and that recommendation needs to be revisited.

What are the consequences of withdrawing and replacing a recommendation? A related question

is, let us contrast two scenarios. And scenario one, five years in a row we make a recommendation in January, and one time it has to be changed in February or March.

The other alternative is five years in a row we defer everything until February or March, and we never have to change our minds, we just don't speak them until we are sure.

Which of those is better for the public health?

DR. COX: Were you directing those questions to me?

DR. DECKER: It seemed like the subject of books, or articles --

(Laughter.)

DR. COX: Yes, indeed. And I think your first question could be better answered by folks from the FDA, since this is the committee.

DR. DECKER: Or perhaps from the manufacturer, because if they start work, is it better to start work and start it over, than to do no work at all?

CHAIR DAUM: Bring this man a mirror. You are the manufacturer, I don't know, you tell me.

DR. DECKER: I'm not speaking as a

manufacturer, I'm not here in that role.

CHAIR DAUM: Oh, okay. Does anyone from FDA want to comment on this question? Dr. Midthun.

DR. MIDTHUN: Karen Midthun, FDA. I think part of the issue is, obviously, the more you know the more certain you can be about the recommendation you are making. And that is offset also by the time factor.

We all know that it is difficult to really gear up and get everything in line to get the influenza vaccine available for when we need it.

And so I guess part of the issue is, if one were to make a recommendation based on the data available, and when one obtained additional data one said, maybe we need to reconsider this, the issue then becomes, and I guess my question would now be to the manufacturer, what kind of impact does that have.

MR. SLUSAW: I am still thinking about this one a little bit, because there are obviously pros and cons either way.

Obviously having selections made earlier would be an advantage, even with the potential risk of having to make a change at some later point if new data were identified.

I guess one thing that I ask myself is,

weighing all the risks and advantages here, what is the likelihood, in a given year, that we would need to make a later change.

Because in the case where we had to make a change several months into the season, that could be catastrophic as well, I suppose, especially if we are starting with a new seed virus, something that we haven't prepared working seed, something that we haven't had a chance to evaluate, really puts us back several months away from monovalent concentrate production and ultimately vaccine production.

So it is really a trade-off, I think, either way. But at least having things to work with earlier help to identify potential problems earlier, and perhaps correct and address those so that it makes working with those strains a bit easier, and more practical.

CHAIR DAUM: Thank you. Dr. Midthun, and Dr. Kohl.

DR. MIDTHUN: I just want to make one comment. I mean, certainly I think everyone would agree that it is best to make a recommendation as early as possible if one feels one has sufficient data.

CHAIR DAUM: Thank you. Dr. Kohl?

DR. KOHL: If there is not a change in the vaccine strain, are there potential manufacturing problems that crop up, or is it a slam dunk? I mean, if you know we are doing last year's vaccine again, is that just very simple to do, or are there risks in that?

MR. SLUSAW: Again, I think from a manufacturing standpoint it probably is a slam dunk, barring any natural disasters like avian influenza sweeping through the northeast.

But as far as from a manufacturing standpoint, and the performance and predictability of purification of the viruses, I think it makes things a lot easier.

CHAIR DAUM: I am going to presume that the other two industry spokespeople would agree, or would now comment. Dr. Manley?

DR. MANLEY: I am concerned about the time line. We have heard several comments that the earlier we make the -- it is better to make a decision earlier. I'm not sure yet that I understand what early is.

This morning we saw some timelines that showed September, October, what is the optimum time to be making the decision for any given year? And does

someone know?

CHAIR DAUM: Dr. Cox seems willing to take that question on. Thank you.

DR. COX: Yes. I think that we all are -- have been working for many years with a balance, and the balance is between giving the manufacturer sufficient time to produce the vaccine, and developing enough data so that we can have a pretty good picture of what is actually going on.

And if we make the decision too early we simply will be stabbing in the dark. So we can't make the decision any earlier than we've traditionally done so, I think, without a risk that we will make a decision before we have as much data as we would like.

I think that one of the things that we have to remember is that until this year we've been on the same time cycle. The manufacturers have been producing more vaccine each year, and we really hadn't stubbed our toes, so to speak, until this year when several things went wrong, not just in the manufacturing process itself.

And so I think that we also have to keep in mind the global picture, and recognizing that many of the manufacturers do manufacture in a global environment, and export vaccine, and we import

vaccine.

And if we have different strain recommendations in the United States to the rest of the world, this also will have implications for vaccine supply here, and for immunization of the military, and a variety of other things as well.

CHAIR DAUM: Thank you, Dr. Cox. Dr. Midthun, and Dr. Kohl.

DR. MIDTHUN: I just wanted to make the point that in general we do like to have vaccine available by September for distribution so that it can get out there, so that you can start immunizing the individuals whom you intend to immunize.

And as such the process of manufacturer, from sort of getting going to getting it ready by September, usually takes in the order of about six months.

So I think it is fair to say that you really want to start at the latest in March to be able to meet that September timeline. And so if you can start a little bit before then, let's say February, then there is a little bit of additional margin in the event that certain problems arise, such as low yield growth of a particular vaccine strain.

CHAIR DAUM: Dr. Kohl.

CHAIR DAUM: Dr. Cox, you mentioned that the H3 selection was critically important because it is such a variant virus. And you said there were possibly new pieces of information that might come in, in the next several weeks.

Yet there are no new viruses, it sounds like, that are coming in. What new information were you alluding to, and how important are they?

DR. COX: Actually there are a few viruses. We don't have any from China, but there are viruses from Korea that have been collected through the military network.

I believe that there are also some viruses from Thailand or Singapore that Dr. Hampson will be analyzing. And we have just three or four additional H3N2 viruses from the United States, I think, that are waiting analysis.

So it will be a relatively small amount of data, but there will be a few pieces of data.

DR. KOHL: And you foresee possible data that might change the current situation?

DR. COX: It is really hard to say for sure. I don't honestly anticipate any large change, but I would hate to tell the committee, no, there won't be a change.

CHAIR DAUM: Okay. Dr. Ferrieri, then Dr. Stephens, then we are going to go to our open public hearing. We are going to take a short break, and then continue this discussion in the form of dealing with the questions and the actual selection.

Dr. Ferrieri, please.

DR. FERRIERI: A couple of quick questions for Dr. Cox, or perhaps Dr. Kilbourne.

Could you refresh our memories on the genetic sequencing, and what you are really doing, is this just interminous sequencing you are doing?

And, secondly, my question is, do we know what the exact protective locus might be on either of these two genes, the HA or neuraminidase?

DR. COX: Sure. We are sequencing the entire HA1 domain of the hemagglutinin, which is the variable domain. No, we do not know the exact protective locus.

We are actually trying to focus on regions, or particular amino acids that have been demonstrated to be under positive selection, and have been working with a group in California to do some modeling in that regard, not only for the H3N2, which we've published on, but we are also moving to look at H1N1 and B viruses in similar manner.

But we can't really, by sequencing, tell what is going on. We use sequencing as an adjunct to the serologic information. And when we see a virus that is reduced in titer in the serologic analysis, we actually look to see if we can find some signature amino acid changes that correspond to that antigenic change.

DR. FERRIERI: What did it mean, then, if there were eight changes in the B virus, B neuraminidase, was that -- I mean, all the others were compared to B/Yamanashi.

So I was confused about, then, what the amino acid changes were for B/Yamanashi, in one of your tables, from CDC. Is that some new variant of the B/Yamanashi compared to the B prototype B/Yamanashi, or what?

DR. GRIFFIN: Those are changes from the consensus slides.

DR. COX: Yes, these are all compared to the consensus. So that just indicates that there are eight changes between the consensus neuraminidase sequence, and that of the B/Yamanashi.

DR. FERRIERI: Thank you.

CHAIR DAUM: Thank you. Dr. Stephens, please.

DR. STEPHENS: This is for Dr. Cox. I'm still a bit confused about the H3N2 story, which we talked about a bit. In terms of this neuraminidase drift, and even the drift towards more Moscow-like strains, is it your kind of recommendation that those drifts are not significant change of action?

DR. COX: You are asking about whether the change in neuraminidase between the --

DR. STEPHENS: I am asking about the general, what I perceive of as a general drift away from our Panama strains, to the more Moscow-like strains.

Is that, in fact, a correct interpretation of the data?

DR. COX: The HA is actually well matched.

DR. STEPHENS: Okay.

DR. COX: It is the neuraminidase --

DR. STEPHENS: It is the neuraminidase --

DR. COX: Which is in a different genetic clave.

DR. STEPHENS: And you think that that is not necessarily an issue that we should concern ourselves with?

DR. COX: I think that this is an issue which is important. I think that because the

neuraminidase isn't actually quantitated in the vaccine, as the HA is, we are not holding the neuraminidase to the same standard in terms of the vaccine process.

And, therefore, and because we recognize that the hemagglutinin is the primary antigen that provides protection, although antibody to neuraminidase is also important, I think we have really tended to focus much more on the hemagglutinin for fairly good practical reasons at the present time.

That is not to say that we can't think about ways to improve the vaccine standardization in the future.

CHAIR DAUM: Thank you very much. I would like to move on now to the open public hearing, then we will take a short break, and then we will come back and begin discussing the questions the FDA has asked us to consider today.

So I understand that there is one speaker in the open public hearing, and that we have a presentation of five minutes or less. May we call on the individual now to speak?

Is there anyone who wishes to speak at the open public hearing part of this session?

(No response.)

CHAIR DAUM: Then I thank you very much. This is the end of the public hearing part of this session.

I would like to ask us to take a 15 minute break, it is 3:02. We will reassemble at 3:17.

(Whereupon, the above-entitled matter went off the record at 3:02 p.m. and went back on the record at 3:22 p.m.)

CHAIR DAUM: I have asked Dr. Levandowski to put the question up on the screen for us.

The question that was passed out this morning is a little longer than that. Which one is from the previous meeting? This one. We will go with what Roland says.

So this is the question, and it has been the tradition of this committee, I think, to consider this antigen by antigen, beginning with H1N1, going then to H3N2, and going to B for a grand finale.

So what I would like to do is to see if there is any more general discussion, or general comments that people would like to make before we begin consideration of the question.

We have had some pretty lively discussion, but if we need to have a little more, that is fine. Dr. Decker, we need to have a little more.

DR. DECKER: Just briefly I want to go back and revisit one question I asked that I didn't get fully answered, that I thought would be helpful in the long run for us.

And that is to ask the Aventis and Letterly reps to compare for us the impact on them of two alternate scenarios. One is they are not given a recommendation until, say, March. Therefore they don't do anything in serious furtherance of the recommendation, because it wasn't given.

The other is they are given a recommendation in good faith at this time of the year, right now, but then a freight train comes roaring out of China bearing new information and people say, wait, we have to change that.

Now, would that latter scenario cause some damage, materially, over and above the effects of the simple delay until March? So that question is addressed to the production representatives from the vaccine manufacturers.

CHAIR DAUM: Is Dr. Slusaw still here, would he care to respond to the question? I think I see him emerging from my visual field, into my visual field.

MR. SLUSAW: Greg Slusaw, Aventis Pasteur.

I think after considering the alternatives it would, obviously, be desirable to have the selection earlier, even with the risk of a potential change later in the process that would mean expending additional resources.

But still assuming that it is relatively low risk, that the decision would ultimately be changed, it would probably be advantageous to be able to begin manufacturer earlier.

CHAIR DAUM: With the recognition that you are not representing the industry today, we had two other spokespeople from two different companies, would they care to comment on this very question?

MR. HJORTH: Well, I think a lot would depend on how far we got with the other strain before the change were made. If we were just doing is development that would be great. If we were actually manufacturing, you know, that is -- those eggs are gone forever, you know, we've used them up.

But it would depend on the relative yield. If the new strain were a much better yielder, we would be happy to change and throw out two weeks of vaccine, or something like that.

So it is kind of hard to give a black and white answer, I think.

CHAIR DAUM: So it just depends, sort of. Thank you very much. Other general questions before we begin H1N1 discussion? Dr. Kim, please.

DR. KIM: Well, I guess one plea that I would like to make is that instead of hearing same kind of data although the presentation, as Dr. Daum indicated, that are much clearer or well done this time, but my plea is that instead of hearing the same kind every year, that perhaps we can have some additional information to those questions which have been raised during the discussion session, that there are no information available to those issues.

Perhaps those issues can be incorporated so that, perhaps, we will have more data, and a little more, perhaps science into this process in future meetings.

CHAIR DAUM: Thank you, Dr. Kim. Other general comments?

(No response.)

CHAIR DAUM: Good, let's move on, then. We have the FDA's question of what strain, I'm going to interpolate to mean what H1N1 strain should be recommended for inclusion in next year's flu vaccine.

And, Dixie, there you are in the hot seat to start our discussion, please.

DR. SNIDER: Actually I think for H1N1 that is an easy question, at least in my mind. It seems to me that all the epidemiologic, serologic and genetic information we have been provided today suggests that we have a vaccine that is well matched.

We don't have any evidence that it is not efficacious. And, therefore, I would recommend, for the H1N1, that we leave in the current A/New Caledonia/20/99 strain.

CHAIR DAUM: Okay. Dr. Stephens?

DR. STEPHENS: I would agree with that. I think that, as Dixie has suggested, the data supports continued use of that strain. We still have, I believe, seven to ten percent of the Johannesburg strain causing disease, and there is, obviously, some concern that we might identify something new quickly.

But I think certainly for right now the New Caledonia strain would be my recommendation.

CHAIR DAUM: Thank you very much. Dr. Kim, please.

DR. KIM: I concur, New Caledonia should be the one for the next year.

DR. GRIFFIN: I agree, New Caledonia.

CHAIR DAUM: We may have started out with a nice simple one to get the juices flowing here. Dr.

Huang?

DR. HUANG: Right. This is a no-brainer. I agree, too.

CHAIR DAUM: Steve?

DR. KOHL: The only reservation I have is Dr. Cox's comment that there is a shipment coming from China. And I agree right now that New Caledonia looks like the best.

But my decision would be a little bit biased if we were sure which H3N2 we wanted to do at this point, and could recommend that first, with confidence.

Then I would be for waiting a couple more weeks to do the H1N1 pending these new strains.

CHAIR DAUM: I am not entirely sure I follow that. Could you clarify for us, please?

DR. KOHL: Well, it sounds like the -- I'm jumping ahead, as usual. But it sounds like the H3N2 story is a little simpler, actually, than the H1N1, because -- the H3N2 is more complicated?

Well, it is more complicated, and this is why I'm jumping ahead, it is more complicated if the neuraminidase issue is a problem. And I was hoping that Dr. Cox, possibly, could clear that up to begin with.

Or do you want to wait for the H3N2? What I'm saying is that my H1N1 decision is tempered somewhat by the H3N2 decision. Because the only really new data we are expecting in the next couple of weeks is H1N1 new strains from China.

And if there is a blast of new strains coming from China, as Nancy said is possible, that would really change what I would feel comfortable with.

CHAIR DAUM: How about if we go ahead and take your H1N1 decision, but allow you to revisit it, depending upon what the H3N2 decision is.

DR. KOHL: Okay. Then it is New Caledonia.

CHAIR DAUM: There. Dr. Manley, please.

DR. MANLEY: I agree. I think the New Caledonia is the strain that I would recommend.

CHAIR DAUM: Dr. Diaz?

DR. DIAZ: I likewise would agree.

CHAIR DAUM: Ms. Fisher?

MS. FISHER: I am going to abstain.

CHAIR DAUM: Could we flesh you out a little bit? It sounds like there is a concern in your part that we haven't heard.

MS. FISHER: I just do not feel that I

should be voting on this particular issue. I don't feel backgrounded enough on it.

CHAIR DAUM: Thank you very much. Dr. Fagget, please.

DR. FAGGET: I agree with New Caledonia.

CHAIR DAUM: Dr. Estes?

DR. ESTES: I agree that this is the simplest decision. I think really the only issue, probably, on everyone's mind on the committee is that when we look at the isolations of the viruses, it is not clear if we've hit the top of the peak, or for the next two weeks that is going to increase, and there will be new viruses that appear there.

But based on all the data that we have at the moment the recommendation, I think, should be to keep the New Caledonia as the H1N1.

CHAIR DAUM: Thank you very much. Dr. Ferrieri?

DR. FERRIERI: I support the New Caledonia/20/99. If Dr. Cox and colleagues find anything that is dramatically different, please let us know.

CHAIR DAUM: Thank you. Dr. Myers?

DR. MYERS: I agree.

CHAIR DAUM: Dr. Goldberg?

DR. GOLDBERG: I agree.

CHAIR DAUM: And Dr. Kilbourne?

DR. KILBOURNE: Based on the information now on hand I certainly concur.

CHAIR DAUM: Thank you. And FDA, there is a box here, but I presume that -- ignore that box, thank you very much.

Then we have a consensus on issue number one, or question one in the way of H1N1.

DR. FERRIERI: What about your vote?

CHAIR DAUM: My vote is to keep the -- thank you, Dr. Ferrieri. I actually totally concur. I think maintaining the present strain is the right way to go. And I will put my name on here. My name is not on here, that is why I didn't call on me.

(Laughter.)

CHAIR DAUM: I'm under fire here all the time, it is not easy.

Let's move on to the next issue, the same question for the H3N2 candidate. And ask the exact same question, and start with the same sequence. Dr. Snider? I'm sorry, Dr. Cox?

DR. COX: If I could just make a technical comment? I realize, during the break, or it was brought to my attention during the break that there is

some confusion about whether Panama and Moscow are considered to be antigenically similar. They are.

So I don't know if that was confusing some people or not. But --

DR. GRIFFIN: For the HA?

DR. COX: The HA is antigenically similar. The neuraminidase is not genetically similar. We haven't tested its antigenic properties.

CHAIR DAUM: Thank you very much. If there was confusion about that, it sounds clarifying.

Dr. Snider, please.

DR. SNIDER: Harry always swap back and forth --

(Laughter.)

CHAIR DAUM: And you saw what happened to him.

DR. FERRIERI: I used to go back and forth, too, and I'm still here.

CHAIR DAUM: Well, good. Dixie, listen, for the B we will not start with you, all right?

DR. SNIDER: H3N2 is a bit more complicated decision, a little bit less clearcut, I think.

First of all there have been fewer isolates this year. I mean, it hasn't been an H3N2

season. So the number of isolates that we have to evaluate is relatively limited.

As I mentioned earlier, we expect that Dr. Cox and presumably some others will be getting some additional H3N2 isolates, although they won't be large in number, given the small number of H3N2 isolates this year, we are really less certain.

And then there is the issue that was just mentioned about the neuraminidase match being not so good in terms of comparison with the consensus.

And, therefore, there is some reason for concern. Nevertheless I think I'm not completely convinced that we have a good alternative in hand right now.

So I'm torn between saying let's wait and get the additional isolate information to make sure that there is nothing new that has popped up on the H3N2 scene versus staying with the current strain.

And I'm not sure what -- how much additional information is going to be available in the next two to three weeks, or what impact a two to three week delay would have in making that decision, or if we would have to wait until a March meeting.

I'm sorry to bring that up at this particular point in time, but this is the point at

which it came to mind. I mean, we have very little information, and a little more information here might increase or decrease our level of comfort staying with the same strain.

CHAIR DAUM: So I am going to try to interpolate what I'm hearing, and that is that you are, at least, tentatively believing that we should remain with the same?

DR. SNIDER: Tentatively remain the same, but inclined, if it is not very problematic, to want to take into account what the new strains that will be looked at demonstrate. And have the flexibility to make a change at that point, if there is something that shows up there that indicates there should be a change.

But if pressed today, if someone said you have to make a decision today, I would say stick with the same strain, because I don't have an alternative that I want to offer that I think is a better option.

CHAIR DAUM: Well, I think the -- I think the practical thing to say back to that is that we are asking you to commit today. At the same time I think everybody's mindful, at least I hope they are, CDC, FDA, and other agencies that are involved, of our comments that if there is a reason to be brought back

to the table by a conference call, or a revisit to this issue, we would like to be consulted.

But I think we are being asked to make the best decision we have.

DR. SNIDER: In that context --

CHAIR DAUM: With the available information.

DR. SNIDER: In that context then, as of today, with the information I have today, then I think I would stick with the A/Panama/2007/99, I think is the one in the current vaccine.

CHAIR DAUM: Dr. Stephens?

DR. STEPHENS: I basically agree with Dixie's comments. I think that as of today our choice is the A/Panama/2007/99 strain. I have the reservations about the neuraminidase issue which have been discussed.

And also a point that was raised earlier, that didn't get a lot of attention, and I think it was by Dr. Hampson, concerning these low avidity viruses strains that are H3N2. I would like to know more about those.

But as of today the A/Panama strain seems the best choice.

CHAIR DAUM: Dr. Kim?

DR. KIM: I guess I concur with the previous two speakers. With the given information available today that if I had to choose, then I think I have to choose the A/Panama with some constraints being outlined by the previous two speakers.

DR. GRIFFIN: I would agree that A/Panama is the best choice for today, with the caveat that I think that the H3N2 strain is the one that we have the most risk, that we might have to change it downstream if we got more important information on new strains that were emerging.

And also would just like to raise the issue, since we know we will be choosing a strain where the neuraminidase is divergent from the strains that are currently circulating, or appear to be circulating in greater abundance, as to whether there is any way to design a study in order to be able to get some information that might shed light on whether having a neuraminidase match is or is not important in this kind of a context.

And so I would just put that out as a thought.

CHAIR DAUM: Thank you very much. Dr. Huang?

DR. HUANG: I think given the current

information that there is drift in the N2, and not very much drift, if any, in the H3, that I would certainly stick with the H3, and certainly would not change H3 just because of the N2 drift.

The other question of the low avidity, or the low reacting strains to the H3, is a bother. And, obviously, one needs to keep an eye on it. I think that Nancy Cox mentioned that for these strains, that if you looked at the N2 pattern, there wasn't any genetic consistency. Correct me if I'm wrong, Nancy.

DR. COX: For the low reacting strains there was no consistency in which genetic group they fell out in, in terms of their HA.

DR. GRIFFIN: For the HA, for the N, right? So, anyway, I come down to the fact that I agree that we should retain Panama.

CHAIR DAUM: All right. Dr. Kohl?

DR. KOHL: Now I can get back to where I was going. I agree with what everyone said. I think right now the Panama looks like the best bet we have.

But I think the pharmaceutical companies have to make a practical decision at this point. They have to go in with one virus to their eggs that are being laid a half a million a day.

And I guess I would ask Nancy, Dr. Cox,

which one should they go with first and give themselves a month more of time on the other one? Is it riskier to go with the H1, or is it riskier to go with the H2? Or whatever.

Would you go with the Panama, or would you go with the Caledonia first?

DR. COX: I would, personally, most likely think that it would be safer to go with the New Caledonia, simply because we have more data, and it seems really solid at the moment.

There could be some surprises with the strains coming from China, but because the picture has been so consistent I feel that we are standing on a firmer foundation with that subtype.

DR. KOHL: With that in mind, then, I would continue to support the New Caledonia first, as the committee has already decided. And then presuming that we will go with the Panama, but we have a month of new data to come in before we have to make that decision firm.

CHAIR DAUM: I am going to put you down as a Panama/defer, and put that flavor in it. Dr. Manley?

DR. MANLEY: In light of all that has been said I concur that we should proceed with Panama. And

that we would expect, certainly CDC and the FDA to be vigilant.

And as you have said if there is indication that this needs to be revisited they would let us know. But I would not defer, I think they should proceed.

CHAIR DAUM: Thank you. Dr. Diaz, please.

DR. DIAZ: Based on my current understanding of the problem, I would concur and be, probably, in the category of continuing with the Panama with a slash defer, as you put it.

I want to make sure that, I guess I'm a little bit confused about the issue. And at least my current understanding of this particular situation, that I guess I'm asking is this correct in my understanding of this.

That the neuraminidase, the differences in the neuraminidase that we are seeing currently tend to fall more along the lines of the Moscow strain, and the Ulan Ude strain, but all three, Panama, Ulan, and Moscow, have similar hemagglutinin.

And that what we are trying to balance here is the question of whether we more selectively go after the neuraminidase change that we are seeing, that seems to be a trend. Or whether we stick with

the Panama strain which will, presumably, if the neuraminidase does not play that large a role in terms of protection, that by going with the A/Panama we will be able to protect ourselves a little bit in case some of that neuraminidase does not continue to progress along the same lines, and perhaps changes and picks up some other neuraminidase characteristics that are similar to other strains, but not necessarily the Moscow or the Ulan.

CHAIR DAUM: Does someone from CDC or FDA want to answer that?

DR. COX: I think that we have, perhaps, injected a little bit of confusion into the process. And I just want to emphasize, again, that when we are looking at hemagglutinin, and we have both antigenic and genetic data, when we look at neuraminidase we have only genetic data at the present time.

And so we don't really know if those genetic changes confer antigenic differences on the viruses. In the past, where we had choices, where we had already clearly decided that we needed to update the vaccine strain based on the HA, then we really tried to match, as closely as possible, the neuraminidase.

But we have never really changed strains

based on the neuraminidase alone, I think. So while we know that in genetic terms the Ula Ude and Moscow have a better matching neuraminidase, we really don't know what that means in terms of protection.

DR. DIAZ: That is a better clarification. Again, I would state --

CHAIR DAUM: That is a very helpful comment. Thank you, Dr. Cox. So where do you come down?

DR. DIAZ: That we should stay with the A/Panama, but if something unusual comes down later that we could defer. But, currently as of now, I would -- the A/Panama seems to be the best choice.

CHAIR DAUM: Thank you. Ms. Fisher?

MS. FISHER: I am abstaining.

CHAIR DAUM: Thank you. And for the same reason?

Dr. Fagget?

DR. FAGGET: Based on the previous discussion I agree that Panama/2007/99 should be the choice at this time.

CHAIR DAUM: Thank you. Dr. Estes?

DR. ESTES: I think based on what we have seen presented today I'm comfortable, I think the A/Panama would continue to provide protection.

Again, there is some concern about where are we on, are we at the peak, or is there going to be some other activity in this curve, because we haven't seen where the end of the curve is going.

So that would be the only concern, particularly with the H3N2 viruses, which do cause more severe disease. So I agree with everyone, but I think this FDA and CDC certainly should have the option to look at that again, and perhaps come back to us if something happens dramatically.

And based on everything that has happened in the last several years, within the next two weeks you should know whether that peak is beginning to go down.

CHAIR DAUM: Thank you very much. Dr. Ferrieri?

DR. FERRIERI: I support staying with A/Panama/2007/99. And based on the information we've heard, it would appear that the antisera to A/Panama neutralize some of these other strains that have been in for studies.

My educated guess is we are not going to see many more H3N2s, and that we will end up staying with this one. I say that for comfort for the manufacturers, and as you are dealing with all those

eggs, I recommend you see the movie "Chicken Run".

(Laughter.)

CHAIR DAUM: Thanks for the recommendation, Dr. Ferrieri. Let's continue with Dr. Myers, please.

DR. MYERS: Like everybody else I would like more data, but I also don't think we are going to likely get much more for this season. So I think that A/Panama makes the most sense.

I think that the many comments about the discomfort about not knowing more about the contribution of neuraminidase in the vaccine is making everybody uncomfortable. And I would hope we collect that data, so that we will make sure what its contribution is.

CHAIR DAUM: Thank you, Marty. Dr. Goldberg, please.

DR. GOLDBERG: I would agree, and I would also echo that we should be collecting some information on the world of neuraminidase.

CHAIR DAUM: Dr. Kilbourne?

DR. KILBOURNE: Well, first I apologize for being a source of discomfort. But on the other hand I'm glad to see a certain amount of discomfort after all these years, in recognition of the probable

important of neuraminidase, and even a trivalent vaccine of the sort.

Having said that, on the basis of Nancy Cox's reassurance that these are just different, at this point, in terms of sequence, rather than prove antigenic differences, I would certainly go along with retention of Panama.

CHAIR DAUM: And I would concur with what you said. I would like to hear more, in future years, about -- as I think Dr. Griffin suggested, and Dr. Kilbourne I think you are suggesting also, to hear more about what these antigenic -- excuse me, what these genetic changes mean in terms of understanding serology, and their importance in protection against disease.

But I think right now we don't know how to factor that information in. And I think that in terms of sending a clear signal to manufacturers so that we have a good vaccine supply next year, there is a lot of solid data to support the fact that Panama is a good choice, and I concur, therefore, with that.

And with that I will launch us into a more controversial area, I guess, and that is the consideration of the type B strain for next year. And if I could be allowed, I would call upon my colleague,

and former Chairman of the Committee, Dr. Ferrieri, to initiate the discussion, lest I go to Dr. Snider yet again.

DR. FERRIERI: Well, very briefly, I think that we have seen data that there has been antigenic drift, and that of these variant strains that have been presented to us, the B/Sichuan is the prototype of such strains.

Although we see no evidence of these moving around in the population, there is the potential that they will, and we would be uncomfortable, I think, staying with the Yamanashi, whatever it is, 166/98.

And so -- and I guess Roland has convinced me, and I reexamined the serologic responses, and I would use the adjective that they are somewhat reduced compared with the newer strains.

And so I think on the basis of data on current strains that might be available to us, and this is where I need correction, the B/Victoria of the A/Sichuan lineage, is that correct, Nancy?

DR. COX: Yes.

DR. FERRIERI: And so -- and that gave moderate growth. So I would make the recommendation that we -- everything works out perfectly in vitro

that -- well, it is in vivo, eggs, sorry. That we would go to B/Victoria/504/2000.

CHAIR DAUM: Thank you very kindly, Dr. Ferrieri. Dr. Myers, please.

DR. MYERS: Let me be sure I understand also, Nancy, the B/Sichuan is of the same as --

DR. COX: B/Sichuan and B/Victoria are antigenically similar to each other, and would be considered equivalent strains, antigenically. And, therefore, in terms of the vaccine properties.

DR. MYERS: I guess what I tend to agree with what Dr. Ferrieri said. I have a concern in that we hear that there is a great deal of activity in China that is B, and that we will have more information in a couple of weeks.

We have spotty geographic activity which is predominantly New Caledonia in this country. So while I tend to agree with what she is saying about the Victoria and Sichuan, the direction we should go, because we are seeing drift, I sure would like to know what those strains in China look like.

I guess -- so I guess this is one I would probably suggest deferring for two to three weeks. But if it is two months until there is another meeting, then I guess I would probably go with the

Victoria.

CHAIR DAUM: Thank you very much. Dr. Goldberg, please.

DR. GOLDBERG: I guess I would like to see more information, also. In lieu of that, the Victoria. But if there is a possibility of deferring anything, I would suggest we do that with this.

CHAIR DAUM: I think that -- let's try and clarify this, because I think you have really two possible decisions to make, and we can certainly have discussion which one is the best.

But one of them would be to say that you believe that a -- I mean, you believe either staying with the same strain, or changing to a prototype such as B/Victoria is what we should now recommend.

The other option is, as Dr. Myers has done, is to say I make no recommendation, but rather defer. I think the decision to pick a prototype now, either the existing Yamanashi strain, or the proposed change of Dr. Ferrieri and now Dr. Goldberg carries with it, and I hope Dr. Cox and Levandowski have heard us, that if something startling happens, or if there is some new information that this committee should consider, we would be delighted to, and in fact want to.

And so that anybody who picks, let's just say B/Victoria, it carries with it that notion that we would like to be informed, and have an opportunity to discuss, again, within the limits of the practicality of the manufacturers, and the eggs, and the chickens, and all the things we've heard that go into this decision, we would like to hear about that.

Deferring, on the other hand means that I give no advice today, and I would like to not do anything until this new information is available in terms of advice.

So I would like people to consider that as they go around the table, and try to help with their best opinion. Granted, it is not a perfect world, but it is where we live.

DR. FERRIERI: Could I add to what I said?

CHAIR DAUM: Yes.

DR. FERRIERI: It is implicit, in what I said, that it would obviously be influenced by new information, and that is the way it has always been in the past, and I don't doubt that we will be hearing from them again.

CHAIR DAUM: Dr. Midthun, did you want to comment?

DR. MIDTHUN: Yes, I just wanted to say that it might be helpful if people said we feel that we need to move away, if they feel we need to move away from the Yamanashi strain to say so, and then if they make that decision and then to say either I need more information before I can give a recommendation, or this is my recommendation.

And that way we would know, at least, if there is a fairly significant trend towards moving away from Yamanashi.

CHAIR DAUM: I'm going to ask FDA to understand that if a person such as Dr. Ferrieri says B/Victoria, we don't have to separately ask her if she wants to move away from Yamanashi.

On the other hand if Dr. Myers says I wish to defer we will ask him whether he wishes to move away from Yamanashi, or he can't say anything to us right now.

So, Dr. Myers, I'm going to dump this back in your lap. Would you like to make no decision at all right now, or do you know that Yamanashi is not your recommendation, can you go any further than just defer?

DR. MYERS: I think I would say we need to move away from Yamanashi.

CHAIR DAUM: Thank you very much. And, Dr. Goldberg, I have your vote recorded. We will go to Dr. Kilbourne.

DR. KILBOURNE: Well, I would vote at this point to move to the Victoria.

CHAIR DAUM: Thank you very much. We are going to do a loop the loop here, and pick up with Dr. Estes on this side of the table, and go up this way.

DR. ESTES: To me the data looks very clear that we need to move away from the Yamanashi probably to a B/Sichuan but I think that picking a specific strain today is too early.

I think more information is needed, in particular how well these various candidates behave in eggs, and so forth.

CHAIR DAUM: Thank you very kindly. Dr. Fagget?

DR. FAGGET: I need one clarification. It would appear that B/Victoria is not isolated as much since April of this year. Am I reading it correctly, that CDC has not really identified that as being present?

DR. COX: The strains, that is just the particular strain. That strain itself was isolated in April. I didn't check, but that is probably right.

But it is a B/Sichuan-like strain, or you could consider it the other way around, that B/Sichuan is Victoria-like, they are antigenically similar to each other. Does that help?

DR. FAGGET: Yes, that helps.

DR. COX: So the viruses like B/Victoria have been isolated.

DR. FAGGET: Been isolated, okay. Well, based on the discussion, and that clarification, I would agree to move away from Yamanashi and to the Victoria.

CHAIR DAUM: Thank you very kindly. Ms. Fisher?

MS. FISHER: I abstain.

CHAIR DAUM: Is it for the same reason?

MS. FISHER: That is correct.

CHAIR DAUM: Dr. Diaz? Thank you, Ms. Fisher.

DR. DIAZ: I would move that we move away from the B/Yamanashi to the B/Victoria, obviously withstanding we need data that may come down the pike, but currently that would be my recommendation.

CHAIR DAUM: Thank you very much. Dr. Manley?

DR. MANLEY: I agree that we should move

to the B/Victoria/504/2000. And, again, that if both CDC and FDA would be vigilant, and if there is reason for us to revisit this in the next three or four weeks, that they would then notify the committee.

That would be my vote, thank you.

DR. KOHL: I agree with the move away from Yamanashi to a Sichuan-like virus that grows well as determined by the manufacturer.

CHAIR DAUM: Dr. Huang?

DR. HUANG: I agree with the move away from Yamanashi, and I would hold a decision on what strain to move to.

CHAIR DAUM: Thank you very much. Dr. Griffin?

DR. GRIFFIN: I think this virus, I mean I think we have more information on the B viruses strains than we usually do, because there has been a lot of B virus around. And it seems pretty clear to me that it has moved away from Yamanashi.

So I would definitely agree that we should move to a strain, it is going to be easier to make one change, at least, at a time. That we should move away to a new B strain, and Victoria right now looks like the one that grows the best.

But if there should be a better one, that

would be fine.

CHAIR DAUM: Dr. Kim, please.

DR. KIM: Yes. I agree that we move away from Yamanashi for all the reasons that have been presented, and to a strain like Sichuan, again, the final selection of the strain will be determined based on the in vivo and other information available.

CHAIR DAUM: I need to clarify that, I apologize. I understand you want to move away from the Yamanashi. But do you recommend B/Victoria today, or do you defer?

DR. KIM: Defer.

CHAIR DAUM: Okay, thank you. Dr. Stephens?

DR. STEPHENS: I agree we should move to a Sichuan-like strain, the choice of which I think should be deferred.

CHAIR DAUM: Thank you very much. And Dr. Snider?

DR. SNIDER: I agree that we should move away from Yamanashi, barring any unexpected events, such as trying to move away from it would substantially decrease vaccine supplies in the country.

And, therefore, I would move to the

Sichuan-like strain, probably Victoria, but I think since the manufacturers are still in the process of evaluating these, it is premature to be too definitive about that.

CHAIR DAUM: Okay. I'm going to record you to be B/Victoria, unless you correct me. Would you like to be a move away from Yamanashi, defer; or would you like to be a B/Victoria?

DR. SNIDER: I think they are going to defer, anyway. They are going to keep playing with this, and if it doesn't work --

CHAIR DAUM: Well, we would like your opinion.

DR. SNIDER: My opinion is that they should choose what works best for them.

CHAIR DAUM: That sounds like defer to me. I'm sorry -- I hope I'm not putting words in your mouth.

DR. GRIFFIN: But I guess I want to clarify, by defer are you implying that they have to come back to us to actually make the strain selection, or that they should defer until they have enough information that they have decided on the best strain?

CHAIR DAUM: That is a good question. Let me ask Dr. Levandowski, or Dr. Cox's opinion about

that.

DR. GRIFFIN: I personally don't think this is where we have expertise.

CHAIR DAUM: It is a reasonable question.

DR. LEVANDOWSKI: Well, I guess we are going to expect the committee to make a specific strain recommendation at some point. I don't think we were expecting that the committee would have to name strains for all the strains today.

And that has been true in the past. But I think that is what you've been telling us about, if we find some new information that we should expect -- and we are expecting, actually, to come back to the committee.

We would be -- we will be continuing to, as we have been, collecting information to try to inform the recommendation. And we do want to come back with that information to you, and have you review it, and make the recommendation at the time that we think that we have as much information as we are going to have.

So I guess I'm just getting a little confused, also, about the terminology that we are using. But I guess what I have been hearing, and maybe you will let me go on with this, and tell me if

I'm right.

Everybody thinks that the strain selection for the H1N1 strain for New Caledonia is really the only choice, and that is where we should go, and the manufacturer should get busy, and they shouldn't expect to have any other changes, barring something really unusual happening.

Whereas with the H3N2, where there is somewhat less information, and we are feeling uncomfortable because it is an important part of the vaccine, and for the B strain because we don't know enough about the performance for the manufacturers, that for those strains you are going to expect us to bring some more information back to you and then you will definitely make the recommendations.

CHAIR DAUM: On the other hand there was a lot of support for the current vaccine strain in the H3N2 situation.

DR. FERRIERI: We voted --

DR. MIDTHUN: Can I make a clarification?

CHAIR DAUM: Please.

DR. MIDTHUN: I guess, really, what I thought I heard was that the majority of the committee said we are comfortable going with the current H1N1, and the current H3N2, barring something that is so

significant that materializes within the next couple of weeks, that we would then let you know about, so that you could reconsider.

However, I think with the B what I'm hearing is that many of you are saying that everyone pretty much has said move away from the Yamanashi. But in several instances people have said, we don't yet have enough information to make a recommendation.

So a deferral in that instance means we will definitely come back to you with information on, further information on B, and get your input on that. That is how I interpret deferral.

CHAIR DAUM: I see three hands. And before I call on them I want to say, give my own vote here. And that is that I believe we should move away from the Yamanashi, and I'm pretty comfortable with B/Victoria as a choice.

So I want to summarize by saying that the committee, that Dr. Midthun summarized the committee's views perfectly, I think, on the 2 A types. And on the B type we are 16 in number voting, one abstention. 15 out of 16 want to move away from the Yamanashi. Nine of those are able to name B/Victoria as the strain they are comfortable moving to, today; 6 are unable to name the strain they would like to move to

today, and would require more information to make that decision.

That is where things stand this minute. And now we will have some more discussion about that. Dr. Kohl, Dr. Stephens, and Dr. Snider.

DR. KOHL: I wonder if I could simplify it, possibly. If we feel comfortable saying a B/Sichuan-like virus, depending on positive growth characteristics for whichever B/Sichuan-like viruses that is, I think that is what Nancy is suggesting.

Because if tomorrow there is a virus that grows better than the Vic, but is still a B/Sichuan like virus, that would fit within our recommendations, and would not have to be a deferral. Would that be simpler?

CHAIR DAUM: It would be simpler. The question is, do all the people that wanted to defer agree with that? Dr. Huang, do you?

DR. HUANG: I do.

CHAIR DAUM: Dr. Estes, do you?

DR. ESTES: Yes.

CHAIR DAUM: Dr. Myers, do you?

DR. MYERS: Yes.

CHAIR DAUM: Dr. Kim, do you?

DR. KIM: Yes.

CHAIR DAUM: Dr. Stephens?

DR. STEPHENS: Yes, that was going to be my point.

CHAIR DAUM: And Dr. Snider?

DR. SNIDER: Yes, that was going to be my point too, not to tie their hands.

CHAIR DAUM: I think we've helped considerably, thank you for whoever raised that point.

DR. GRIFFIN: And then on the other side, all the people who voted for B/Victoria would also be happy if there was another Victoria-like strain that grew better, and that would be better for manufacturing purposes.

CHAIR DAUM: I think that is true. I think the concern about the Victoria is largely the manufacturing issues. And so we should be able to say that as well.

Dr. Goldberg?

DR. FERRIERI: It is actually just as good in manufacturing, it is as good as Yamanashi, probably.

CHAIR DAUM: We heard that from one company.

DR. FERRIERI: Sorry, you are right.

CHAIR DAUM: Dr. Goldberg?

DR. GOLDBERG: I guess I would propose that certainly my vote for B/Victoria would fit into a good Sichuan-like virus with good growth properties. So I would change my vote to go with the other.

CHAIR DAUM: I think we have come to a nice closure on this. Does anyone want to make any other points that haven't been made regarding this issue?

Then I would like to adjourn the meeting today, and remind the committee members that tomorrow the good news is 9 o'clock is your starting time.

(Whereupon, at 4:09 p.m. the above-entitled matter was concluded.)

CERTIFICATE

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

Before: DHHS/FDA/PHS/CBER

Date: January 30, 2001

Place: Bethesda, MD

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