we get local inflammatory reactions and, hopefully, local immune reactions as well as systemic immune reactions. And so we would expect some local reactions as well as some systemic reactions. And so I think, you know, the eye symptoms, perhaps some muscle aches as well as nasal congestion are to be expected.

The conjunctivitis is an interesting issue, particularly as it relates to the allantoic fluid versus the vaccine, which is not -- I haven't sorted out completely in my mind and would like to have sorted out.

Other people have mentioned the rare events, and the way we're going to find out about that is if we do have larger sample sizes and that becomes a tough issue with regard to whether you require more trials, pre-licensure or post-licensure monitoring. It also impacts on what kinds of recommendations you make down the line and how rapidly you want uptake. And these are some issues that are going to be discussed by other groups, I know, but I'm already beginning to worry about them.

And then there are issues around the genetics that have been raised that I won't go into again, but they do concern me. There is the issue of

transmission, of course. That could be good, that could be bad of transmission of the vaccine virus. But, of course, if there's reassortment, particularly if there's reversion to a virulent strains that obviously is concern from the safety of a population standpoint, as others have already mentioned.

So, I guess -- you're going to pin me down, so I'll go ahead and say it's a provisional no we don't have it in hand right now, but I would anticipate that FDA would be able to get these data, that the manufacturer will work to get these data. And I would hope that it would be possible to get enough information to utilize this vaccine in the near future, because I think it does fill a nitch and would be helpful for preventing what is a very significant disease.

CHAIRMAN DAUM: Thank you very much, Dixie, and particularly anticipating that I would pin you down. I'm very grateful to not have to do that.

I guess I'll finish the discussion by saying that I think Dr. Myers may have been the first one to speak my mind, and that is that there's a great deal of data that bear on safety that are in the process of analysis and being integrated into the database here at the FDA. So, I must join the people

who voted not, but with the caveat that it be sort of a work in progress kind of no.

I would love to have a chance to revisit this issue when all of the data that are available have been processed by both the sponsor and the FDA. I again believe that a tremendous amount of progress has been made since I last heard about this, and that I'm on the whole, excited about the prospects for this vaccine being part of our armamentarium in the future.

A couple of things that I would highlight are (1) I believe that there is a risk for -- at least potential for risk for a flu-like illness in the days following vaccine, and I'd like to hear more about that. I mean, we've sort of heard about it in Houston children when cultures weren't really being encouraged in that period. And I'd like to see that studied in a little more detail.

The transmission issue is an important one, although I suspect from what I've heard today it's not going to turn out to be an important clinical problem. But I think in the climate we have today with vaccines and new vaccines we've got to be very sure, perhaps even a priori sure that it's not a problem.

The asthma issue, I think, is an important

one. I'm not sure that asthmatic children would accept this vaccine if they knew there was a higher risk for an exacerbation following its receipt. And I think that given the data we've had, they may be a tip of the iceberg phenomenon and biased against people who weren't able to report that their child had asthma. And I'd like to see some more systematic study of that.

Pneumonia and conjunctivitis and nasal congestion, I think there's more data that's in the mill and being processed. And, again, I'd love to hear those data when FDA and sponsor have finished reviewing them.

The annual dosing issue I think really hasn't been addressed and I think is an important safety issue. Although, again, I suspect that when it is addressed, it's going to be a safety concern. But without data, who can say for sure.

I feel very confident in the safety data I saw for healthy adults over 50, but many adults are not healthy over 50. And it would be, I think, important although perhaps not directly germane to this indication to have some sense of what happens when you immunize people who are not 100 percent healthy.

So, that's my view on it.

Now, stepping back into the Chair's role, there are four votes yes and 8 votes no. Sorry 9 -- 10. That can't be. What do you have?

MS. CHERRY: I had ten counting you.

CHAIRMAN DAUM: I have 9. One second, please. I'm sorry.

There are 10 no's. There are 4 yes's and 10 no's. Of the 10 no's, 6 people commented that they view this as a work in progress situation and would like to hear and review the data when the processing part has been finished. So, that's an important qualification, I think, on a large part of the no vote. And I think that it's important convey to the sponsor that there is a lot of interest in the progress of this vaccination and that we feel like more data on these safety issues, particularly that have been raised, would be very important.

Dr. Midthun is concerned that we really can't accept provisional votes. We do have the provisions that people have raised, not as provisions per se, but everybody's comments have been recorded and notes in the register and available for people who want to review the record of what was said here.

So, I'm going to read out the votes that

I have and I'm going to ask each person to at least confirm by nod of the head that they're not provisional, these are your votes. If someone wants to discuss that again, please feel free.

DR. EDWARDS: Could we ask a question just about that? If the FDA in their review find something problematic, I think that there are many of us who would be uncomfortable with that. I guess that how are we to interrupt what they find?

CHAIRMAN DAUM: Well, I think that's always an issue, right? Because we're looking at one frame of the movie right now.

DR. EDWARDS: But we're looking at an earlier frame than we usually see.

CHAIRMAN DAUM: Indeed, but that's still the frame we're shown.

So, does someone from FDA want to comment on that?

DR. MIDTHUN: I think we're voting on the information that we have in front of us today. I think that it's not uncommon for people to say I vote yes or no, I have certain caveats about that. But I think what we do need to have is a yes or a no and, of course, we will note the caveats in the record. And, of course, you know take that under advisement.

Does that help?

CHAIRMAN DAUM: So here's what I have. I have starting from your side, Dixie: Dixie no; Kohl no; Goldberg no; Fisher no; Stephens no; Griffin no; Katz yes; Schild yes; Cox no; Eickhoff yes; Myers no; Edwards no; Steinhoff yes; Daum no. That I believe is what you all said.

There's your comfort, Dr. Midthun.

DR. MIDTHUN: Thank you.

CHAIRMAN DAUM: I won't reread the summary, because it's what I said a moment ago, but the Committee would like an opportunity to reconsider this and readdress this when the agency and sponsor working together deem it appropriate to do that.

I'd like to, I think probably briefly, because I suspect that things have been said already that deal with discussion points 3 and 4, at least I hope FDA has heard things that deal with discussion points 3 and 4. But what I'd like to do is give each Committee member a chance to speak to these.

And with all due respect to the agency, I think I'll take them together and ask people go once around and ask for comments on items 3 and 4.

We have item 4 on the board, which is good. Well, we could leave 4 up. And just to remind

you that 3 is Dr. Cox's favorite issue today, please discuss the need for data on concurrent immunizations, for example, in children and travelers.

And that's not to single you out, Dr. Cox, I think many of us feel that way, as we'll see in a moment.

So, Dr. Snider, would you start us off, please, and we'll try and get this done.

DR. SNIDER: Three and 4, or just 4?

CHAIRMAN DAUM: Three and 4, please.

DR. SNIDER: Well, everyone -- or many people, at least, have mentioned the need for data on concurrent immunizations. And, of course, would agree with that. I think in both populations that have been identified here, children and travelers, but children in particular we know what vaccines are likely to be used concurrently because we know what vaccines are recommended at the particular ages that these children would be vaccinated. So, no need to go through identifying those.

For travelers, this could be a little bit more problematic, but we at least know the range of vaccines that are recommend for various parts of the world. For some of those, it's going to be more common than others. And I don't think it's going to

be possible for some of the rarer vaccines, more unusual vaccines to get a lot of data real quickly. Nevertheless, it would be nice to have that. .

With regard to point 4, we've had a lot of discussion about the use of this vaccine in high risk subjects. The sponsor is not asking us at this point in time to allow them to or to make a recommendation to FDA for those indications. At the same time, we were reminded that, at least in one of the trials here, that many children either were not diagnosed with asthma, for example, or the parents did not acknowledge the presence of asthma. So, asthma is something that is going to be problematic, it would appear, no matter if you do put it in as a counterindication right now. So it would be, I think, very useful to gather additional data about asthmatics.

Clearly, high risk populations, immunocompromised populations in particular are of interest. They're of interest with regard to this being a live virus, albeit attenuated, and how it might perform in various immunocompromised individuals. We have some reassuring data from small numbers of HIV infected people, but it would be useful to know more about those.

High risk subjects also can refer to those who are at risk of getting influenza. And, again, I guess the approach I would be interested in is what I had already indicated with regard to those over 65, which would be useful since there's already some suggestive data that it might be that the live attenuated vaccine would give added protection above what the inactivated vaccine gives to be able to look at populations who receive the inactivated vaccine and have one group, one arm also receive the live attenuated vaccine.

You just alluded to he issue of annual revaccination in adults. We don't know what's going to happen with regard to yearly administration or if we have to have it the yearly administration. I presume we're going to start out of wanting annual revaccination. We're likely to strains every year and we're going to have to be on the lookout for what happens with regard to safety and efficacy in that regard.

Assessment of attenuation has been discussed, as has the potential for transmission and reversion and reassortment by those who are much more knowledgeable than I am. All I'll say, again, is that those are issues of concern, issues for further

investigation.

CHAIRMAN DAUM: Thanks, Dixie. We have two members, Mr. Kohl and Dr. Eickhoff who are needing to leave by 3:00. So I'll ask Dr. Kohl to go next -- sorry. A whole lot more of us.

Well, then we'll do the best we can. Who has to leave at 3:00 besides Dr. Kohl and Eickhoff. Dr. Myers, okay. No comments.

So, let's go with Dr. Kohl, Dr. Eickhoff, and Dr. Myers and try to get them up and down by 3:00 and then we can have the rest of the Committee finish off.

DR. KOHL: I think it's pretty much been said, so I'm not going to repeat what we've already discussed.

I would like to see in addition to concomitant immunization, in travelers I'd like to see a small study looking at immunization and then anti-malaria use. Because in other live immunizations there's some doubt that anti-malaria may be immunosuppressive, if you will.

I think some of our discussion about the risk in high risk hosts in terms of transmission has to be tempered by the fact that this is an ambiguous virus, and it reminds me a little bit of the Varicella

discussions that we've had in the past, namely I think I would much rather have a high risk host get this virus than get the wild virus, and the same thing for an asthmatic. Having said that, I still would like to see data in those subjects to reenforce that feeling that this will be a milder to asymptomatic infection.

I think I'll stop there.

CHAIRMAN DAUM: Dr. Eickhoff?

DR. EICKHOFF: Well, this is sort of a motherhood and apple pie list, it all needs to be done.

For the concomitant vaccines, yes, this is an absolute must, particularly I'd be concerned about the live virus antigens that may be given concomitantly. But the killed antigens need to be looked at as well.

In the case of adults, this would certainly include hepatitis B as well as pneumococcal vaccine and there are, you know, a number of others that would apply to children.

High risk subjects, certainly those need to be examined within detail.

Annual revaccination need more data, not only in adults but in children as well.

And the last three items, again, like

Dixie I think others who are more knowledgeable than I have commented and I'm sure will comment further.

CHAIRMAN DAUM: Thank you, Ted.

Dr. Myers, can we hear from you.

DR. MYERS: It'll be brief because everybody has listed everything on my list.

CHAIRMAN DAUM: Brief is good.

DR. MYERS: We've already talked a lot about the 12 to 24 month data that's needed. I guess I would encourage the sponsor to consider that 6 months to 24 months because of the data that Dr. Glezen showed in the burden of disease in the younger infant.

The one versus two dose schedule needs to be examined systematically so we can make decisions about whether it's one or two. And if it's two, at what age.

And then more seasons of adult data I think would be very desirable.

I think everybody else has covered everything on my list.

CHAIRMAN DAUM: Thank you very much. I think that covers the folks that have to leave at 3:00, not that it's 3:00 yet.

But Dr. Goldberg, could we resume with

you, please?

DR. GOLDBERG: I don't have much to add. Everything I have is covered.

The only other thing that I think at some point ought to be studied is the method of administration in relation to the risks of transmission and the variability in administering the nasal dose, whether that effects complications in the child. As well as the probabilities of transmission should be looked at.

And I think the other issue is I think perhaps some consideration should be given as to whether or not there's a way of assessing the presence of asthma prior to vaccination in a structured way so that you might be able to do a better job of identifying children at risk, in particular, or adults in the presumably healthy.

CHAIRMAN DAUM: Thank you very much, Dr. Goldberg.

Ms. Fisher, would you care to comment on these two discussion points?

MS. FISHER: Well, I think it's important that whatever trials are held to generate data on concurrent vaccination or high risk individuals that the same follow-up protocol and exclusionary criteria

should be used and that there should be an attempt to specifically identify biomarkers, not only for those who would be more likely to have an adverse event, but also those who are non-responders.

I think the issue of reassortment of vaccine strains with wild-type virus is extremely important, and there should be much more investigation into this possibility that could generate more virulent or vaccine resistent strains.

CHAIRMAN DAUM: We thank you.

Dr. Stephens?

DR. STEPHENS: I think we all share similar feelings about that we need -- we have concerns and we need more data on both of these points. Just a couple of quick points.

One is the fair testing model for attenuation. I think I would like to see a better, a more robust model. I realize this is the traditional model, but certainly a better model for attenuation or better issues addressing attenuation would be an area.

Thank you.

CHAIRMAN DAUM: Thank you, David.

Dr. Griffin?

DR. GRIFFIN: Again, most of the points have been covered, so maybe I'll just come in on some

of the virologic ones at the bottom that have been less adequately addressed, although the other side of the table will be able to do this.

Attenuation, I feel quite comfortable with the attenuation of this virus with its stability in a number of situations, so I really don't regard that as -- I mean anymore data is fine, but I don't regard that as really a major issue.

Potential for transmission, clearly it can be transmitted. Obviously it doesn't occur too often.

I think, again, reversion is not a big issue, but just because I think the vaccine really is very stable. I think it's just one of those things that's going to have to be monitored as far as transmission, and there the risks are really to other populations that perhaps would be more vulnerable when they -- that wouldn't normally be included in the normal vaccinees, you know, asthmatics or whatever.

Lastly, I think the potential for reassortment, again, I don't consider this a major concern as long as new H1N1s aren't introduced in a pandemic kind of a situation that would have the opportunity to reassort with wild-type viruses. And the background genes are clearly attenuated, so any reassortment that would occur in the normal kinds of

situations are going to give you less virulent viruses rather than more virulent viruses. It would be only the potential for reintroduction of new H1N1s and pandemic type situations which, obviously, would not be voluntarily done.

And I can also represent Sam here.

So he says you need to complete the 2000 child study on concurrent MMR. Also might consider concurrent VZ, as well are concurrent nonreplicating vaccines, pneumococcus, H. flue, b-conjugates, DTAP, etcetera. That's number 3.

And number 4, more data on vaccine in asthma patients. Issue of reassortment of vaccine strains with wild-type influenza viruses. The question is whether in vitro and in vivo and experimental animals studies would be appropriate.

CHAIRMAN DAUM: Thank you Dr. Griffin and Katz.

Dr. Schild.

DR. SCHILD: I would include among long term strategies the setting up of reasonably intensive viral surveillance if and when this vaccine was introduced to look for the virus itself, reversion to virulence, the presence of genes that might become linked to other viruses through reassortment and so

on.

I would also like to address issue of introduction of additional strains of vaccine that might be used in the future, new antigenic varriants. And I think it's completely essential that we don't rely too heavily on genetic information on the vaccine strain itself, but clinical data ought to be produced in relation to every single new vaccine produced by this recombination process.

And I think, again, looking to the future it needs to be careful discussion about under what circumstances one might use such a live vaccine in the face of a pandemic.

CHAIRMAN DAUM: Thank you, Dr. Schild.

Dr. Cox?

DR. COX: Yes, most of my comments have already been covered by others. I believe it was Marty who suggested that having data in the 6 months to 12 month old children would be extremely useful given the burden of disease in that age group.

In addition, I think it would be really useful to have information about -- information in the 50 to 64 year old high risk group.

I think that with regard to the virologic and genetic issues, there is a certain amount of data

that are available but it would be -- there are a lot of virus that could be analyzed in detail. They're available, it's relatively easy to do the genic analysis. It would give us just a higher degree of certainty about what is actually going on with the individual mutations that are occurring.

I was very pleased to hear that the sponsor is actually going ahead with reverse genetic experiments to determine the contribution of the individual mutations to attenuation. And I think then once those studies are done, it will be very easy to screen for reversion of the key mutations.

CHAIRMAN DAUM: Thank you very much.

Dr. Edwards?

DR. EDWARDS: Obviously, lots of the ideas have already been expressed.

I think one possibility that is intriguing would be that if this vaccine were to be given to a large target population that could be very, either with government and industry funding that could be carefully assessed in terms of outcomes, adverse events, virologic studies and really have a very, very extensive evaluation of it in the real world given to real children and real adults. And I think that might give us all a measure of safety and a much more

controlled way that the vaccine might be introduced.

I think the one and two dose question is very important, particularly for the public health issues that Dr. Glezen addressed.

I think the travelers issue is very difficult, because I'm not quite sure which vaccine you would be giving to the travelers and whether everybody should have in their freezer leftover vaccine for the next year, because I can't imagine that the company would be making both North American and South American vaccines in different times, but maybe they would. But I think the practicality of a travelers vaccine and how you would get it, and for the small number of individuals that you would be delivering would be somewhat of a difficult issue for the practitioner.

I think repeated vaccinations in adults is very important, whether they continue to be efficacious. And I guess whether this will ever be done is another question, but I think a head-to-head comparison of the two vaccines, TIV and CA vaccine, in terms of different populations might be intriguing.

CHAIRMAN DAUM: Thank you, Dr. Edwards.

Dr. Steinhoff?

DR. STEINHOFF: It's funny. Either I'm

the first and I don't know what to say or I'm the last and it's all been said already.

CHAIRMAN DAUM: It's that end-of-the-table problem.

DR. STEINHOFF: Right. You know, many of the comments I have mentioned earlier or have been mentioned by others --

CHAIRMAN DAUM: That's fine. I mean, you don't --

DR. STEINHOFF: I just want to make a couple of points.

The first one is that I agree that we need the concurrent immunization. I think that's clearly needed, especially for infants.

I also think that the issue of the use of vaccine in high risk subjects repeatedly mentioned, but let's not forget the major high risk group which doesn't have a disease are infants under one year of age. So once we get down to 1 year, we need to think about the lower group where there's a lot of hospitalization and clinic visits.

The annual revaccination of adults, repeatedly said we need to look at that and it's overall effects in comparison with the current strategy of annual revaccination of adults over 65.

That's all I'm going to add. Thanks.

CHAIRMAN DAUM: Thank you very much.

Before I make a few comments or call on Dixie, can I ask if there's Committee members that would like a cab at the termination of the meeting? Dr. Goldberg, Dr. Snider, Dr. Schild. We have four customers.

Now, Dr. Snider?

DR. SNIDER: Just one point that is not directed to the FDA or the manufacturer, or anyone in particular, but just a notation that clinicians, I think, are going to have to address is the question of antivirals and at what point in time they can give a person antivirals in a circumstance in which there is an influenza outbreak. And it would be nice if someone were able to answer that question for the clinicians, because otherwise they'll be struggling with that question.

CHAIRMAN DAUM: Thank you.

I'd like to conclude by adding a few comments of my own. I think that everything that's on the list for discussion points 3 and 4 does need to be done. I guess I'd express my own surprise if the concurrent immunization studies produce clinically important messages, but I do think that people will be

satisfied having them done and unsatisfied if they're not done.

One of the things that intrigues me about all this is the lack of understanding about how this vaccine protects against influenza. I voted yes on the efficacy question because I thought the data were convincing, but I'm not sure I know how to measure a surrogate for that. And so when we approach things like these concurrent studies, I'm not sure I know how to do them or how to interpret them, and that's going to need some thought by everybody that's involved with them.

I'm going to also mention my usual influenza saw horse. This can be everything I'm saying does not necessarily need to be done prelicensure, but I think needs to be done at some point.

I would like to study vaccine failures. I don't think we really understand much about them, and I'm amazed that with influenza vaccine, unlike almost every other, we're not really focused on them. And I don't know who fails vaccine or why. And I'd like to put in place some kind of surveillance study and monitoring process to learn something about that.

I'd like to know a little more about --

this is certainly a post-licensure issue -- of what the real world delivery of this vaccine is going to be. I mean, in study conditions you can restrain an infant and give him the 0.25 mls pretty easily. But what happens in a busy clinic or busy inner city clinic when people attempt to do this? Will it be done carefully? Are there cold-chain issues that are going to have to have special considerations.

We didn't hear much about ethnic diversity in terms of subjects and most of the subjects were the kind of subjects that usually end up in these studies in their first phases. And at some point people might want to ensure that people of racially diverse backgrounds respond with appropriate side effect profiles and immunogenicity to these vaccines.

People have talked about young infants under a year, and I echo that. And preparing to be sort of old-folk myself, I'm also interested in hearing more about the elderly because they, after all, are at real high risk for serious influenza. And I think that's an important group to target for study.

So, most of these things are suggestions for additional investigation as opposed to regulatory issues.

And that's all I have to say.

So, with that I'll just check with my FDA colleagues to make sure they feel like they got their money's worth, and we declare the meeting adjourned.

(Whereupon, at 3:11 p.m. the meeting was adjourned.)

CERTIFICATE

This is to certify that the foregoing transcript

in the matter of: VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

Before: CENTER FOR BIOLOGICS AND RESEARCH

Date: FRIDAY, JULY 27, 2001

Place: GAITHERSBURG, MARYLAND

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