occurring with the unexpected complication of GBS occurring, there actually were many substantive studies of those vaccines in larger numbers of patients. You would have only detected a rare adverse event like that if you had done pre-licensure studies, let's say, of a million individuals. So the question is what do you get for additional studies and the investment?

We're not here in any way to say they shouldn't be done. We do want input about that. But I just think it's important to give the context that this is not -- that while the dose is twice the level of antigen in the single -- total antigen in the single inoculation and it is less immunogenic, essentially this is the same vaccine. So we welcome the comments, but I think it is, as several people have said, an unusual situation, but --

In terms of your other question, there are other options for how vaccines

could be used. And under licensure, there is a so-called emergency use authorization if the national emergency is declared, etcetera, etcetera. But our goal here isn't to lower standards for licensure. What we look at in licensure is does the potential benefit of the vaccine in this situation outweigh the risk, and what you're hearing here is that an indication is for not going out and immunizing the entire population tomorrow but being prepared if there were a pandemic to immunize people or to immunize people who potentially are at a high risk o exposure to the avian virus or a virus that's transmitting among humans.

But again, to go back to it, we do every year with a vaccine that is only minimally different from this under licensure -- the annual vaccine, tens or fifty million people are immunized annually. So there's a context with the existing vaccine that gives us information that's

applicable to this. Let's say that it's information that we would consider, and then there's a context with the proposed use and the risk situation that needs to be considered.

DR. KARRON: Dr. Webster?

DR. WEBSTER: Thank you. I would like to follow-up the comment to Bob Couch and support his attitude regarding acceptance of licensure of this vaccine. It's an interim vaccine. We have to look upon this as an interim vaccine. It does not meet the standards of the seasonal vaccine.

But this is an avian vaccine, and we don't know what the correlates of protection are. We will not know what they are until the pandemic comes. And with the numbers that we have, this is a very serious situation. The modelists tell us that this virus, if it does acquire human-to-human transmissability, the first wave will go

through in three months. When are we going to prepare the 600 million doses of vaccine? We need this pre-pandemic stockpile, and we need to use it to determine whether we can prime people.

There are many additional things to do with this. We're only at the beginning, and it worries me that if we don't like this one, there are more better ones in the pipeline. What are the consequences -- my question is what are the consequences if we don't license this one, acknowledging it's the best we've got and it's not all that great?

DR. COUCH: Just a quick comment that I think you should say we'd rather not use this vaccine, but if we have to use it, a vaccine for H5, we'd rather have a better vaccine. But that's all out in front of us.

DR. MODLIN: I just wanted to say I concur with both Dr. Couch and Dr. Webster on the issue at hand. And secondly, I want

to both acknowledge and express my appreciation to both the agency and the sponsor for bringing this forward in a pubic way. I think it's -- we all are agonizing a bit over the uncertainties and clearly agonizing over what we would also consider, I think, a disappointing immunogenicity for this vaccine.

But nonetheless, I think it's very, very important that the press and the public hear this and this open and transparent way, not only to understand the uncertainties and the anxiety but also to understand the progress has been made and look at the progress we intend to make over the next few years. So again, I want to express my thanks.

I -- even though the immunogenicity is disappointing, I'd just like to point out that it's in a range that's not a whole lot different than the efficacy that we already recognize from

inactivated vaccines in very young children, even with two doses. And these are vaccines that are already licensed down to age 6 and so that there is precedent for using licensed vaccines in a certain population already.

And then finally, I'd just like to say that I think that the consequences of any other action would provide -- would be far worse. I think the last thing that we'd want to do would be to discourage manufacturers from collaborating with public health authorities in all of this. And if we were to set a roadblock at this point in time, I think there would also be a considerable concern that we would complicate distribution of a experimental vaccine should it need to be used. So I would be very supportive.

In terms of safety, there may very well be that we can learn a little bit from our experience from just a few years

ago with smallpox. Smallpox vaccinia, when we were considering how the vaccine would be used, we were identifying certain groups that would be prioritized to receive vaccine much in the same way that the influenza plan is unrolling. And it was pretty clear that we weren't going to be able to anticipate all of the adverse events that may arise.

At the time, there was aa group formed by the ACIP. The CDC and the Department of Defense, the Armed Forces Epidemiology Board collaborated on basically a safety monitoring board that was put -- that was established at the time that the vaccine program, the vaccinia vaccine program was being rolled. And it actually turned out to be a very effective step in that this was a group that was able to establish thresholds for concern for certain adverse reactions, to set up surveillance mechanisms for monitoring for unanticipated adverse reactions. And indeed, they did

come along such as the myocarditis that occurred with vaccinia that was completely unanticipated. And these were dealt with in a rather effective way.

And so maybe some sort of a similar mechanism case would be very useful as we're planning to deal with these pandemic influenza vaccines.

DR. KARRON: Thank you. Actually, I think that's a good segue also into what I'd like to do now which is o have a larger discussion on if this vaccine were to be licensed, plans for post licensure monitoring of safety, immunogenicity, effectiveness. In listening to the earlier presentations this morning, I was a bit struck with the probably exception of the DoD, there's a bit of a mismatch between our existing monitoring systems and the population most likely to get this vaccine, so that our monitoring systems are largely targeted at children and we're talking about

vaccination of first responders. So maybe we could have some discussion of what kind of information we would want to collect and what kind of systems might help us collect that kind of information. Dr. Wharton?

DR. WHARTON: Following up on Dr. Modlin's comment about the smallpox vaccination program, I do think there may be some lessons learned from that program in terms of under those kinds of extraordinary circumstances what kind of safety monitoring systems, in fact, work.

And I -- at least my impression is that, really, the enhanced passive surveillance system that was implemented as part of that program was effective at identifying the unexpected severe adverse events which occurred as part of that program, because this is not -- this vaccine is not going to be administered, in all likelihood, in anything remotely the same as the seasonal vaccine program. It's likely

to be administered in special clinics. There's an opportunity to provide some special guidance information, facts sheets and so forth.

So I do think it's possible to do an enhanced passive surveillance system that I expect would be much more effective than our usual approaches to passive surveillance as part of the influenza vaccination -- as part of our seasonal influenza vaccination program.

DR. KARRON: I'd actually like to hear from committee members about their thoughts about monitoring immunogenicity of this vaccine in a larger population, if they think that that would be useful post vaccination?

DR. SELF: I'll pile in first. Yes. So given the limited immunogenicity data that's available to date, having some program to monitor, at least under random sample, immunogenicity in the roll out just

would absolutely be key in my opinion. In terms of effectiveness, I think it's going to be hard, if not impossible, to really define in anything but the most crude way what the effectiveness of this vaccine is. And ordinarily, that would trouble me greatly, but the way this is being characterized as a stopgap and as a vaccine that's not likely to have legs for the future, that actually doesn't worry me so much.

The information, though, that I think would be -- that could be obtained that would be really critical would be the relationship between these assays and clinical outcomes. And if there could be a program for -- among the first responders or the high risk of storing a sample so that then one could go back and relate those outcomes and define, at least in some way, correlate protection. That seems to me to be the most critical information around

effectiveness that could be obtained from this type of vaccine. I guess I'll stop there.

DR. KARRON: Dr. Eickhoff?

DR. EICKHOFF: I'm going to what Dr. Self just said. Yes. Immunogenicity data would be useful but not as an end to itself, only as supporting clinical efficacy by HAI titer. That much is, I think, a bare minimum in terms of efficacy.

In terms of safety, I don't have a clear idea -- I mean the issues in safety are not so much what we've heard about today in the couple of hundred volunteers because that's a given -- unusual neurologic events and totally unanticipated events such as carditis in smallpox vaccine. I'm not exactly sure how to go about setting it up, and it would require extended conversations with folks from CDC and Sanofi about how to go about this. Because I don't see it clearly right at the moment.

But those two issues, I think, would be important in following licensure and use of this vaccine.

DR. KARRON: Dr. Goodman?

DR. GOODMAN: A couple of comments. I think we totally agree that trying to better define correlates of immunity would be really good, and so I think that's a good suggestion and we should think about if we can practically do some of that. For example, if the vaccine is used for a high risk individual, storing serum to then allow correlate with efficacy.

I would say we shouldn't give up on the idea that I think it will be extraordinarily difficult and, as you said, it will be only gross measures, like does a vaccine protect you from hospitalization or death or something like that. But I think we should think about how we can measure that during a pandemic, because I think a couple of things.

I think, yes, this vaccine could be less effective than we think. It could also be more effective than we think. You know, essentially, if you prime the immune system, it may be that you'll get substantial protection irrespective of antibody levels. You know? It's a race between the immune system and the -- but we just don't know.

It could also be not effective. And I think that could also be true even of next generation vaccines, which -- so we need to be able to evaluate those in a pandemic. I mean -- so I think irrespective, we would welcome, and I'm sure our colleagues, how we'd do that.

And then on the safety thing, I think per Dr. Eickhoff, you know, this is a challenge that the entire medical product industry, the FDA, CDC is facing now, which is how do we detect rare events, how do we determine whether they're really due to a

product. And again, I think the challenge, and Melinda Wharton has really defined it, is how do we set that up ahead of time for the populations that are likely to get this early in its use.

Now again, some of that, if there are people who are going to go out and get exposed to human clusters or in these areas, some of that data may be obtained before a pandemic potentially. But I think, again, in a pandemic, how do we get robust detection signals that are oriented towards the first people likely to get the vaccine. And, you know, the Defense Department's is one very good example of where there may be potential to do that. But I'm not sure there aren't other approaches we could take.

DR. SELF: So just to clarify. I wasn't suggesting that the cohort or the case control studies to try to estimate effectiveness shouldn't be done, but just from a practical point of view, if the

response rate of this vaccine is 40 or 50 percent, and because this is built a priori, if there is a mismatch with the emerging strain, you know, cut that down by another half or two-thirds.

You know, the prospects of enough efficacy to distinguish from the sorts of selection biases that those study designs are going t have seems just very low. So, yes, you should them, but in my opinion, I think the real value over the long run is going to be in those correlate studies.

DR. KARRON: Dr. Hachey?

DR. HACHEY: Just one point of clarification as far as DoD. Our current concept is not to start providing the vaccine to our active duty personnel as soon as it's licensed.

What our concept is is when the pandemic appears to be imminent, so we have a robust, let's say, WHO base for -- that's -- the writing is clearly on the wall that

we're going to be evolving to Phase V and then to VI to a true pandemic, that's the kind of trigger that we're looking at as far as providing the vaccine to our personnel.

So, yes, there would be a window of opportunity to get some of that data, but right now for our active duty members who are, let's say, stationed in high risk areas where there's avian disease but still WHO Phase III, at least at today, our plan is not to provide the vaccine to those folks. I mean that may change as vaccine supplies change.

But right now out concept is when the pandemic appears to be quite imminent, that is our trigger. And with the amount of vaccine that is likely to be available to us, clearly we won't be immunizing DoD totally but fairly select groups. With our current vaccine supply, we have probably enough for about -- I think it's about 700,000 personnel. So a decent end but

we're not talking millions.

The other point is as far as looking at efficacy, one thing to keep in mind is that I think a lot of the first responders are probably also going to have access to antivirals. So I don't know how that would kind of cloud the efficacy question.

And just one additional advantage to actually using this vaccine is that many of the folks who are likely to receive it are also likely to be in that top tier for the pandemic specific strain vaccine. If it does turn out to be a decent primer, than that does decompress that top tier and allows you to fill that top tier with the pandemic specific strain much quicker.

DR. KARRON: Dr. Word, did you have a comment?

DR. WORD: It workshop just related to when you were talking about how to gather more immunogenicity as well as

safety data and just made me think back of one of the -- the first time that we had a delay in the production of seasonal influenza vaccine. And one of the first things we recognized was that the Government had no control over distribution.

And I think we're in a different situation if this is approved whereas the Government will have it. And I guess I'm looking at it in terms of you have a designated administrative cite. You're sending people there. You can collect the data on them. You'll be able to obtain it and store it. And whereas the Government, you have more control to gain that data.

So the gap may not be as great as or as challenging as we may see and just say this is the first time we will have something nationalized as opposed to looking at what distributor will provide it for us.

DR. KARRON: Dr. Jackson?

DR. JACKSON: My recommendation

would be that any program of actual use of this vaccine would incorporate a method to obtain at least a post second dose blood sample for storage on vaccine recipients, because I, of course, think we need to know a lot more about the immunogenicity of this vaccine, plus I think we'd really want to know how response to this vaccine would predict subsequent boosting response to a different pandemic-formulated vaccine. And I don't think we'd want to lose that opportunity by failing to collect blood specimens that might prove to be extremely useful later on.

DR. KARRON: I think if there are no other comments or questions from the committee, we are probably ready for our vote, and I'd like to ask that the first question be productive.

Okay. The first question is are the data sufficient to support these effectiveness of this product for use during

a pandemic or in situations of potential high risk exposure. Dr. Modlin, we're going to start with you.

DR. MODLIN: I've read this question over a number of times and recognize that it actually is very well-worded. Somebody spend a lot of time working on that I'm certain, Dr. Baylor, Dr. James. Obviously, the data are not sufficient to give us any confidence with a degree of effectiveness, but the data are sufficient to support the effectiveness, so I will vote yes.

DR. KARRON: Dr. Couch?

DR. COUCH: Despite the fact that Dr. Modlin said he spent a lot of time on the language, I would change it. Are the data sufficient to support a degree of effectiveness for this product? By all means, yes. And I would say yes to that and to the question.

DR. KARRON: Okay. Dr. Cox, I

know you're not a voting member for these proceedings. I don't know if you would like to comment at all.

DR. COX: Sure. As a person who sort of lives and breathes influenza and has been involved in H5 preparedness since 1997 and having seen a lot of data over the years and having been in the meeting in Geneva last week or the week before where some additional vaccine data were presented and sort of taking into consideration the real risk that we see for this virus to evolve into a strain that could become transmissible, I would vote yes if I were able to vote.

DR. KARRON: Dr. Farley?

DR. FARLEY: I will vote yes as well. I think the question, as it's worded, really gives us the sense of the special circumstances that we're dealing with that I am very much in support of.

DR. KARRON: Dr. Self?

DR. SELF: I would vote yes as well, although I would also say that the clarification about this being a stopgap, that there is a vaccine and the intended use is as that, although it's not perhaps reflected in the nuance of the wording of the question, with that understanding, I would vote yes. I'd also just go back to the slide 31 from Dr. James' presentation which was the litany of unknown efficacy, unknown correlative protection and all that. I suppose that slide is in there just to give me heartburn.

(Laughter.)

DR. KARRON: Dr. Eickhoff.

DR. EICKHOFF: I vote yes without further comment.

DR. KARRON: Dr. Wharton?

DR. WHARTON: I hope we never have to use it, and I hope if we have to use a vaccine, we have a better one, but this is the vaccine we have now. I vote yes.

DR. KARRON: Ms. Krivacic?

MS. KRIVACIC: I vote yes. I agree with Dr. Wharton as well.

DR. KARRON: Dr. Hetherington, I know you're not a voting member, but would you care to comment?

DR. HETHERINGTON: Just highlight a couple of things that have already been mentioned. This is a vaccine with limited immunogenicity and the response itself reflects some limitation on protection and with a clade change that sounds like it's imminent, if not here, you even have a lower likelihood of success.

However, let's now forget among human cases to date, we've got a 60 percent mortality, and we don't know what that translates to our society, but clearly it's going to be -- this is not a deliberation on a seasonal vaccine, and I think that it really behooves us to approve this vaccine to have something available. So I agree

with all the prior comments.

DR. KARRON: Dr. Word?

DR. WORD: I think that as struggled with this initially, I kept on thinking about it as a seasonal vaccine. And then as the more I read, I realized this isn't a seasonal vaccine. So based on that, and particularly the way it's worded, during a pandemic, then I would definitely vote yes.

DR. KARRON: Dr. Jackson?

DR. JACKSON: Well, I don't think the data are sufficient, but given that it's our only alternative, I think it should be made available. And if that requires an answer of yes to question one, then I'll vote that way.

DR. KARRON: So that's a yes. Okay. Dr. Gellin, you're also not voting. Would you care to comment?

DR. GELLIN: Well, I mean as Nancy has taught me in this, that there's

nothing about any of this is easy, and every step forward reveals the next, you know, cascade f complexity, and we've heard some of that this morning. So I think that that's -- you know, so I think this is an important step but recognizing that, as has been discussed here, there's a lot about this that is going to require a lot further work in addition to assessing further future vaccines.

But I think, as John Modlin highlighted, I think that the importance of having this meeting can't be under estimated, that if this was just a seasonal vaccine, we wouldn't be here talking about it in this way. But because everybody's got a stake at this, the opportunity to have a public discussion about this, and to have that reported on so other people can consider what we did today is really critically important. So I'm glad that John brought that up, but I think that is

probably the most important thing we're doing here today.

DR. KARRON: Ms. Province?

MS. PROVINCE: I am also going to vote yes. I concur with all the previous comments. I think that it is extremely difficult to make what's been called a static evaluation of a risk-benefit analysis in this atmosphere of extreme uncertainty. But -- and part of which, a huge part of which, of course, is just the extreme limitations of the data. And so I echo the concerns that have been expressed here, but I think as a stopgap measure, we really -- you know, the answer to the question must be yes. So I do vote yes.

DR. KARRON: Dr. Stapleton?

DR. STAPLETON: I concur with the previous comments, and I do think that we can use the data on immunogenicity to say that it does support effectiveness, although it's a limited titer or the amount of

immunogenicity is poor, but it's better than nothing. And given the stopgap, we have no choice but to say yes.

DR. KARRON: Dr. Hachey, again, I know you're not voting. I didn't know if you'd like to make a comment.

DR. HACHEY: I concur with the previous comments. I still think it's an important step towards combating what will be a pandemic sooner or later. And if the animal data is somewhat predictive of what we can expect in human models, then this vaccine may not be quite as bad as we think it is.

DR. KARRON: Dr. Webster?

DR. WEBSTER: This is like a child taking its first step, very tentative and necessary to do, and I see this as the very first important step, and the vote is yes. There's a long way to go yet, though.

DR. KARRON: Dr. McInnes?

DR. McINNES: I have confidence

in the process whereby the vaccine is made. I think this manufacturing process is tried and tested. I think the NIAID trial showed a dose response curve, so I think the -- it is immunogenic at the 2 to 90 microgram -- 2 doses of 90 micrograms. I don't think this is a bad vaccine. And so I pragmatically accept this package as a measure of a degree of effectiveness. So I vote yes.

DR. KARRON: Thank you. And I would also echo everyone else's votes and say that I think this is an important first step in the development of pandemic influenza vaccines.

We're now going to move to the second question which is are the data sufficient to support the safety of this product for use during a pandemic or in situations of potential high risk exposure. And this time, Dr. McInnes, we're going to start with you.

DR. McINNES: The only safety

data we have on hand is essentially local and systemic reactogenicity as measured in the particular NIAID trial. If that is all we have on which to base this and given the confining around the circumstances on which this would be used, then I accept this as yes. When that use becomes broader, I become much more uncomfortable about it.

DR. KARRON: Dr. Webster?

DR. WEBSTER: The data available is extremely limited, but in the face of a pandemic, the answer would be yes at this time.

DR. KARRON: Comment, Dr. Hachey?

DR. HACHEY: Just that I agree with the previous comments and that because of DoD being the way DoD is, we are fairly well-positioned to monitor the safety of this vaccine.

DR. KARRON: Dr. Stapleton?

DR. STAPLETON: I concur that the data are very limited and difficult, and

from that sense, to draw conclusions from, but based on its relationship to the current seasonal vaccines and the manufacturing process, I am comfortable with saying yes.

DR. KARRON: Ms. Province?

MS. PROVINCE: Again, in the context in which we find ourselves with the limited data and the scenario that's been presented to us, or one of many possible scenarios, I do vote yes on the question.

DR. KARRON: Comment, Dr. Gellin?

DR. GELLIN: Thank you. My comment -- again, I won't be voting -- is that the data on this specific vaccine are limited as has been highlighted, but this rests on I don't know how many years of experience with seasonal vaccine for which this is the same exact process. So I think that Lisa's highlighted there are some specific differences here in terms of antigen content that raise some issues, but I think we can't forget the fact that this

is built on a large experience of safety information of a vaccine prepared this way.

DR. KARRON: Dr. Jackson?

DR. JACKSON: Yes. I've expressed my opinions about the safety data before, but I would vote yes on this.

DR. KARRON: Dr. Word?

DR. WORD: I'm sorry. I would also vote yes on this question.

DR. KARRON: Comment, Dr. Hetherington?

DR. HETHERINGTON: I have nothing to add.

DR. KARRON: Okay. Ms. Krivacic?

MS. KRIVACIC: I'm having a real difficult time with this one, and I think, you know, part of it is the issue of safety and the fact that this is going to be going into first responders who are healthcare workers, and those people are not necessarily volunteers as we have been testing them in this 452-volunteer trial.

So I don't know. This is a tough one for me, and I think I'm going to abstain.

DR. KARRON: Okay. Dr. Wharton?

DR. WHARTON: For the question we are asked, I would say yes, but that's with the understanding that we will make provisions when we're actually using the vaccine to collect additional safety data.

DR. KARRON: Okay. Dr. Eickhoff?

DR. EICKHOFF: Similarly, I vote yes subject to some of the questions that will be addressed under question three.

DR. KARRON: Dr. Self?

DR. SELF: I vote yes as well on this. The -- you know, the balance of risk for use during a pandemic, I think, are -- you know, that's pretty easy to balance out even with the limited data. For the high risk exposure, that application, that causes me a little more of a problem. The case fatality rate is so high, though, that that high risk exposure would have to be awfully

low to counterbalance the safety concerns, even given the limited amount of data. So I guess, with that sort of thinking, I would vote yes.

DR. KARRON: Dr. Farley?

DR. FARLEY: And I would vote yes as well given the question and in the setting of the high risk exposure and pandemic.

DR. KARRON: Dr. Cox, an opinion?

DR. COX: Nothing to add.

DR. KARRON: Okay. Dr. Couch?

DR. COUCH: Yes.

DR. KARRON: Dr. Modlin?

DR. MODLIN: Well, again, focusing on the wording here, the data support safety -- are they sufficient? Obviously, no. I guess like -- Bruce Gellin brought this up and I think it's a concern we have to recognize that we're using a lot more antigen than we currently use with the seasonal vaccine. Therefore, it's at least

biologically plausible that this vaccine could be associated with a higher risk of adverse events, even though we don't even recognize occurring with a current vaccine. So I think that does raise the issue, not just for this vaccine but also for its successors, if they require high antigen contents, that we need to keep that in mind in terms of designing studies to ultimately try to assess safety issues that we don't fully understand now.

I think it will be critically important to set up an adequate monitoring system, but that's what -- I guess, we'll be talking about that when we discuss the next question.

DR. KARRON: Okay. And I would also vote yes. I think there's a -- the safety data are adequate to support licensure for use in first responders during a pandemic, but as for -- I think about to talk about -- it will be important to

establish safety monitoring programs for the target population for this particular vaccine.

Okay. The third is really just asking for comments, and we've had many of these already, on studies to collect additional information about the effectiveness and safety following this vaccine's use. Just to remind the committee of what we've discussed already, I've heard discussion of an enhanced passive surveillance system. I've heard discussion of a monitoring system similar to what was set up with smallpox vaccine use. I've also heard discussions about a need for collecting immunogenicity data, particularly as it relates perhaps to being able to get some sense of correlative protection. And I'd just like to ask the committee at this point in an open way if there's anything that they'd like to add. Dr. Wharton?

DR. WHARTON: I think that the

Department of Defense is uniquely situated to provide information in a timely way once the vaccine begins to be used. I understand it won't be used initially, but at the point it is used, it seems that DoD does have some infrastructure and capacity in place that can provide really important information for the whole country. And in this particular circumstance, giving the likely initial vaccinees, I think the DoD population is less different than it sometimes is for other vaccines from the population and the civilian sector that will be a target of the vaccination program. So I think there -- DoD has the potential to teach all of us a lot about this vaccine in its early use.

DR. KARRON: Okay. Yes, Dr. Webster?

DR. WEBSTER: The other topic that was raised was the question of prime-boost. It's, I think, very important to consider additional work on prime-boosting,

particularly with the development of clades and new sub-clades, whether the clade 1 will prime sufficiently. I think it's a very important question and to go ahead and boost or prime a substantial number of people to find -- to answer that question.

DR. KARRON: We'll have some of that discussion this afternoon. Other comments? Dr. Farley?

DR. FARLEY: We didn't spend much time on this, but I -- given the low rate of Guillain Barre Syndrome and other unusual neurologic complications, and the point being made that you couldn't do clinical trials of size to pull out, that is a safety issue.

But -- so I would just like to encourage the fine-tuning of use of large population-based data sets, electronic data sets that can pick up signals on, you know, where you have a large denominator and validating the use of those before the onset

of the pandemic, so we can say that we are able to pick up trends and changes in low incidence diseases that might be associated, so that we're in a good position to know what the baseline is, and then it could be used in a setting of the onset of a large scale use of these vaccines in the setting of a pandemic.

DR. KARRON: Dr. McInnes?

DR. McINNES: It seems like this setting up the surveillance system is going to be intricately linked with actually specificity around who are these high risk -- these populations and these first responders. And so I would urge that that move forward in a very active way and that that be clearly articulated. And then the plans can be more specifically more tailored.

And in fact, one might even be able to hierarchically rank where you're going to lead with this from and not have

everybody simultaneously -- but I can imagine that if these are not put in place, then you're going to be playing catch up all the time and not have an adequate system in place. But until the people are defined, you can't really design a system.

DR. KARRON: Dr. Eickhoff?

DR. EICKHOFF: I would simply caution that these kinds of post use studies, desirable though they be, are going to be conducted in the early stages of a pandemic in all likelihood. And whoever plans these trials or these follow-up surveillance studies needs to be very much aware of that, because it could be pretty horrendous, I think, carrying out some of these surveillance studies.

DR. KARRON: Dr. Self?

DR. SELF: So that point, to the extent that some of the characterization of immunogenicity and safety could be done in studies before we get to that chaotic

situation, I think that would be very, very useful. It also might help in defining some strata that could be helpful in looking at measures of effectiveness as well.

DR. KARRON: If there are no other comments, I also would like to echo Dr. Gellin and Dr. Modlin's earlier comments and actually thank the FDA for bringing this topic before the committee. I think having an open public discussion of this issue is really important. We're going to adjourn for lunch. We will reconvene at 2 p.m. for the afternoon session. Thank you.

(Whereupon, off the record at 12:43 and back on the record at 2:07 p.m.)

DR. KARRON: I'd like to call the afternoon session to order, if people would please take their seats. Our first speaker this afternoon is going to be Dr. Jesse Goodman from the FDA who will introduce the topic of Clinical Development of Influenza Vaccines for Pre-pandemic Uses.

DR. GOODMAN: Okay. Good afternoon. My purpose here is to frame a discussion that is sort of, to some degree, an opposite place of where we were this morning in talking about what would one do in evolving emergency, etcetera, to what are some of the issues involved in potential pre-pandemic use of pandemic vaccines and to get input from the committee on issues like priming and how to do studies, etcetera. And I'll just -- we realize this is a huge issue. It requires much more time than there is here, but the point is to begin to get your input and to begin to have people thinking about it and just to say this -- we are having sponsors, etcetera, now consider some of these issues, so this informs our dialogue with them.

Now where are we right now? Well, it's very important to re-emphasize, and I think this is a huge issue for pandemic preparedness, emergency

preparedness in general, that we live in a world of uncertainty. And I think it is very important -- you know, I -- we get asked by colleagues, family, reporters, etcetera -- it's very hard to calibrate the message somewhere between the sky is falling and there's no problem. We don't deal with those calibrated messages. But, in fact, here the probability, timing, severity, and identity of a future pandemic are unknown. But the reality is that I think H5N1 starting, as Nancy put back in '97, is a bit of a wake-up call. This is out there. It persists. There are more deaths. And there are other sera types out there that could emerge.

There has been -- there's the possibility that we would observe evidence of increased human-to-human transmission, perhaps with relevant genetic or antigenic in the virus. There's a possibility that we would observe that before a pandemic, but

waiting until such evidence occurs may leave very limited time to have a vaccine produced and available. Okay. And certainly these uncertainties complicate our planning.

Now why even consider the possibility of immunization strategies that are prior or early in a pandemic, and I think the prior is a harder one for people to get their arms around, but early is the biological relevance is similar. Well, I think everybody knows that with current vaccine technologies, production times are fairly long. We've done a lot. Dr. Webster mentioned reverse genetics can speed this a little bit. The companies are very efficient at this. But it's still talking tree to six months at the lower end, absolutely everything goes perfectly with current methods. And that's for the first vaccine to come out. And then, of course, capacity to ramp up for the population, that magic, hundreds of millions of doses, is

limited. And then when you consider global vaccine needs as has been so poignantly pointed out recently by countries who have no vaccine capacity, this is a huge problem.

Now the stockpiling you've heard about has provided at least the potential flexibility to consider early use, and we heard this morning this structured around well, if there started to be evidence of human-to-human transmission, etcetera.

Okay. There is evidence, and we're not going to have time to review it today, but there is emerging evidence, and I'll talk a little more about it, that priming and cross-protection can occur just like with annual flu strains among so-called heterologous H5 strains, in other words isolates from Vietnam versus Hong Kong that are H5N1 or even some of the more diverse isolates like among the clades. And then as we discussed a little this morning, modeling suggests benefits to the early use of a

vaccine, even one with fairly limited efficacy and potentially even in single doses, and I'll show you a little bit about this.

Well, what are the things we should be doing to remediate the situation, and some of this fits in with what Robin Robinson talked about this morning. So we're taking efforts along with out colleagues globally and at CDC and industry to make strains and reagents and testing processes which, really, you know, many of which are very old methodologies. The reverse genetics is one example. But to make this happen faster, we are all exploring dose-sparing strategies which not only might help overcome this rather poor immunogenicity of this antigen but could obviously make more doses be available more quickly.

Could there be ways to more rapidly induce immunity? Well, as for that,

enhanced cross protective properties, the next line, there is some suggestion that perhaps live vaccines could be helpful in this respect. There's a lot of early studies about conserved genes. So these are all things that can make us get ready faster. Scalable rapid production methods -- there's a lot of U.S. Government and industry investment in cell culture technology that doesn't get it done a lot faster, probably not faster, but it may have certain advantages and scalability as would, of course, recombinant strategies. And then there is a lot of investment which the world, not just the U.S. needs, but the world needs in manufacturing capacity, and in this country, in stockpiling.

And I will say I always like to take the opportunity of the Bully Pulpit in a sense to say I think we should not only think about that it's not just H5N1, it could be another strain, could be H7, could

be H1, whatever, H2, but we think about it may not be influenza either. So our public health response capacity, we should think about how we leverage this in general.

Okay. So what are the approaches to sing a pandemic vaccine? What are the different timings? Well, we talked most about, and I think there's the highest comfort level with during a pandemic so there's a very clear benefit risk. So we heard this in the opinions ventured this morning. But frankly, as was indicated in 1976, even with a proven vaccine, a strain could have an uncommon or unforseen adverse event, and we need to be very transparent with the public about that. You know, you could do the best studies in the world, but if something occurs in 1 in 50,000 people, we have to be prepared to deal with that. And the biggest con here is that it's just simply too little too late, and I'll get to that.

Then in an emerging pandemic, this is sort of what we talked about again this morning, vaccination could begin if you had a stockpiled vaccine. You could target individuals such as were discussed or geographic areas such as a country if human-to-human transmission began to emerge somewhere. And these may be effective strategies both in saving lives but potentially in pandemic control. And as I mentioned, even at reduced efficacy, models predict benefit. And this could be a temporizing strategy, again, as discussed today, until a matched vaccine was available.

The benefit-risk ratio is clearer than in pre-pandemic use, although, again, as we saw in 1976, sometimes our ability, even as events unfold in front of us, to predict whether a virus will become pandemic is not -- you know, it's not a fine-tuned ability. And of course, ths stockpiling is

quite expensive, and there is the potential need, based on either stability or change in the virus, to replace or rotate stockpiles.

Now what about pre-pandemic immunization? This could be potentially considered as an option separately from or as part of annual immunization program. And this could either be done to individuals who are perceived as having increased risk either of bad outcomes or potentially, again, as discussed this morning, in an emerging pandemic, of early on exposure.

If successful -- if you have what makes a pandemic a pandemic, because you don't have population immunity and individual immunity so it's successful, such strategies could potentially blunt or maybe even prevent a pandemic. And there are obviously human and economic benefits. It requires less search capacity and could reduce the need for a number of emergency measures and stockpiles.

But the problems are ones that everybody is familiar with. You could immunize people and have a completely different strain emerge, so if you don't have strong cross-protection, there may be a mismatch and limited efficacy. And of course the biggest one is the uncertainty of whether a pandemic will occur and, if so, what it would occur with, so you're measuring a potentially small risk from a vaccine safety issue against what essentially is a hard to predict benefit or unknown benefit. It's the unknown risk of a pandemic.

I'm trying to find -- I had another slide that I thought I had in here -- oh, there it is, but it -- look at that. See, there's a slide that refuses -- I'm going to -- well, I bet you when I put it up, it won't -- yes, I've encountered this once before. There's some kind of control that changes the slide, but I'm just going

to show this. I think this is sufficient.

But this was the point I had meant to make early on which is that if you look at vaccine production capability and this is preparing the seed, making the monovalent, filling and testing it, and then under this rather aggressive scenario, let's say in four months your vaccine begins to become available, you can see here that in this crude presentation of the first wave of a pandemic, basically that first vaccine is becoming available as the first wave is receding. So this is not a highly effective immunization strategy in dealing with that first wave. And then you consider that, you know, it's probably going to take you a week or two to get meaningful immunity, even limited immunity, from a first dose much less to then come and administer a second dose a month later. So this was the background that I wanted to share before that.

And I knew I had that there. I once had that happen to me in front of about a thousand people, and I had about eight slides like that that wouldn't let me show them.

So that's the pre-pandemic issue. So the big issue here is the uncertainty of the risk of a pandemic. But the big benefit is if people -- you know, this is a viable strategy to get immunity into the population as opposed to six months after a pandemic starts.

Okay. So what is the background in terms of priming and cross-protection? Well, we know that natural infection provides long-term protection against that strain, invariable but sometimes surprising degrees of protection against related strains. We know that inactivated vaccine provides some protection also beyond one flu season, even though we see, as you saw today, the way the antibody levels tend to

fall off in the 6 to 12-month period after immunization and also against related strains. And there are some recent randomized controlled studies that, in fact, show protective effects against fairly drifted strains of annual vaccine. And this may be increased with live attenuate vaccines because of the nature of immunity that they induce and probably also because of the presence of additional conserved antigens, etcetera.

Now what really is moving this field and I think will inform it considerably is that, for example, as Rob mentioned this morning, there's preliminary animal serologic and clinical studies of H5 that do provide evidence of variable degrees of cross-protection between heterologous strains. And there's also evidence that some of the novel adjuvants may boost that cross-protection. We don't know whether that's because they induce a different

immune response or just a better, more robust one. But there is some evidence for many of them, for example, that they may prime cellular immunity, etcetera. And there's also a suggestion that priming, and Dr. Treanor, I think is going to present some of his data, may in fact be possible and durable with these H5 antigens.

The big caveat, though, here is that the predictive science, again, is not great here. It's not clear how well-matched strains need to be, to what degree serologic studies or molecular studies could predict this. But I think the science is advancing there, again, as we get a lot more sequence data and start to correlate that with serologic data and animal data, and Nancy has done a lot of work in this area.

A very important point, and came up this morning, is certainly that the surrogates for protection are also not well defined and the assays are highly variable.

So when we go to a meeting hearing about multiple different vaccine candidates but they've all been studied with different assays, you have to really take that with a grain of salt. And at WHO we had a recent discussion. There was general agreement of the desirability for standardizing these antibody assays so we can compare one vaccine to another better. But until then, everybody needs to take this with a grain of salt.

Well, there were questions about the modeling, and as I mentioned this morning, to me, a model is just a model. There are many, many assumptions, but it's worth looking at this a little. So this is -- there are two groups that have actually had surprisingly similar results looking at it form slightly different directions. But this is the one group of Ferguson. There's some more things from Longini's group. This is very complicated but what I would say is

that over here it shows, for example, the effects of a delay in vaccine availability.

Now if you look at that backwards, it shows you what are the effects of having vaccine ready right at the beginning of a pandemic. And here is where vaccination at a certain rate -- I'm not remember it offhand -- I think it might be a million doses a day -- begins within days of the pandemic versus 30 days versus -- no excuse me -- day 30, 60, blue or 90.

Okay. So if you begin right away, cumulative attack rate of 1 percent. If you wait even 30 days -- second bar is -- beginning on day 30, 1 percent; 60 days, 13 percent; 90 days, 31 percent. And this is a high transmissible virus and a medium transmissible virus. But you can see the dramatic increase in disease or conversely the dramatic decrease through immunization becoming rapidly available to the population.

Okay. This is a pre-immunization strategy. Again, this is very complex. But this shows if you could pre-vaccinate 20 percent of the population with a low efficacy vaccine, in this case 30 percent reduction in susceptibility, so this would be half as effective as we might expect an annual vaccine to conservatively be, and just give one dose here, added to some other measures like household quarantine and some antiviral measures. But the addition of this vaccine policy, pre-immunization of 20 percent, you can see results in a fairly dramatic reduction when added to these other strategies and also overall.

Now, again, I'd like to stress that this is modeling. It's very dependent on the infectivity of the virus. It's very dependent on multiple other assumptions. But when you think about this, if people -- people cannot only potentially benefit from being personally protected, but if they then

transmit virus less, this is how you begin to have population impacts of immunization.

However, there are many, many unanswered questions, and that's why we're beginning this dialogue. Certainly, how can we better measure and predict both protection and cross-protection. We discussed that this morning, and it's very important to mention that for a pandemic vaccine, hospitalization, death, in fact, infectiousness may be much more relevant and even more immunologically achievable measures than just infection.

Animal models were beyond our scope but we heard how we can't tell from these possible correlates, you know, how effective a vaccine -- can we develop animal models that tell us more? Can we use them and correlate them with immunologic correlates? What dose and dose intervals are need for priming or boosting, and Dr. Toerner is going to discuss this some. How

durable will priming be, and Dr. Treanor's results may help address this. Are specific levels of antibody needed? Must they be maintained.

And then we come down to -- and again, we heard some data suggesting this at WHO recently is people are looking at some cross-serologic cross-reactivity data, that this may be very not just sera type specific or clade specific but even virus specific, so we're seeing some viruses behave differently. In general, the more genetically-related you are the better you cross protect, and I think that's safe to say. But there are some things that may defy prediction, although Nancy may have more to say about this.

So what we have here is data needs. We have a possibility for something potentially effective, but we have data needs. And these pertain to either early pandemic use such as the possibility we

discussed this morning with the vaccine under discussion, but it also pertains to potential pre-pandemic use. How should we design clinical trials to evaluate immunogenicity? And there's an opportunity here now. I think this is a very important point. Lots of companies are studying lots of vaccines. There's an opportunity to build into these studies cross-protection studies, immunization with one vaccine followed by another. And these are studies that take a long time and cost a lot of money, so getting them right and getting your input and getting FDA's input and companies' input, there's a lot data that could benefit a lot of people.

What should our standards be? You saw how you wrestled with that this morning. These are very arbitrary numbers. Beyond such arbitrary numbers, what should we be thinking about? And certainly, these scientific data, public discussion are

important in considering any of these types of vaccine use. And certainly a substantial safety database will be needed in considering pre-pandemic approaches. And I think that drove a number of the questions today, even about a vaccine using a very well-characterized manufacturing method. And certainly when you consider novel vaccines, this is something we're not here really to discuss in detail today, because it's a whole discussion, but we wanted to bring up.

And so we both want to further the data-gathering process and begin these kinds of discussions, because I think the successes in vaccine development , actually, the good news is that they're going to bring these questions to us. And the sooner we start trying to effectively get the data, the less likely we'll be to be scratching our heads quite as much as we did this morning.

So thank you very much. And now I guess we'll leave discussion for later, but Dr. Toerner's going to follow-up with this.

DR. TOERNER: My name is Joe Toerner. I'm a Medical Officer in the Vaccine Clinical Trials branch at the Division of Vaccines and Related Product Applications. My goal today is to enhance what Dr. Goodman had just mentioned to you and provide you with a bit more summary data on the rational for why we might consider an influenza vaccine to be used in the pre-pandemic setting, also provide for you hypothetical clinical development scenarios that would help your discussion this afternoon on a determination of efficacy and safety.

We're all familiar with the current situation with influenza H5N1. The host has expanded outside the avian species and to date, there 278 cases that have been

reported to the World Health Organization of human infection, and the case fatality rate is greater than 60 percent which highlight the nee for urgent vaccine development.

Dr. Baylor this morning had mentioned that the U.S. Government is involved in influenza pandemic preparedness, and as our part of helping develop a plan for use of an influenza vaccine during a pandemic, we issue draft guidance industry on the clinical development of an influenza vaccine to be used during a pandemic or in situations of potential high risk exposure.

And in the guidance document, we had outlined immune response criteria that are reasonably likely to predict clinical benefit, and that is the hemagglutination inhibition antibody assay in different proportions, a fourfold increase versus the proportion greater than or equal to 1 to 40. We're in the process of revising that to further clarify that it would be either or

to demonstrate an immune response reasonably likely to predict clinical benefit.

As well, our guidance documents outline safety database requirements, and those differ based upon whether or not a sponsor has a long-term manufacturing experience with a seasonal influenza vaccine.

However, the discussion this afternoon, again, as Dr. Goodman pointed out, there are many limitations to the production and ultimate availability of a pandemic vaccine in a pandemic situation. So what we're interested in is your feedback on a different strategy of use of a vaccine prior to a pandemic or the so-called prime-boost or cross-protection that might be demonstrated in adequate and well-controlled studies.

And so for discussion today, we'd like some feedback on the adequate and well-controlled studies of clinical trial design

endpoints and the duration of those clinical trials as well as some discussion of what we might require as a size of the safety database.

So the issue of priming is illustrated in the pediatric population where children are felt to be naive to the seasonal influenza antigens in circulation. And it's for this reason that children below nine years of age who are receiving influenza vaccine for the first time, two administrations of vaccine approximately one month apart are recommended for adequate immune response.

Two recent studies had evaluated the prime and the boost dose that were given approximately six months apart and whether -- and these were seasonal influenza vaccines --and whether the seasonal influenza vaccine remain the same or whether the seasonal influenza vaccine had differed in the antigen content, there appeared to be

similar immune responses when these children had vaccine administration more widely separated in time.

And following my talk, Dr. Treanor's going to provide an overview of immune responses that were observed among study participants who had the remote administration of an H5 antigen that also illustrate this concept of priming.

Data from observational studies indicate that prior antigenic experiences protect or ameliorate influenza illness, and this appears to be true even in individuals who have had antigenic experience with the same influenza virus in circulation or whether the influenza virus in circulation represents an antigenic drift.

And as well, seasonal influenza vaccines appear to offer cross protection against antigenically drifted influenza strains, and this has been demonstrated in two culture confirmed studies, one more

recently published in the New England Journal of Medicine where vaccine efficacy appeared to be greater than 70 percent for -- even when influenza virus in circulation differed from the vaccine strain.

When considering pre-pandemic vaccination, it's been mentioned earlier in today's session that we'll have to consider the risks associated with administration of a vaccine that may or may not have potential benefit. The risks and benefits for a seasonal influenza vaccine are known. For example, the Institute of Medicine performed an exhaustive review looking at neurological adverse events following administration of contemporary seasonal influenza vaccines and found that data do not support an association between administration of seasonal influenza vaccine and the development of Guillain Barre Syndrome with the exception of one observational study in one year in the early 1990's where it was

estimated that the risk of Guillain Barre Syndrome appeared to be 1 additional case per 1 million person vaccinated.

So currently, the Advisory Committee on Immunization Practice, in their publications, indicate that if an association exists, it's estimated to be a risk of 1 additional case of Guillain Barre Syndrome per 1 million persons vaccinated, and therefore the risks versus benefits of a seasonal influenza vaccine are well balanced.

However, we have the historical experience with the swine flu vaccine in 1976 where the Institute of Medicine found that the data did support an association with administration of that particular vaccine and Guillain Barre Syndrome where the risk of Guillain Barre Syndrome was 1 case per 100,000 persons vaccinated.

And so for consideration of rare serious adverse events, they become

highlighted when there is the unknown potential benefit.

And now I'd like to move on to a hypothetical clinical development scenario, and this is a straightforward slide that demonstrates clinical development that might occur for demonstration of adequate immune responses to be used during a pandemic or a high risk situation. However, for pre-pandemic use, in order to demonstrate this issue of priming, administration of the vaccine more widely separated in time might provide adequate data that would begin to support the concept of homologous immune protection over time. And similarly, in order to gather data on the issue of cross protection, we outlined a clinical development scenario here where individual cohorts would receive a monovalent influenza vaccine that represented a different clade. And immune responses following the administration of subsequent different

vaccine would be evaluated for evidence of cross protection.

And so for discussion this afternoon, we would like for you to comment on the use of immune responses in order to determine efficacy of a vaccine to be used for pre-pandemic use or for priming and is the immune response assay following the prime alone adequate to support demonstration of pre-pandemic use. Should we require that immune response assays be obtained following a boost at future time points, or in particular, for administration of a heterologous antigen in order to gather information on cross-protection? Or can we rely on immune response measurements following the prime using assays that involve the heterologous antigen? And if there's time, to comment on the use of hemagglutination inhibition antibody as an immune response endpoint versus other immune response assays such as microneutralization.

And related to this is clinical trial design, if you could discuss the feasibility of requiring longer term clinical studies of the prime and the boost in pre-pandemic vaccine development and what would the duration of such a study be -- six months out to one year or perhaps longer than one year. And we recognize that this might require collaboration among different sponsors who may or may not be developing monovalent influenza vaccine strains with a different clade.

And for a safety database discussion, we wanted you to keep in mind that for a pre-licensure safety database, it is not likely that we will be able to detect rare or serious adverse events, for example, at a rate of 1 per 100,000. So keep that in mind in your discussions when we ask you to comment on the safety considerations for licensure.

As well, we believe that safety

database requirements may differ for a sponsor who is seeking licensure of a vaccine with a novel manufacturing process or the use of a novel adjuvant. And so that will conclude my talk, and I'd like to turn the podium over to Dr. Treanor.

DR. TREANOR: Okay. Thanks. What I'm going to present is really the same presentation that one of our infectious disease made at IDSA in October, and it's basically an analysis of the immune responses of healthy subjects who received a single dose of the Vietnam virus after they had previously received vaccination with an H5 vaccine for the A Hong Kong/156/97. And this was presented at IDSA by one of our ID fellows, Nega Gogi.

So as we heard this morning, the non-adjuvanted, inactivated, subvirion vaccine required two 90 microgram doses to elicit a neutralizing antibody, and we knew that in a previous study that was done by

Iain Stevenson and Karl Nicholson, they looked at a vaccine for H5N1 based A/Duck/Singapore, which is a low-pathogenicity avian virus that is antigenically similar to A/Hong Kong/97 that was used to make a subvirion vaccine back in 1997 and which was then evaluated either with or without MF-59 in a study that was published in early 2000-2001. That study showed, as you know, that adding MF-59 had a very significant dose-sparing effect on that vaccine, but that responses to the unadjuvanted vaccine were relatively low.

They took a subset of those same subjects and revaccinated them 16 months later with those who had received unadjuvanted getting unadjuvanted vaccine and those who had received vaccine with MF-59 getting MF-59 adjuvanted vaccine. And what they found was that in both groups, after a third dose administered 16 months later, there was a significant enhancement

of the antibody response so that individuals after that third dose achieved levels of neutralizing antibody that were higher than they had achieved after the first two doses.

So pre-priming is a strategy that might generate better immunity. It would potentially allow a single dose in the face of an emerging pandemic which would be logistically, I would think, more feasible, but in reality, using that strategy for an emerging pandemic would probably represent boosting people with an antigenic variant because of continued antigenic evolution of H5 and other avian viruses.

Now we had done a study back in 1997 using a baculovirus expressed recombinant H5 of the A/Hong Kong/156/97. Now despite the chronology of these viruses, the 1997 viruses are referred to as clade 3, the 2004 viruses are referred to as clade 1, 2005 being clade 2. So we took advantage of the fact that there were still many people

around who had been in this study evaluating the recombinant H5 clade 3 virus vaccine to bring them back and give them a single dose of the vaccine we were evaluating, the Vietnam/1203/04 (clade 1), to see whether or not there was, in fact, evidence that that previous vaccination with the baculovirus-derived Hong Kong vaccine had primed them to respond to the Vietnam vaccine.

Now just to refresh your memory, when we had done the study with the baculovirus-derived vaccine, we looked a neutralizing antibody which was measured by Jackie Katz at CDC, and we looked a two-dose schedule. We did several time points to look at the kinetics of antibody, but the two doses were separated basically by 28 days. And we found results which actually were very, very similar to the ones that we just presented with the subvirion vaccine in that there was a very strong dose-dependent effect and the best responses were seen when

subjects received two doses of 90 micrograms of baculovirus-expressed recombinant hemagglutinin where they generated antibody with a neutralizing GMT on the order of about a 160.

So the objectives of this study were to determine the ability of the clade 3 H5 recombinant vaccine to prime for immune responses to a subsequent clade 1 H5 subvirion vaccine in health adults. Now to do this comparison, it's important to understand that we did not randomize people to be primed or unprimed. People were primed because they had previously been in the study. We simply gave a dose of the subvirion H5 vaccine and compared their responses to the ones that we had seen in unprimed subjects in the 063 study. We also wanted to determine the safety of revaccination.

The subjects then were participants in the previous study which was

conducted in late 1997 and early 1998 who had received a clade 3 recombinant H5 baculovirus-derived vaccine at any dose. And these subjects were administered in open label fashion a single 90 microgram dose of the subvirion recombinant A/Vietnam (clade 1) vaccine. They completed the same kind of diary card that was used in study 063. Adverse events were recorded over 56 days, and we tested both serum HAI and microneutralizing antibody against the Vietnam virus on days 0, 28 and 56.

Now the primary analysis here was to compare the results of a single dose in the primed population versus the results of a single dose in an unprimed population. That was our primary evidence of whether these individuals had been primed. If they were primed, they should respond to a single dose with significantly better responses than seen in an unprimed population. As a secondary analysis, we also compared the

responses to that seen after two doses of 90 micrograms in 90 subjects.

So this lays the study out sort of diametrically. Here's the original study in 1998. Individuals in that study received the recombinant clade 3 vaccine at a variety of different doses. Any individual who had received vaccine at any does, not the placebo recipients but vaccine recipients, were eligible to participate in the open label study. All of these individuals, and there were 37 of them, received 90 micrograms as a single dose in open label fashion in study 0043 conducted in 2005. So approximately a seven year interval between these two studies. Their results are compared to those which have already been presented in H5 naive subjects who received two doses of the same clade 1 vaccine at 90 micrograms.

Here are the demographics of the two population. The results are compared

to, again, that same 90 microgram group we talked about before. This is the demographics of the 37 subjects from the previous study who came back to participate in 043. You can see it's a largely Caucasian population. Slightly more than half of them are female, and the age of these people who are correspondingly about seven years older than the volunteers we typically have in our studies is slightly older than the median age of the people who were in the 063 study.

These are the rates of solicited adverse events within seven days of receiving the vaccine. And it simply shows that the rate of local pain, tenderness and other side effects in those who had previously been primed and received a single dose of 90 micrograms are not different than those which were seen in naive subjects who received 90 micrograms. The rates of all of these effects after one or two doses in

naive subjects or after what amounts to a third dose in primes subjects are all essentially the same.

This is the results of the serum hemagglutination inhibition assays, titers following either two doses of H5 vaccine in the naive subjects or one dose in the primed subjects. Now again, these analyses use the 1 to 10 definition as the starting dilution, so everything is on the same frame. And you can see this is the same data that I presented earlier in the 063 study that after two doses of 90 micrograms on day 56, the GMT of HAI antibody is 27.7. This is the 95 percent confidence limits. This is the result in the open label study in primed subjects. And you can see a significantly enhanced response to a single dose and that after a single dose, these subjects actually have higher levels of antibody than those individuals in the 063 study after two doses.

Similar results are seen with the microneutralizing anybody. Again, this is the 063 study. These are the neutralizing anybody responses. Again, using 1 to 10 as the definition of the starting dilution, after two doses of 90 micrograms, the GMT of neutralizing antibody on day 56 is approximately 23. Individuals who had been primed by previous exposure achieved a GMT of 94 after a single dose of 90 micrograms. This is clearly higher than seen after a single dose in unprimed subjects showing that the subjects are, in fact, primed and is actually higher than we're seeing after two doses in unprimed subjects.

And this is a summary of response rates looking at the percent either who responded or the percent who achieved a titer of 1 to 40 by either HAI or neutralizing antibody by day 28 after the second dose in the 063 study or day 28 after a single dose in the 043 study. And again,

you can see that the proportion of subjects who respond with a fourfold response is higher after a single dose in the primed subjects than it is after two doses in the unprimed subjects.

And similarly, the percentage of individuals who achieve a titer of 1 to 40 is higher in those who had previously been primed even after just a single booster dose than were seen after two doses in those who were naive at the beginning.

Now one of the things we tried to look at is whether or not it made a difference what regimen a recombinant baculovirus vaccine was received back in 1998. This gets into very small numbers, but it did not look like ti made a substantial difference whether you received 25, 45, 90 or a total of 100 micrograms of baculovirus vaccine back in 1998. Both the GMT of HAI and neutralizing antibody as well as the response rates are fairly similar

with the proviso that it's a very small number of subjects in each subgroup.

It did look like perhaps it made a difference whether you responded back in 1998. If we divided those 37 subjects into those who had a neutralizing antibody response against the Hong Kong virus, you could see that those who had responded against the Hong Kong virus in 1998 were somewhat more likely to respond when boosted with the Vietnam virus with a response to Vietnam. Again, none of these differences are statistically significant because of the very small numbers.

Now this is some preliminary data from Dave Topham who's been looking at memory B cell responses. This is an assay that was developed at Emory by Shane Crotty and Rafi Amed and looks at the proportion of all immunoglobulin-secreting cells that are making ELISPOTS specifically against the antigen of interest. And you can see that

after vaccination, there is an increase on day seven in the numbers of memory B cells that recognize either the recombinant hemagglutinin of the Vietnam virus or the recombinant hemagglutinin of the A/Hong Kong so that of these go up immediately after vaccination in the 043 vaccinated subjects.

Unfortunately, we don't have the comparison data from naive subjects, so all I can say is that these go up, but we don't know what we would have seen in naive individuals.

So in conclusion, the antibody responses to a single dose of unadjuvanted vaccine support the hypothesis that previous vaccination with clade 3 primes for a response to a clade 1 H5 vaccine. The antibody responses did exceed those that we saw after two doses in naive subjects and actually were somewhat better than those that were seen in the original study. And the reasons for these vigorous responses are

not clear. Whether or not individuals have memory B cells that are sitting around ready to respond or whether there's something else, it's just not clear. Revaccination was well tolerated. The side effect profile is similar to that of vaccination of naive subjects.

And clearly, further studies, which I think were nicely outlined earlier, to evaluate different schedules to really verify these results in larger populations are needed. But if you were confident that this would happen, then you could consider pre-pandemic vaccination programs, at least for some populations which we've talked about, potentially healthcare workers, first responders or the military or individuals who would be likely to be exposed and need to stay on the job early in a pandemic.

So I'd just like to thank the individuals who collaborated in the study, particularly Tom Rowe who did all the

serology; Mark Wolff and Heath Hill who were responsible for the data analysis; and my collaborators at DMID and at the University of Rochester. Thanks.

DR. KARRON: Thank you. At this point, we'll take questions for Drs. Treanor, Toerner and Goodman. And actually, I'd like to lead off with one question for you, John, which is I was wondering did you see cross-boosting at all? In other words, if you looked at HA responses back to the '97 strain? Did you look at that?

DR. TREANOR: We haven't looked at that and that's partially because we don't have a similarly, at least to my knowledge, have a similarly reverse genetically- engineered low pathogenicity variant of the H5 from 1997 that's easily available to work on. So although that's in the cue of things to do, to my knowledge, that hasn't happened yet.

DR. KARRON: Dr. Jackson?

DR. JACKSON: I just wondered -- I mean it sort of raises the question on how much antigen you need to produce the boosting response, so I was wondering if that was something you're exploring?

DR. TREANOR: It's very possible that it requires less of a dose to prime someone than it does to generate antibody, and so some of the lower doses might be effective for boosting, and that's something we're eager to look at.

DR. KARRON: Dr. Modlin?

DR. MODLIN: John, I know your study didn't look at this, but I think in terms of future studies, it might be real interesting to look ant see what the kinetics of the response is to that third dose. We're talking about trying to prevent a disease that can kill within days after exposure with a short incubation period and so that knowing how quickly you induce protective antibody with that third dose,

all the studies that have been done very recently with meningococcal disease and meningococcal conjugate vaccines for that, but the timing of that response to a booster dose appears to be critically important in preventing disease. So in terms of future studies, I think that would be something that would be very interesting to look at.

DR. TREANOR: I agree. That would be very important.

DR. KARRON: Dr. Webster?

DR. WEBSTER: Really the same question that Ruth asked, did you find any evidence of original sin?

DR. TREANOR: Well, unfortunately, we have not assessed any type of immune responses to the 1997 Hong Kong except for the memory B cell responses which do appear to recognize the Hong Kong virus.

DR. KARRON: Dr. Cox?

DR. COX: Yes, John. I think I

know the anser to this, but I just wanted to be absolutely sure. Were the serologic tests done at the same time for the two groups --

DR. TREANOR: No.

DR. COX: -- or were they done at different times?

DR. TREANOR: The data that -- the comparison in the naive subjects is exactly the same data we talked about this morning. It's the published -- well, not the published data, but it's the data from the 90 microgram group in the original study compared directly to the assays done on the open label study.

DR. COX: Right. So theoretically, if you have enough serum left, you could go back, test those two sets of sera at the same time with clade 1, clade 2 and clade 3 viruses and rally get quite a bit of interesting information about --

DR. TREANOR: That absolutely

could be done.

DR. KARRON: I think if there are no more questions at this point, we'll proceed to the open public hearing.

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

DR. KARRON: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages

you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting, for example, the financial information may include the company's or group's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from s peaking.

MS. WALSH: I have received a request form Dr. Bruce Innes representing GlaxoSmithKline. Dr. Innes? You can come up to the podium for your slides.

DR. INNIS: Good afternoon. My name is Bruce Innis. I'm an employee of GlaxoSmithKline. We're a manufacturer of licensed vaccines, licensed influenza vaccines in the United States and in many countries around the world. I'd like to make a public statement regarding our ongoing development of a novel influenza vaccine against pandemic strains.

This morning we've heard an awful lot about the challenges of using vaccines to reduce the risk of pandemic influenza. GSK has a strategy to confront these challenges, and that's what I want to describe. So we'll skip that slide and go right to GSK's position, which is that advanced production and stockpiling are the foundation, the foundation of pandemic preparedness. And the ideal vaccine to support this approach has three attributes. It should be effective against drift variants and elicit immunological memory

against them. It should be antigen-sparing, and if it's going to be stockpiled, it needs to have shelf life.

We are developing pandemic vaccines with just these attributes, and I'd like to share a little bit of data with you. Now here you see immune responses from a dose-ranging study in which healthy adults 18 to 64 years of age were randomly allocated to 8 formulations of Vietnam/1194/H5N1. They received 2 doses of the vaccine 21 days apart with or without a novel adjuvant system. The doses ranged from 30 micrograms down to 3.8 micrograms. The endpoint that we're showing here is hemagglutination inhibiting antibody response, the proportion of volunteers that achieved a post vaccination titer of greater than or equal to 1 to 40. And I'm showing an orange reference line which indicates the 70 percent response threshold that CEBR has articulated in their draft guidance as

evidence of an adequate response to reasonably infer clinical benefit.

So if you look on the blue, the dark blue bar, that's the 30 microgram dose without adjuvant. That group failed to meet the criterion. But if you look on the other end of the graph, the light yellow bar, that's the 3.8 microgram group with adjuvant, and they exceeded the CEBR criterion. So these results show that the adjuvant system confers a very marked antigen-sparing affect.

Next week our colleagues will be presenting new data in an international scientific meeting in Hong Kong regarding the ability of this vaccine to immunize against H5N1 drift variants. That's a second important attribute of an ideal pre-pandemic vaccine. Now you may ask is there a regulatory pathway for pre-pandemic vaccines. And the answer is yes, there is. The EMEA in Europe issued comprehensive

guidance on the 24th of January, and I'd like to go over its salient features. Their guidance says that applicants for licensure should evaluate as the primary efficacy surrogate the homologous HI anybody response but that also they should characterize vaccine cross-protection. This is considered important, and three types of evidence are requested: cross-reactive neutralizing anybody responses; cross-protection of ferrets; and the ability of vaccination to support a booster response to a subsequently administered drifted strain.

GSK has been and is continuing to generate these data for its pre-pandemic vaccine candidate that's manufactured in its facility in Dresden, Germany. For that vaccine, we have already filed an European Union license application, but currently we are discussing with FDA the evidence that would be required to support a U.S. license application for our pre-pandemic vaccine in

our facility in Quebec, Canada.

The plan that's under discussion with FDA is divided into three parts: the conduct of pivotal trials of our vaccine under an IND in 2007 and then immediate application for a BLA for the use of the vaccine in the face of an imminent threat; and while the application is under review, and our understanding is that it would be reviewed under the accelerated approval regulations, we would extend the development by evaluating the vaccine in children and generating data regarding the ability of the vaccine to prime subjects for a subsequent heterologous booster response; and lastly, we would propose post licensure to conduct large, large safety trials in adults.

Now ultimately GSK is interested in developing a product that's suitable for general use prophylaxis, not only stockpiling, against various forms of pandemic influenza. This type of vaccine

conceivably could be used in a routine national immunization program, and this could be the best possible form of risk reduction against any future subsequent pandemic.

Let me close by saying that GSK has committed to developing a new generation of influenza vaccines against both seasonal flue and pandemic flu and the use of the adjuvant system that I've briefly mentioned to day is certainly central to that vision. Thank you very much.

MS. WALSH: Thank you, Dr. Innis. I have also received a request to speak for Ms. Manon Cox representing Protein Sciences. Ms. Cox?

MS. COX: Okay. I would like to take the opportunity to update the committee and the public today on the recombinant hemagglutinin vaccine that was so nicely introduced by John Treanor before, because you may wonder what happened in the last

eight years. In principle, it became clear to Protein Sciences that it was important to first develop a vaccine for inter-pandemic use, so we embarked on the development of a trivalent recombinant hemagglutinin-only vaccine which is produced in vitro using insect cell culture technology. Every year we will clone the HA's from the WHO-CDC recommended strains and since this is a recombinant DNA approach in principle, you do not need eggs. It is easier to produce. And you also do not need to produce live viruses prior to inactivation. There's no bio containment required and we also do not plan to use preservatives.

The hemagglutinin antigens are then highly purified and they have the correct three dimensional structure as is demonstrated by their biological activity, hemagglutinin activity and by the fact that they produce protective immune responses.

I would also like to outline our

approach to watch a potential pandemic. As John indicated, in 1998, we very rapidly, after NAID approached us to produce a pandemic vaccine produced vaccine that could be used in the clinical trials that were described earlier. It took us six weeks to get from gene to product and eight weeks to get from genes into humans. We also demonstrated that we could fully protect chickens against a lethal challenge. And in a very short period, this vaccine was given in 1998 already to 200 healthcare workers of which a little over 50 percent reached titers that were greater than 1 to 80, titers that were found in convalescent sera. This was the first pandemic vaccine in clinical trials, and it didn't really help the development of Protein Sciences' vaccine, because the fact that you needed two doses of a relatively high amount of hemagglutinin left people to believe that a recombinant vaccine would not be as