UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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VACCINES AND RELATED BIOLOGICAL PRODUCTS

ADVISORY COMMITTEE

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MEETING

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Friday, January 30, 1998

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The Advisory Committee met in Versailles Rooms I and II, Holiday Inn Hotel, 8120 Wisconsin Avenue, Bethesda, Maryland, at 8:00 a.m., Patricia L. Ferrieri, M.D., Chairperson, presiding.

PRESENT:

PATRICIA L. FERRIERI, M.D., Chairperson

NANCY CHERRY, Executive Secretary

MICHAEL A. APICELLA, M.D., Member

MARY LOU CLEMENTS-MANN, M.D., Member

REBECCA E. COLE, Member

KATHRYN M. EDWARDS, M.D., Member

PRESENT (Continued):

MARY K. ESTES, Ph.D., Member

CAROLINE B. HALL, M.D., Member

ALICE S. HUANG, Ph.D., Member

GREGORY A. POLAND, M.D., Member

ROBERT BREIMAN, M.D., Consultant

CLAIRE BROOME, M.D., Consultant

ROBERT B. COUCH, M.D., Consultant

THEODORE E. EICKHOFF, M.D., Consultant

DAVID KARZON, M.D., Consultant

EDWIN D. KILBOURNE, M.D., Consultant

JOHN LaMONTAGNE, Ph.D., Consultant

DIXIE SNIDER, JR., M.D., M.P.H., Consultant

ROBERT WEBSTER, Ph.D., Consultant

ROLAND LEVANDOWSKI, M.D., FDA Representative

NANCY COX, Ph.D., CDC Representative

KEIJI FUKUDA, M.D., Speaker

DOMINICK IACUZIO, Ph.D., Speaker

KUNIAKI NEROME, Ph.D., Speaker

ALEXANDER KLIMOV, Ph.D., Speaker

JOHN WOOD, Ph.D., Speaker

MARIA ZAMBON, M.B., B.Ch., M.A., Ph.D., Speaker

RALPH VOGDINGH, D.V.M., Manufacturer's Comment

PRESENT (Continued):

DR. SING CHUNG LEE, Manufacturer's Comment

PAUL PETERSON, Manufacturer's Comment

ALSO PRESENT:

DR. MICHAEL PERDUE

BETHANY WILKINSON

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

(8:11 a.m.)

CHAIRPERSON FERRIERI: Good morning. Could we all gather at the table, those of you who have a place, please, and we can start the day?

I'd like to call the meeting to order of the Vaccines and Related Biological Products Advisory Committee.

I'm Patricia Ferrieri, the chair.

And before we do introductions at the table, I'd like to turn the meeting over to Nancy Cherry, who has some important announcements.

MS. CHERRY: Good morning, and I say welcome also.

My only announcement is the reading of the conflict of interest statement, which at this time is not very long.

This announcement is made a part of the record of this meeting of Vaccines and Related Biological Products Advisory Committee on January 30th, 1998.

Pursuant to the authority granted under the Committee charter, the Director of the Center for Biologics Evaluation and Research has appointed Drs. Claire Broome, Robert Couch, Theodore Eickhoff, David

Karzon, and Dixie Snider as temporary voting members.

Based on the agenda made available, it has been determined that all Committee discussions at this meeting for the influenza virus vaccine formulation for 1998-98 and an update on influenza A H5N1 subtype viruses present no potential for a conflict of interest.

In the event that the discussions involve specific products or firms not on the agenda for which FDA's participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the public record.

With respect to all other meeting participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they wish to comment on.

CHAIRPERSON FERRIERI: Thank you, Nancy.

We'll start introductions then at the far in. Dr. Couch, would you start and give your affiliation, please, as well?

DR. COUCH: Robert Couch, Baylor College of Medicine, Houston, Texas.

DR. CLEMENTS-MANN: Mary Lou Clements-

Mann, Johns Hopkins University.

DR. APICELLA: Mike Apicella of the University of Iowa.

DR. HALL: Caroline Hall, University of Rochester.

DR. POLAND: Greg Poland, Mayo Clinic, Rochester.

DR. EDWARDS: Kathy Edwards, Vanderbilt University, Nashville.

MS. COLE: Rebecca Cole, consumer representative from Chapel Hill, North Carolina.

DR. ESTES: Mary Estes, Baylor College of Medicine, Houston.

DR. HUANG: Alice Huang, Cal. Tech.

DR. SNIDER: Dixie Snider, Centers for Disease Control and Prevention.

CHAIRPERSON FERRIERI: Patricia Ferrieri, University of Minnesota Medical School, Minneapolis.

DR. KARZON: David Karzon, Vanderbilt Medical School, Nashville, Tennessee.

DR. EICKHOFF: Ted Eickhoff, University of Colorado, Denver.

DR. BREIMAN: Rob Breiman, National Vaccine Program Office.

DR. KILBOURNE: Edwin Kilbourne, New York

Medical College, Valhalla.

DR. WEBSTER: Bob Webster, St. Jude Children's Research Hospital, Memphis, Tennessee.

DR. COX: Nancy Cox, Influenza Branch, CDC.

DR. LEVANDOWSKI: Roland Levandowski, Center for Biologics Evaluation and Research, Division of Viral Products.

CHAIRPERSON FERRIERI: Thank you.

We will have additions to the group. Dr. Broome and Dr. LaMontagne will be here later.

I'd like to start then by turning the meeting over to Dr. Roland Levandowski, and he will proceed with the program then until we're ready to take a break.

DR. LEVANDOWSKI: Thank you, Dr. Ferrieri.

I'd like to welcome everybody here this morning, and I think we'll get down to business because we have a very tight schedule for the program. All of us are going to have to be right on time. All of us speakers will have to be right on time to be sure that we can get in everything that we want to.

I'd like to just start with a few remarks. I think everybody knows why we're here, but I will state it. We're here today to begin the process of

selecting the strains that will be used in the influenza virus vaccine for the United States in the 1998-99 season.

And the question for the Committee is: what strains should be included, what strains should be selected based on the scientific information that we have available for that inclusion?

If I could get the first overhead.

Just as some background remarks, we're kind of stuck between Scylla and Charybdis in this process because there are two competing forces here. One is the force of nature, the strains that are out there circulating in people, and the other one is the schedule for trying to produce vaccines for the United States.

This slide has been updated. You've probably seen this several times in the past, but I just would like to point out that the number of doses of vaccine that are being produced, manufactured for the United States had been increasing steadily, and over the last two or three years, you can see that we're reaching something that looks like it might be a plateau.

So it indicates, I think, that we may be reaching our vaccine capacity for current

manufacturing facilities.

That is quite remarkable, however, that the number of doses has increased from about 20 million doses produced in the late 1980s to around 80 million doses of vaccine that are produced today, and this is part of what causes the concern about manufacturing.

If I can get the next slide, next overhead.

Just to give an indication of what's happening for vaccine production, there is literally something happening all year long for this process. It's a never ending type of story that goes in a very large circle, and I won't go through everything that's on this slide, but I want to emphasize a few things.

One is that surveillance, of course, is the key behind everything. Without surveillance, we don't really know what's happening. We're essentially blind and can't see.

That is going on continuously, and there's a fairly concentrated effort during this time of year to try to identify the strains that will be necessary for use in the vaccine. Obviously there comes a time where the manufacturers have to go and make vaccine or they won't have something that's available.

But during that same period of time, we are busily trying to find strains that will grow well, not only the right antigenic composition, the right antigenic characteristics, but also strains that will permit the manufacturers to make that 80 million doses that they're producing currently.

And not to emphasize too much, just again there are many steps that are intricately connected in producing the vaccine any one of which, if there's a failure at any one of these steps, the vaccine may not be available.

If I can get the next slide.

So the information that we're going to be considering this morning for strain selections can be broken down into really four categories.

Very importantly, what the antigenic and genetic composition and characteristics of the strains are that are out circulating in people right now.

We also need to know whether these strains are -- how much they're spreading in human populations and where they exist. That information is very important to knowing whether the strains that look very different are unusual in being just an isolated case or whether they represent something that has the opportunity for spreading very widely.

We also need to know whether the current vaccines are likely to be effective against the strains that are present in human populations.

And finally, we need to have availability of candidate vaccine strains that can grow well for the manufacturers. If we don't have a strain, then we really can't do very much about things.

So you can take that off, please.

So I will stop there, and I will ask Dr. Keiji Fukuda from the Centers for Disease Control and Prevention if he'll come and give us some information on U.S. surveillance.

DR. FUKUDA: Good morning. I'll be very brief going over the U.S. surveillance data for this year.

Just to remind people here, I think most of you know this, but basically CDC collects surveillance information on influenza from four major sources. The state and territorial epidemiologists provide weekly estimates of influenza activity in their states. There is a group of about now 500 physicians in the United States which provide data on influenza-like illnesses on a weekly basis in the United States.

Then the network of WHO collaborating

laboratories, of which there are, I think, right now 76, provide information on isolates Ns (phonetic) and isolates to CDC.

And then finally, morality data, pneumonia and influenza related mortality data, is sent in from 122 cities, and these 122 cities represent about one-third of the aggregate mortality data in the United States.

Now, this bar graph here represents the reports coming in from state and territorial epidemiologists for the year, and basically you can see that somewhere toward the end of 1997 and the beginning of 1998 estimates of flu activity really picked up in the country.

The blue bars represent regional activity and the pink bars represent widespread activity, and you can see that right now we're on the ascending part of the curve.

These two maps here basically reinforce that message. You can see on the top map the reporting as of January 3rd, 1998. The pink states represent the states reporting widespread activity, and the blue states represent the states reporting regional activity.

You can see that two weeks later, during

the week ending January 17th, that the reports of widespread and regional activity have greatly increased in the United States.

Now, one of the other components, the sentinel physicians are the group which send in reports on how many patients are showing up in their offices for influenza-like activity, and you can see that at the end of week one, which ended January 10th, the number of reports coming in for those visits exceeded the baseline, which is three percent.

And so right now about four percent of visits coming into the sentinel physicians are for influenza-like illness.

Now, this graph here represents the information on isolates coming into CDC, and again, you can see that, in general, it parallels the reports of illness coming into CDC.

The bars in green represent reports of influenza A viruses which have not been subtyped. The pink bars represent -- the pink and blue bars represent the subtypes of the influenza A viruses, and you can see that of the influenza A viruses which have been subtyped, by far the vast majority have been influenza A H3N2 viruses, and there have been very few reports of influenza B viruses.

Finally, the last component of the surveillance system is on mortality, and you can see that the 1997-98 year is represented by the end of the curve over there.

The sinusoidal part of the curve represents the expected number of deaths from pneumonia and influenza related causes, and then the top part of that, the top line of that sinusoidal curve represents basically the threshold, when it goes statistically above what we might expect to see at that time of year.

And so you can see that at the end of week ten again we went above that threshold, and currently the threshold is somewhere about 7.3 percent, and right now we're at 9.1 percent as of a couple of days ago.

We haven't yet seen the peaking of influenza/pneumonia related deaths, and so anyway, right now we're still on the ascending part of that curve.

So I think the take home message from U.S. surveillance is that influenza is definitely here. What we're seeing is predominantly influenza A viruses and predominantly influenza A H3N2 viruses.

We are seeing excess mortality over the

past three weeks, and we have not yet seen the peaking of that.

I think I'll stop there, if there are any questions.

DR. LEVANDOWSKI: Okay. If there are no questions for Dr. Fukuda, then I guess we'll move on.

Dr. Nancy Cox, who is the Chief of the Influenza Branch at CDC, will present the information on world surveillance, strain characterization, and molecular analysis of those strains.

DR. COX: Good morning.

First, I'd like to say that it's been a very interesting and exciting influenza year, and we've been extremely busy, but excited because we are learning a lot of new things about influenza viruses.

If I could have the first overhead, please.

As Roland mentioned this morning, surveillance for influenza viruses is really the key to vaccine strain selection, and the way that we've come to look on global influenza surveillance is that we're tracking a moving target in a rapidly changing world, and we all know what some of these changes are: changes in population density, demographics, immune status of the population, changes in the environment,

in health care practices and priorities, changes in political boundaries and resources devoted to influenza surveillance, and of course, changes in the perception of the threat to human health posed by influenza viruses.

Now, the viruses themselves are also changing in a very unpredictable way, and I want to sort of lay this out at the beginning.

Of course, there are two types of change that can occur in influenza viruses. One is the gradual occurrence of change called antigenic drift, and the other is antigenic shift, which occurs at irregular and unpredictable intervals.

And please keep in mind that what we are talking about this morning is antigenic drift, the gradual change where we're trying to update the vaccine strains. This afternoon we'll be talking about antigenic shift.

Okay. As Roland mentioned, we have three types of data that we use to guide our selection of influenza vaccine strains, and these three types of data that we use have structured my talk today.

So we're, first of all, looking for emergence and spread of variant viruses, and we look for these variants using hemagglutination inhibition

tests and using sequence data derived from sequencing the hemagglutinin gene.

We look to see if there's been significant influence activity associated with the circulation of these variant viruses, and we find this out by looking at WHO or domestic reports of high levels of influenza-like illness during the time the variant viruses were isolated.

And of course, we look for a reduced post vaccine immune response to these variant viruses as a clue that we need to update the vaccine.

Next, please.

Now, I'll start out by talking about influenza B viruses, which this year I think are the most straightforward of the three groups of viruses that we'll be considering this morning.

Influenza B viruses have continued to circulate worldwide over the past 18 months or so. I'd like to point out right from the beginning that there are two lineages, two very distinct antigenic and genetic groups of influenza B viruses, one represented by B/Beijing 184-like strains and the other represent by B/Victoria 02/87-like strains.

We had some activity caused by influenza B viruses in the United States last year toward the

end of the season. We had some influenza B activity at the outbreak level.

Influenza B caused more difficulties in Europe and in Asia, in particular. During March there was epidemic activity in China associated with B/Beijing and primarily B/Victoria-like strains. That activity continued on in south China during our spring and summer months, and again, it was associated primarily with B/Victoria-like viruses.

In the southern hemisphere, in both Central and South America and Australia/New Zealand, influenza B/Beijing-like strains circulated and caused a certain amount of epidemic activity.

In the most recent period, October '97 to January '98, there has been relatively little influenza B activity, and there have been few viruses isolated. All of them analyzed so far are B/Beijing 184-like.

Next overhead.

If we look at the antigenic properties of these influenza B viruses, we can see very clearly the two groups that I mentioned before, the B/Victoria-like strains represented here by a recent B/Victoria-like virus, B/Beijing 243/96, which was chosen as being representative of the currently circulating

Victoria strains and which was used in a vaccine trial which will be described later on by some of my colleagues.

And this virus, antiserum to this virus does not inhibit the B/Beijing 184 B/Harbin-like strains very well at all.

Conversely, antiserum to the B/Beijing 184 and B/Harbin strains do not inhibit the Victoria-like strains very well. So you can see very clearly, using hemagglutination inhibition tests that there are two distinct lineages.

We'll look a bit more at the particular antigens, the particular test antigens that we have here. This particular strain was isolated in January of '97. So it's a year old.

This strain is the most recent U.S. strain that we've characterized, isolated in mid-November of '97 from North Carolina.

The majority of the strains shown here were isolated last summer during activity that occurred between April and August. We do have this one B/Hong Kong strain which was isolated in mid-October of '97 that is Beijing/Harbin-like.

I forgot to mention that B/Harbin is the strain that is actually in the current influenza

vaccine, and what we can say very clearly is that viruses which are on this B/Beijing 184/Harbin lineage are very homogeneous, and they are very well inhibited by antiserum to the prototype B/Beijing 184 and B-Harbin 7 antisera.

I should mention that the strains that we have used in the serologic that will be described later are asterisked here. They are the four reference strains here, and in addition we had chosen this B/Argentina strain for the southern hemisphere to look at the serologic response to this particular antigen.

Next, please.

Now, Alan Hampson, who runs the WHO Collaborating Center in Melbourne, Australia, unfortunately is unable to be with us today, and I thought I would just present one of his tables. It's a bit busy and complex, but I simply want to make one point.

They did have a reasonable number of influenza B viruses isolated in Australia and New Zealand during their influenza season during our summer months, and as I had shown you before, the antiserum to the Beijing and the Harbin strains inhibit these strains very well.

So what we can say is that there's been no detectable antigenic drift among the viruses related to Beijing 184 and Harbin 7.

Next, please.

In spite of the lack of antigenic drift among the Beijing 184 strains, we do have continuing concerns about the circulation of the Victoria-like strains in Asia, and you can see that during the period October '96 to March '97, in other words, last influenza season, the Victoria-like strains predominated in Asia while the Beijing 184-like strains were present in the rest of the world.

Similarly, during the period April '97 to September '97, the Victoria strains predominated in Asia, while Beijing 184-like strains were present in the rest of the world.

We've just done antigenic analysis on two influenza B strains isolated during the period October '97 to November '97, and they both are Beijing 184-like. This is the North Carolina virus that I showed you, and this is the Hong Kong virus that I showed you in the last HI table.

Next overhead, please.

I think sometimes a map is really the very best way to get a handle on where different influence

variants are circulating, and here we are looking specifically at the geographic distribution of B/Victoria-like strains, and of course, the representative I had in my HI table was the B/Beijing 243 virus.

Shown here in red squares we have isolates identified during the winter of '97 in Japan and Taiwan and in June of '97 in Singapore, and then in red circles we have approximately 130 isolates that were reflected in the previous frequency table that I showed you, which were identified in China and Hong Kong during the period '96 through '97.

So we have the B/Victoria virus is clearly circulating in this part of the world, but not having been detected elsewhere.

Now, I'm not going to spend very much time on the genetic characteristics of these viruses because we really aren't seeing antigenic differences, but I would like to present this overhead because I think that it's important to understand that we really do use the genetic data as an adjunct to the antigenic data to help guide our ongoing analysis and certainly to guide vaccine strain selection.

Here you can see in blue HA, the relationships among hemagglutinin sequences of

influenza B viruses related to the Harbin 7 and Beijing 184-like strains. There isn't a great deal of genetic heterogeneity among the current '97 strains. Here is our Harbin 794 vaccine component right here, and as I showed you before, we can't distinguish these viruses antigenically.

Down here shown in green are the HA sequence relationship for the Victoria 2/87-like strains, and you can see that there's not a great deal of genetic heterogeneity among these strains either.

Here is the Beijing 243/97 reference strain, which is the recent Victoria-like strain used in serologies that I mentioned before.

Next, please.

My colleagues will be talking in much greater detail about the serologies that were done at CDC and elsewhere, and they'll be trying to synthesize the results that have been obtained in a variety of laboratories, but I just wanted to show this one table showing serologic responses in adult populations to the B/Harbin component and additional antigens that were asterisked in the HI table.

And what we see is that we have nice post vaccination geometric mean titers for the relevant strains, including the more recent strain from

Argentina.

We do see decreased response to the Victoria-like reference strain in all the different serum panels that we've tested, but there does seem to be a very nice response, indeed, to the B/Harbin component.

Next, please.

So I guess before we move on to the H1N1 viruses, I should summarize that for influenza B we have worldwide activity attributable to influenza B viruses continuing.

There are two distinct lineages of influenza B viruses circulating, and only one of these lineages is represented in our current vaccine.

Antigenic variation has not been detected among the currently circulating Harbin or Beijing 184-like strains, and the distribution of Victoria-like and Harbin-like viruses worldwide remains much the same as what we had seen in previous years.

Okay. Now we'll move on to page 18 of your handout, and we'll consider the picture that we're seeing with influenza A H1N1 viruses. These viruses have really caused less influenza activity worldwide than influenza B or H3N2 viruses. I'll concentrate mainly on this period when there was some

epidemic level activity in Central and South America associated with influenza A H1N1 strains and also some outbreak level activity associated with H1N1 strains in Asia.

Once again, I should note that there are two quite distinct antigenic and genetic groups of influenza A H1N1 viruses. In some ways the picture is quite similar to that that we see for the influenza B strains.

The Bayern 07-like strains are represented in our current vaccine by the Johannesburg 82 antigen. The other group, which we call the deletion mutant group, is represented in my tables by A/Beijing 262/95, and we know that viruses in this group have a single amino acid deletion at amino acid 134, which is in site A in the hemagglutinin, and we believe that this deletion may be responsible for the antigenic differences that we see among strains.

Now, in the most recent time period, October '97 to January '98, we've had very little -- in general, very little -- activity associated with H1N1 viruses. There has been some in Europe, a bit in the United States, and some in Asia.

So, in general, activity, influenza activity caused by H1N1 viruses has not been very

dramatic over the past few years.

Next overhead, please.

Now, here we see the antigenic relationships among these influenza viruses, and once again, a for the B viruses, we can see two very distinct groups, one represented by the Bayern and Johannesburg reference strains here, and the other represented by the Beijing 262 and Wuhan 371 deletion mutant strains here.

It's very easy to see the antigenic differences between these two groups of viruses.

Here we have some recent viruses isolated from the United States. These viruses were not reflected in the report given by Dr. Fukuda because they had not been subtyped by the states. All of the viruses, influenza A viruses that had been subtyped by the states were H3N2s. However, some of the strains that were sent to us before they had been subtyped turned out to be H1N1 viruses, and we can see that these strains are Bayern-like and very well inhibited by antiserum to Bayern and Johannesburg 82.

Likewise we received some strains from Maria Zambon, and she'll probably talk about these in more detail in her talk, but they are also clearly Bayern-like, and so there's no evidence for antigenic

drift among the Bayern-like strains.

This is a virus from the southern hemisphere from activity that occurred in September in Argentina and was used in our serologies, and it also is a typical Bayern-Johannesburg-like strain.

We received these viruses here, antigen 17, 18, and 19, from Hong Kong very recently. They are from activity that occurred in Hong Kong in December, and they very clearly belong to the Beijing 262/Wuhan group of strains. This is a typo here. It should be 320 instead of 32.

Next overhead, please.

Now, if you were at this meeting last year, you'll recall that the Beijing 262-like or Wuhan 371-like deletion mutant strains had been detected only in Asia. These are data from Dr. Alan Hay, who runs the WHO Collaborating Center in London, and he shared his data with us showing that deletion mutant strains related to Wuhan and Beijing 262 have been identified in Senegal and also in South Africa, and you can see these viruses were isolated in August and September of '97 and these viruses from South Africa in November of '97.

So very clearly we have movement -- next overhead, please -- we have movement of these viruses

out of Asia to another continent.

If we look at the frequency of antigenic groups that have been characterized -- of viruses characterized by CDC, we can see that in the period October '96 to March '97 we did have Beijing 262-like deletion mutant strains circulating in Asia, and we had some Bayern-like strains in Europe and also one from Asia.

In the period April '97 to September '97, we had a fairly large number of Beijing 262-like strains, most of which came from China, and then we had from Central and South America Bayern-like strains, as well as a few strains from Australia and New Zealand.

In the most recent period, we have the five Bayern-like strains from the United States. We have four Bayern-like strains from Europe, and we have the four strains that you saw in the HI table from Hong Kong, which are Beijing 262 deletion mutant type strains.

Next overhead, please.

This map shows the geographic distribution of the Beijing 262-like deletion mutants. You should keep in mind that the Bayern-like strains are distributed worldwide. We're concentrating here just

on the deletion mutant distribution.

And during the period October '96 to September '97, we had a total of 63 isolates identified from China, Hong Kong, Singapore, and Senegal.

In the period October '97 to January '98, five isolates were identified in Hong Kong, Johannesburg, and Taiwan.

So now we have a wider distribution of the Beijing 262-like strains than we did last year.

Next overhead, please.

I will spend just a moment on the evolutionary relationships among the HAs of influenza A H1N1 viruses. You can see that the genetic data very clearly reflect the antigenic data, and we have two very distinct groups, one here represented by the Beijing 262-like reference strain, and here is the Beijing 262-like or Beijing 262 strain itself. Here is the RESVIR-10 experimental vaccine strain that was used and will be described. The vaccine trials using this strain will be described in more detail by my colleagues later.

There is some genetic movement of viruses between '95 and '97. I think there are about four amino acid changes that are shared by the '97 strains,

but that's not reflected clearly in antigenic analyses that we've done on these viruses.

If we look at the Bayern-like strains, we can see that there is some antigenic heterogeneity, but clearly the -- sorry -- some genetic heterogeneity, but clearly this is not reflected in the antigenic analysis.

Next overhead, please.

I'll just spend two seconds on this table, which shows the antibody response to the Johannesburg component of the vaccine. Once again, we see that if we focus on the post vaccine geometric mean titers, we have a very nice, robust response to the vaccine strain itself and good responses to other strains, except for the Beijing 262 when we have a much reduced response to this particular strain compared to the homologous titer that we get for the vaccine strain itself, but the vaccine appears to work very well, this particular vaccine strain.

So in summary for the H1N1 viruses, we did change the H1N1 component of the vaccine last year and updated it to a Bayern-like strain, and this has been a very good choice for the viruses that are currently circulating in Europe, the Americas and Oceania.

The so-called deletion mutant virus is

represented by B/Beijing -- sorry -- A/Beijing 262, continue to circulate in Asia, and there's evidence for spread of these viruses to Africa and continued circulation in China and Singapore.

Okay. Now we'll move on to the H3N2 viruses. The H3N2 viruses have really posed a constant challenge to us. They are really responsible for more epidemic activity worldwide and more severe disease than viruses in the other two groups.

And this is reflected in this worldwide activity overhead here, where we see and we can remember very well that influenza A H3N2 viruses caused epidemic level activity during last year's influenza season in North America, Europe, and Asia.

Likewise in the southern hemisphere A H3N2 viruses caused epidemic level activity in Australia and New Zealand, particularly in Australia, in Central and South America, and caused outbreak level activity in parts of Asia.

I do need to mention right away that a new variant of H3N2 emerged and was identified last autumn in Australia and New Zealand, and this new variant is represented by the A/Sidney 05/97 reference strain.

So you can see that the activity that was occurring in the southern hemisphere was caused by

both Wuhan-like and Sidney-like strains. Sidney is related to Wuhan, but clearly antigenically distinguishable from it.

If we move to the current time period, October '97 to January '98, we see that in the United States we are now having epidemic level activity caused by a combination of Wuhan and Sidney-like strains. Canada also is in somewhat the same situation.

Europe seems to be having somewhat less activity caused by H3N2 viruses, and there is some activity in Asia, and we hope to get more information about this.

Next overhead, please.

So the next table shows us how the Wuhan reference strain and the Nanchang vaccine strain are related to this new variant Sidney 05/97, and you can see quite clearly that ferret antiserum to the Wuhan virus does not inhibit the Sidney virus as well. There's an eightfold difference in titer between the Wuhan homologous titer and the titer against the Sidney strain.

Likewise we see a reciprocal difference when we look at the homologous Sidney titer of 640. We can see that this antiserum to this strain does not

inhibit the Wuhan and Nanchang viruses particularly well, and that general picture is reflected below when we look at the test antigens.

Here we have a group of antigens that are from the United States. Unfortunately the dates of isolation have been left off of this overhead, but these strains were isolated in the United States between November 18th and December 18th, and these strains are all Wuhan-like and well inhibited by antiserum to Wuhan and to Nanchang.

In contrast, we have another set of viruses from the United States which were isolated between the 18th of November and the 30th of December, and these strains are not as well inhibited by antiserum to the Wuhan and Nanchang reference strains, but are very well inhibited by antiserum to the Sidney virus.

We also have a Sidney-like strain which was isolated during late activity in Australia in September of '97, and we have a group of viruses isolated in Thailand during June, July, and August, which are Wuhan-like.

Left off of this table, but in your handout you will also see two strains isolated in Korea during December of '97, and these strains are

Sidney-like.

So if you go on to the frequency table and look at the viruses that we've characterized antigenically, we can see that the strains that were circulating during last year's H3N2 epidemic were Wuhan-like viruses, and this was true pretty much worldwide.

During the summer months, during our summer months, the Wuhan-like strains continued to circulate, but we were beginning to see the Sidney-like viruses pop up, and they were first isolated in Australia and New Zealand during June and July of '97.

If we look at the most recent period, we can see that from the United States we have characterized a total of 72 influenza isolates, 61 percent of which are Sidney-like. We have a single strain from Canada which is Sidney-like. We have a Wuhan-like and a Johannesburg-like strain from Europe. We have several Sidney-like viruses from Asia, including the ones from Korea and some from Hong Kong, and we also had some Sidney-like strains from late activity in Central and South America and from Australia and New Zealand.

Next overhead, please.

So if we look at the distribution of

Sidney-like viruses worldwide, we can see that the strains at least according to the information that we had when we made these overheads a couple of days ago, the Sidney-like strains were first isolated in June and July in Australia and New Zealand.

Guam had an isolate in November, Taiwan in September, Hong Kong in July, Korea in November, and so on, and these strains have been popping up during November, December, and January in Europe, as well as in North America.

The first Sidney-like strains that were isolated in North America were actually isolated during a cruise ship outbreak where some tourists from Australia boarded a ship, and it's reported that some of them had respiratory illness when they boarded, and so the viruses that were isolated on that ship were Sidney-like, and it's likely that this was a travel related outbreak caused by Sidney-like viruses.

We also had Sidney-like viruses in Hawaii and, of course, I mentioned in Argentina.

Next overhead, please.

When we look at the evolutionary relationships among hemagglutinates of these H3N2 viruses, we can see that although we really have one, it's not the same situation that we have for the

influenza B viruses in the H1N1 viruses where there are two very, very distinct genetic groups, but we have a lot of heterogeneity among them.

Here we have in green shown the old Wuhan 359-like strains, and here is the Wuhan reference strain and our vaccine strain, Nanchang 933.

Those of you who were at the meeting last year may recall that we talked about the South Africa strain, and it also was shown in the HI tables, but I pretty much skipped over it. South Africa exhibited some genetic differences from the Wuhan-like strain that were quite interesting. The antigenic differences were much less striking, but what we have found is that the Sidney-like strains actually evolved from this South Africa virus.

And so now what we have circulating are viruses -- the viruses that are in this genetic group are beginning to predominate worldwide.

Next, please.

We actually have done RFLP or restriction fragment length polymorphism analysis for each of the three groups of viruses, but I'm only going to present our data for the H3N2 strains because it's only here that the data actually add to what we know from the antigenic analysis.

Here we can see that during the period from October '96 to March '97, we could -- I mentioned we could distinguish the South Africa genetically by sequence analysis from the Wuhan strains. We had a majority of Wuhan 359-like viruses when we're talking about genetic analysis.

And then from the last -- and I'll talk about the picture worldwide, but here I'm talking about the picture for the U.S. -- for the U.S. during the period April '97 to September '97, we had three Wuhan-like strains, three South Africa-like strains, and three Sidney-like strains, and these were from the cruise ship outbreak.

Then during the current period, October '97 through January '98, we've analyzed a larger number of viruses by RFLP than we have by antigenic analysis, and here you can clearly see that for the United States Sidney viruses are beginning to predominate.

We have a total of 72 Sidney-like viruses or 73 percent of the viruses analyzed by RFLP and 24 that fall into the South Africa genetic group that actually look antigenically like Wuhan and then two that fall into the old Wuhan genetic group.

We're moving to the worldwide picture now,

and it looks very similar to what we're seeing in the United States in that we had a majority of Wuhan-like strains circulating last winter. Then during the summer months, the Sidney variant emerged, and approximately 20 percent of the isolates that we genetically analyzed fell into this group. Forty-two percent fell in the Wuhan group, and about 37 percent in the South Africa genetic group.

During the most recent period, October '97 to January '98, we have about 74 percent of the strains that we've analyzed genetically falling into the Sidney 05-like group and only about 23 percent of the viruses falling into the Wuhan group.

Next overhead, please.

Once again I'm going to just only briefly mention the serologies that were done at CDC because they'll be covered in more detail later on, but I'd like to point out a couple of things at least in our hands in some groups, in some population groups.

For example, in the European adult population, we found that the post vaccination geometric mean titers were very low to the Nanchang strain, the vaccine strain, and there was a clear reduction in titer to the Sidney variant.

For the U.S. adult population, we saw a

better post vaccine response, a higher geometric mean titer, but once again, we saw a reduction in the post vaccine response to the Sidney variant.

The New York strain here is a Sidney-like virus that was isolated this fall, and you don't see quite the same level of reduction to this particular strain. So that's interesting.

Okay. You can take that down.

So in summary for the H3N2 viruses, I'd like to say that these viruses certainly do continue to cause epidemics in serious disease as they evolve, and I'd like to emphasize that these viruses have circulated for 30 years, and they don't seem to be losing any of their punch.

The second point is that a new antigenic variant related to, but distinguishable from, the vaccine strain and represented by the reference strain A/Sidney 05/97 has spread worldwide.

And my third point is simply that sequence heterogeneity is certainly more prominent among the H3N2 viruses related to the vaccine strain than in the B or H1N1 viruses related to the vaccine strain.

I think I'll close there and open the floor to questions.

DR. LEVANDOWSKI: Are there any questions

for Dr. Cox and her presentation?

Dr. Couch.

DR. COUCH: Nancy, have you had enough isolates analyzed in the past few years from China and maybe other parts of Asia to say whether they experienced a transition for H1 viruses from Taiwan to Texas, to Bayern to the newer strains?

DR. COX: We have seen -- yes, I mean, we have seen that kind of transition. We've had relatively few strains that were related to Taiwan, Texas, and Bayern over the past three years from Asia, but we can say that when we do see a strain that's on that lineage isolated from China, that antigenically it looked similar to the Texas-Taiwan Bayern-like viruses, but we've had very few of them.

The majority of the strains isolated over the past three years from China have been the Beijing 262/Wuhan 371 deletion mutant-like viruses.

DR. COUCH: But do you have enough before, say, three years ago to say that Texas or Taiwan were dominant?

DR. COX: Yes.

DR. COUCH: They were?

DR. COX: Yes.

DR. LEVANDOWSKI: Dr. Kilbourne.

DR. KILBOURNE: Nancy, going back to page 29 of your handout, we have the old recurrent problem here of the single ferret. When you talk about the response of the Wuhan antigen, I guess, a Sidney, you chose to talk about one Sidney. That was the Sidney which is not the recombinant in terms of showing an eightfold difference in that direction, whereas it's twofold if you look at the recombinant.

Now, has additional work been done to establish really whether there's that much difference between the reassortant, the Australian reassortant and the wild type?

DR. COX: We have sequenced the Sidney 05 and the IVR 108 reassortant, and they are, I believe, identical to each other in sequence of their HI1 domains.

So I can't explain, and we've seen this before where the high growth reassortants sometimes exhibit much higher reactivity with the ferret sera, and we've never been -- maybe you have an explanation for it. I've never been able to adequately understand or explain that phenomenon, but we do see it occasionally.

DR. KILBOURNE: Well, you and I have published on this, but I just think it's a point worth

noting if anybody's going over the data, that one does have this quasi species effect here.

DR. COX: Well, when we did our paper, we actually did see molecular changes that sometimes could be correlated with the antigenic differences. In this case we don't see changes.

DR. KILBOURNE: Could it be influenced by differences in neuraminidase?

DR. COX: It could possibly be. We have not explored that.

DR. KILBOURNE: Okay.

DR. COX: But what we can clearly see is that when we look at the test antigens, the field strains themselves, there are these two distinguishable, very distinct groups.

DR. KILBOURNE: Yeah.

DR. LEVANDOWSKI: Dr. Eickhoff.

DR. EICKHOFF: Nancy, I'm impressed with the extraordinary rapidity with which the A/Sidney strain is spread around the globe, you know, from being not even on the map a year ago when we were at this meeting to suddenly being the predominant virus, well, globally.

It is sort of reminiscent of introduction of antigenic shift, introduction of a whole new H2 or

H3.

Do you remember any precedent in your experience that a drifted virus has spread this rapidly around the globe?

DR. COX: During the ten years that I've been intimately involved in this process of vaccine strain selection, I can't remember of another instance. I'm hoping that Dr. Nerome will talk a little bit about strains that were isolated last winter in Japan that may shed some light on this question.

DR. LEVANDOWSKI: Any other questions?

(No response.)

DR. LEVANDOWSKI: If there are no further questions at this time of Dr. Cox, we'll move on with the program. We do have on the program some reports from international guests.

Our first guest speaker is Dr. Kuniaki Nerome, who's from the National Institutes of Health in Japan, and he will give us some information on influence and activity occurring in his country.

DR. NEROME: Mr. Chairman, distinguished members of this Committee, ladies and gentlemen, I'm honored and proud to have been invited to speak at the annual meeting of your distinguished congress.

Today I would like to talk to you about the influenza activity of this season in Japan and antigenic properties of epidemic strains, mainly H3N2, Hon Kong influenza virus, not H5N1 Wuhan viruses.

In the human history, an avian influenza virus, H5N1, was first isolated from a three year old boy who died of multiple medical complications. Although the occurrence of bird influenza virus in Hong Kong has aroused attention and interest, we never ignore marked antigenic change of another H3N2 Hong Kong virus.

Please.

This figure shows a number of virus isolation with the span over time. In the spring of last year, B/Victoria 287-like strain appeared to predominate in Japan, and in 1997-1998 influenza season began with isolation of H3 Hong Kong viruses around mid-November.

As can be seen here, the numbers of virus isolation are extremely small, suggesting low activity of influenza in this season in Japan.

Next.

Since early 1997, Japan has adopted data regarding influenza-like illness, absentees, class closures, and school closures in primary school,

junior high school, and high school to monitor morbidity.

In order to compare magnitude of epidemic in this season with data of 1995 to 1996 and in 1996 to 1997, a series of data obtained from schools were presented in this figure. As can be seen here, the number of influenza-like cases, absentees, class closure and school closure that were indicated by broken line are baseline and very small. So as can be seen here, the red arrow indicates three or four absentees, even light cases, in Japan, extremely, very low when compared with last two seasons.

Next slide, please.

This is the map of Japan mainland and islands. Numbers shown in the map represent order of virus isolation in this season. In right portion, the data of virus isolation was shown.

As you can see here, the first virus isolation was reported to our national center on November 26, and it is very late when compared with that of last two seasons.

Also, number of local governments which reported virus isolation are small when compared with last two seasons.

Sorry. This is mistake.

This table indicates antigenic characteristics of Hong Kong influenza viruses. You can see here. So this is Wuhan viruses. This is Wuhan viruses does not inhibit. So most of Japan isolated from this season.

This is Saga 128 strain. It's very similar to AH3 variant. This is variant is markedly inhibited so H activity of this, most of Japanese isolates.

As you can see here, most of Japanese Hong Kong viruses belong to the H3-like variant.

Next slide. Sorry. May I have slide, please? May I have slide, please?

This is map of Japan, mainland and islands. Numbers shown in the map represent order of virus isolation in this season. In right portion -- sorry -- in that portion was shown data of virus isolation. In Japan, the first isolated H3N2 viruses, November 26 in 1997, 1997.

As you can see here, the first isolation was reported to occur, national center on November 26, and it is very late when compared with that of last two seasons.

Also, numbers of local governments which reported virus isolation are small when compared with

those over the last two seasons.

This slide shows numbers of viruses isolated in 29 local laboratories. With exception of the Hokkaido, northern part of Japan, few prefectures of central Japan and west part of Japan, numbers of virus isolation in each prefecture are not so high.

Next. Okay.

Now, our next concern is the antigenic change of H3N2 Hong Kong viruses. As can be seen in this HI table, of 29 strains examined two are apparently different from the A/Wuhan 359/95 strain and S/South Africa and A/Nanchang strain.

It is particular interest to reveal that the above two strains, A/Saga, the A/Sidney-like strain, and A/Hiroshima were already isolated in 1996-1997 season in Japan. As indicated by red square, a state of antigenic change is further emphasized in the strains isolated in 1997-1998 season.

The 94 percent of Japanese isolated belong to the A/Shiga-like strain.

Next slide.

This HI table indicates antigenic analysis of A/Hong Kong viruses isolated in Hong Kong and China and Korea. As you can see here, all the strains isolated in Korea belong to A/Shiga-like strain, and

two strains isolated in China are basically very similar to the A/Shiga-like strain, and also two strains isolated in Hong Kong are identical to H3-like variants.

So most of H3N2 viruses isolated in Asian countries already belong to A H3 like a new variant.

Next slide. That you.

It was of particular interest o know -- okay.

However, a final evaluation of antigenic draft of epidemic viruses should be undertaken in humans who receive the vaccine. This figure shows that immune responses in people vaccinated with 1996-1997 season's flu vaccine containing A/Wuhan 359/97, A/Beijing 262/95, and one B/Guangdong 05/94 and B/Mie 1/93 strain. However, Japan uses the four vaccine strains in that season.

As can be seen here, open circle, antibody type before vaccination. Broken bar indicates antiviral titer after vaccination. As can be seen here, A/Wuhan, A/Beijing, a higher immune response, but B strain antivirus titer, these did not so good.

We look at this antivirus response, A/Saga 128/97 strain. This strain is acts very similar to H3-like new variant. Even after vaccination,

antiviral titer, less than ten.

In conclusion, although the detailed analysis represented by viruses isolated in 1996-97 and 1997-98 season are not finalized, according to update of late January, we may arrive at the following conclusions.

First, A/Saga 128/97, basically all five 97-like new variant, but appear to be pubent (phonetic) in many part of the world. Antibody isolated by South Africa, A/Nanchang and A/Wuhan 359/95 viruses may not effectively prevent the infection with A/Saga 128/97, A/Sidney-like variant.

So although the data of molecular evolution was not shown in the present report, H3N2 Hong Kong viruses have survived by exchange of internal gene between old and new viruses since the early 1997.

Fourth, antigenic analysis of H1N1 viruses isolated in Japan in this season indicated its (inaudible) to the identical A/Wuhan 371/95 over A/Hong Kong 378/97, respectively.

Two B viruses were also isolated in Japan in this season, and they were antigenically indistinguishable from B/Guangdong 05/94 and B/Beijing 91/84/93, respectively.

Does a quiet influenza seasons as symbolized in the 1997-98 season mean the prediction of a new pandemic era being symbolized in the emergence of H5N1 virus, Hong Kong?

Thank you for helping.

DR. LEVANDOWSKI: Thank you, Dr. Nerome. That's very interesting information.

Are there any questions for Dr. Nerome?

Dr. Huang?

DR. HUANG: Is there any age clustering of the susceptibles to the new variant?

DR. NEROME: You mean Sidney-like variant?

DR. HUANG: Yes.

DR. NEROME: Yes. Sidney-like variant already distributed so many parts of the Asian country, I think this first may appear in the coming season.

DR. HUANG: I really was asking about the age susceptibility of the individuals that came down with the new variant. Is there any age clustering of the susceptibles?

DR. NEROME: I cannot understand the words there.

DR. HUANG: Are there specific age groups that were affected with the new variant?

DR. NERONE: No. All age groups do not contain antibody to this Sidney-like variant.

DR. LEVANDOWSKI: Are there other questions for Dr. Nerome?

I actually have one. You mentioned the exchange of internal genes of some of the strains. Can you elaborate on that and tell us which genes you're talking about?

DR. NEROME: Well, at the time we looked at the (inaudible) of more than H3N2 viruses, 1990. So most of that epidemic strain contains six internal genes between old strain and new strain. So from this analysis, recent Hong Kong viruses can survive by exchanging with the internal genes, old or new strain. Yes.

DR. COX: Could you tell us which old strains the internal genes come from?

DR. NEROME: Old strain isolated in 1993. New Hong Kong viruses isolated after 1996.

DR. LEVANDOWSKI: Okay. Thank you very much, Dr. Nerome, for that interesting presentation.

And we'll move on if there are no further questions. Dr. Maria Zambon, who's at the Public Health Laboratory Service at Colindale in the United Kingdom -- I guess I should say England -- is here to

give us a presentation about the activity of influenza viruses in England.

DR. ZAMBON: Thank you very much for inviting me.

In England, as many of you may recall from previous talks which I've given here, we use a number of indices to follow a monitor influenza activity clinically. The most important index that we use is an indicate derived from sentinel practitioner continuous morbidity registration, which I will refer to as the RCGP index.

This index is derived from approximately 100 sentinel physicians scattered throughout England and Wales who monitor a population of some 800 to 900,000 and allow, therefore, the derivation of a weekly consultation index rate for influenza and influenza-like illness.

And if we look on the top panel of my slide here, the yellow line here represents the consultation index for the current winter season, the '97-98, and you can see by comparison with last winter, '96-97, and the last really major epidemic here in England, 1989-90, but essentially this year we have had very little clinical morbidity estimated from influenza by sentinel physician network reports.

This is supported by evidence from other sources, including all laboratory reports from all hospitals in England, Wales, and Scotland of influenza A infection and of influenza B, and once again, the yellow represents the current year, not as shown on the panel here, compared with red, last season, and blue, 1989-90.

And, indeed, when we also look at death registrations from all causes in England and Wales, we find less than expected numbers of deaths in association with influenza activity.

So, therefore, the remarks that I'm going to be making about the influenza viruses that we have isolated are to be taken in the context of little influenza activity so far in the United Kingdom.

If we turn now to our directed virological surveillance, that is, community-based virological surveillance, the sentinel physicians who are conducting the continuous morbidity registration, a subset of those submit swabs for analysis from cases of flu and flu-like illness.

So the red line here represents the RCGP index. If we look at '97-98, we have essentially a flat line. The gray bars represent the numbers of samples submitted from cases of flu and flu-like

illness, and the yellow bars represent influenza isolates.

And it can be seen that although we are getting samples from cases of what appear to be flu and flu-like illness, the isolation rate continues to be rather low. Indeed, the isolation rate to date is of the order of ten percent, whereas when we are in a flu season in the United Kingdom, we normally expect an isolation rate from such samples of the order of 30 to 40 percent. So, once again, little evidence of extensive influenza activity, although we have obviously isolated some viruses.

If we turn now to looking at the isolates that we have received and analyzed, they are in total approximately 60 or so isolates, which contrasts quite markedly from the situation last year at this time where we had analyzed -- we had actually characterized some 700 isolates.

So, therefore, what we are looking at is low levels of isolates from essentially sporadic cases.

The first isolates that were received were -- well, in fact, all of the isolates that we've characterized have been influenza A, and really before Christmas these broke down into a mixture of H3N2

isolates and H1N1 isolates.

However, since Christmas we are predominantly seeing H1N1 isolates, and the other point to make is that the majority of the isolates that we have characterized have come from GP surveillance or community illness rather than hospitalized cases.

If we turn now to the age distribution of the isolates that we've looked at, and again, I'd like you to bear in mind that this actually represents data from relatively few isolates, what appears to be the case at the moment is that the H1 isolates that we've looked at are predominantly in younger age groups in comparison with the H3N2 isolates, which appear to come from predominantly slightly older people, but again, this is really data from only about 15 or so isolates in total throughout the United Kingdom.

If we start with the antigenic characterization of the H1N1 isolates that we've looked at from a mixture of GP surveillance and hospitalized cases, the important point to bring out is that all of the isolates that we've looked at have good antigenic activity with antiserum raised to Bio (phonetic) 795 and do not have reactivity with antiserum raised to the deletion mutant, which now HI

tables are represented by A/Wuhan 371/95. So there's good reactivity in all of the isolates that we've looked at so far.

Interestingly, when we look at the genetic characterization of these viruses, the ones that we have sequenced the HA1 portion of the H1 -- of the HA gene, we find that isolates are very similar to H1N1 viruses that we saw towards the end of last season and similar to each other.

We have of some interest identified an England strain, A/England 728/97, which is genetically rather closer to the deletion mutants mentioned, but does not itself contain the deletion and reacts well with antisera II, Bio N7 (phonetic), and this indicates to us that we need to focus a little more on the H1N1 strains to see exactly what is happening and whether there is some genetic heterogeneity in there.

Turning to the H3N2 strains that we've seen, as has already been mentioned, the first strain that we saw in England was, in fact, a virus which reacted rather better with an older strain, Johannesburg 34/94, and not particularly well with Wuhan or later derivatives.

We do occasionally see this in England in that the first H3N2 strains right at the beginning of

the season are not representative necessarily of what is circulating or what will circulate, but are occasionally a mixture of older strains.

Then the H3N2 viruses that we've looked at, and again, I would remind you this constitutes a total of about 15 or 16 isolates, clearly fall into two groups. There are those which react well with the Wuhan 359/95 antisera and those which react better with the Sidney 05 antisera and have a lower reactivity to Wuhan 359/95.

And the current distribution is that roughly about 70 percent of our strains have good reactivity to Wuhan 359 and 30 percent have good reactivity to Sidney 05.

This analysis is supported genetically from sequence analysis in that the majority of our strains we have sequenced come out very closely to Wuhan 359. We have some evidence of Sidney 05-like viruses genetically, and the first variant is genetically closely related to Thesalonika 01/95, which was a prototype strain for European-Johannesburg-like isolates.

So the conclusion so far from our analysis with limited data and limited numbers of strains is that we have clear evidence of circulation of at least

two lineages of hemagglutinin in the H3N2. However, we do not have extensive disease in association with either of these isolates yet, and that may reflect the fact that the influenza season, if you will, has not yet taken off in the United Kingdom.

Earlier this week there were a number of reports of outbreaks of influenza, which has turned out to be influenza A in association with boarding schools reopening in the U.K. after the Christmas break, and very often for us that signals the beginning of our true influenza season, and it may well be that in the coming weeks we will have more strains to isolate and focus on, hopefully before the Geneva meeting.

With respect to influenza B, as has already been mentioned, our last season, '96-97, towards the end of the season we had a large number of influenza B viruses, all of which were B/Beijing 184-like, both genetically and antigenically.

This season we have no influenza B isolates and, indeed, only occasionally one or two through the summer months of influenza B, and really it's actually not worth saying too much about the antigenic properties of those.

That can actually be summarized very

adequately by saying that they are really entirely antigenically similar to Beijing 184/93 and similar to each other, and the latest B virus which we obtained in England in April of 1997 is very like all of the other England viruses that were sequenced during the last season and similar to the Harbin group of viruses and Beijing group of viruses that we have seen circulating in the last year.

So in summary, in the United Kingdom we have little evidence of extensive clinical morbidity in association with influenza B -- influenza. We have -- what isolates we have had so far have been influenza A, predominantly influenza A, H1N1, and within the H3N2 viruses we've seen some antigenic and genetic heterogeneity as with the H1N1 viruses, where we have evidence of Bayern 07-like strains, and the possibility of some genetic heterogeneity which needs to be amplified by more data analysis.

Thank you.

DR. LEVANDOWSKI: Thank you, Dr. Zambon.

Are there any questions for Dr. Zambon?

Dr. Cox.

DR. COX: Was there any travel history that you could ascertain for the patient from whom the England -- the H1N1 England 728 strain --

DR. ZAMBON: We haven't been able to pursue that, but that is certainly something we can try to catch up on.

DR. HALL: May I also ask is that particular strain close to any of the ones that Nancy presented here?

DR. ZAMBON: I'm not quite sure about that in the sense that we'll have to look at it. We'll have to compare our sequence data in order to get at that information.

DR. LEVANDOWSKI: Okay. Do you have a question?

DR. COUCH: In looking at your tables, despite their being quite Wuhan and your England strain being quite close, the Wuhan antisera was not very good at inhibiting the strain. Are you making the England antiserum to look for the --

DR. ZAMBON: Yes.

DR. COUCH: -- opposite effect?

DR. ZAMBON: Yes. That's in progress.

DR. LEVANDOWSKI: Are there further questions?

(No response.)

DR. LEVANDOWSKI: I'm sorry if I don't see somebody. You have to make more noise.

If there are no further questions for Dr. Zambon, then I guess we'll move on, and I'll ask Dr. Ferrieri if this is a convenient time for the break. I think we're right on schedule as of this time, and I'll ask for your advice on this.

CHAIRPERSON FERRIERI: Yeah, I think we should take a break now and reconvene at 10:15, and we'll be right on target. Some people may wish to check out of their rooms so that we can move forward this afternoon.

So 10:15.

(Whereupon, the foregoing matter went off the record at 9:48 a.m. and went back on the record at 10:18 p.m.)

CHAIRPERSON FERRIERI: We will resume the morning session if everyone could please sit down. Those at the table, please rejoin us.

We'll continue on then with our agenda on the influenza virus vaccine formulation issue, and the next talk will be on vaccine responses, and Dr. Levandowski and Dr. Wood will present.

Dr. Levandowski.

DR. LEVANDOWSKI: Okay. Thank you.

We will get started. I know that there are people who are still kind of trickling in.

We're going to be having a somewhat different set of presentations than we normally do on the vaccine responses in at least one sense. I'm going to be presenting information on the typical types of clinical trials, serologies that we normally have to discuss at this meeting. When I'm finished with that, Dr. John Wood from National Institute of Biological Standards and Control in England will be describing a very interesting study done with an experimental vaccine that contained the H1N1 deletion mutant as one component and a B/Victoria-like strain as another component.

So I'll start with the information that I've got here.

Those of you who have the handout, particularly on the Committee, to follow along, there's a handout that's called "Summary of Preliminary Data on Serologic Responses." All of the overheads that I'm going to show are contained in there, and I'll try to make sure I tell you what page I'm on so that you can follow along.

I don't intend to describe all of the individual studies. I'm going to try to highlight some specific studies that are illustrative and then make some general summary statement at the end about

the studies.

If you go to page 1 of the handout, there's a list of the serum panels that were used for the studies, where they came from. We had serologic panels from Alan Hampson in Melbourne. John Wood supplied a panel of sera from people immunized for the European Union clinical trials. We had sera that were made available to us from Stefan Gravenstein's program at East Virginia Medical School.

We had a panel of sera that were made available by John Treanor at the University of Rochester, and his sera were somewhat different from the others in that there were more types of individuals immunized. In particular, I'd call your attention to the fact that in addition to the normal healthy adults and ambulatory elderly, there were patients who were immunized who were renal patients and also institutionalized elderly patients.

We did not have from this year, but we did have retained, some small portion of antisera from a study done last year for us by Bill Gruber at Vanderbilt University.

The particular vaccines that were used for these trials are shown under vaccine components. The vaccine for this year used -- in the northern

hemisphere was the one that included an A/Johannesburg 82/96 H1N1 component, an A/Nanchang 933/95 H3N2 component, and a B/Harbin 07/94 component, and I will try to refer to those strains as the vaccine strain when I point out the serologies.

For the children who were immunized last year, the H1N1 component was an A/Texas 36/91 component. For the serologies from Australia, the H1N1 component was an A/Texas 36/91. So I will not be concentrating on those aspects for those particular panels.

If I can get the next overhead, which is page 2, these are the different antigens which were used for serologies at different institutions. Many of the antigens were the same between the institutions, but there were some differences.

For the B strains, all of the strains that were used for serologies were ether treated, and I guess I would call attention to the fact that the B/Argentina 218/97 and B/Argentina 275/97 strains are both B/Yamagata. I should say they're B/Beijing 184 or B/Harbin 07/94-like strains, so that they're on the B/Yamagata 16/88 lineage.

The B/Beijing 243/97 strain is a B/Victoria 02/87-like strain.

For the H1N1s, again, I just would point out that the strains that are included here are predominantly like the A/Johannesburg 82/96 vaccine component, including the A/Argentina 974/97 strain.

Also included in the studies were H1N1 deletion mutant viruses represented by A/Beijing 262/95 type strains.

For the H3N2 studies, the strains that are represented here include those that are like the A/Sidney 05/97 strain that we've been hearing about, and also some other variants. The A/Wuhan 254/97 is a recent non-Sidney type H3N2.

The next overhead is from page 3, and many of the laboratories performed serologic testing on serum panels that were shared among the laboratories. Those are shown here.

You can see that the sera from Australia, from Europe, and some from the United States were shared amongst the different laboratories.

And if we go to page 5, which is an influenza B table, this is a study that was done using sera from adults in Australia. The serologies that I'm showing here were done by CSL. Actually they were done by the WHO center at Melbourne and by the CDC in Atlanta.

And I'll just call your attention to the geometric mean titers that are shown here, the post geometric mean titers, to point out that the vaccine strain B/Harbin 07/94, it was a very immunogenic strain in these studies at least for strains that were similar to B/Beijing 184/93, including the B/Argentina 218/97 strain.

However, strains that are more like the B/Victoria 287 strain represented here by the B/Beijing 243/97 showed substantial decreases in antibody responses for persons immunized with those vaccines.

Those differences were not always as marked, and page 6, a study done in elderly from Virginia with serologies done, again, at a WHO center in Melbourne and at CBER. The responses were somewhat lower than seen in the previous panel for the vaccine strain, but that often happens in elderly populations. We see somewhat lower responses.

And in this instance the difference between the vaccine strain, the B/Harbin and the B/Victoria-like strain, the B/Beijing 243/97, was not quite as marked, did not reach the same level of difference as was seen in the first study that I pointed out.

Moving on to the H1N1s on page 9, a fairly typical study here, again, in adults in Virginia with the serologies done at Center for Biologics and also at WHO center in Melbourne.

This vaccine contained or these vaccines contained the A/Johannesburg 82/96-like strain as the vaccine component, and you can see, I think, that the vaccine was highly immunogenic. the individuals all developed antibody responses for the vaccine component and also for more recent H1N1 strains that are related that were similar to the homologous antigen.

In the case of the Beijing 262/95 strains, however, you can see that there was a very marked difference here between the vaccine component and the H1N1 deletion mutant.

I will move on to the H3N2s, and on page 12 we have some serologies that were done for the children for which we had retained some serum from last year, and unfortunately we had so little of it we were only able to do one test. So this is it.

These studies were done both at the Center for Biologics and at University of Rochester in John Treanor's lab, and I think even though the titers are a little bit different here, they show the same thing, that the antibody responses to the A/Nanchang vaccine

component were somewhat low as compared to what we were seeing for the H1N1 certainly.

And that's not necessarily unusual. We sometimes do see from time to time that the antibody titers themselves appear low.

The more important thing from these slides is that or from these tables is that the response to the Sidney 05/97 strain and the A/Wuhan 254/97 strain were quite low in comparison to the vaccine strain.

Moving on to page 13, this is a study that was done in adults from NIBSC who were immunized with a vaccine that contained the Nanchang 933/95, and the studies were done at CDC and at WHO center in Melbourne.

Again, the antibody titers for the homologous strain in comparison to that, the antibody titers for the new variants, the A/Sidney 05/97, A/Wuhan 254/97, and A/New York 19/97 were quite low. They were at least 50 percent lower, twofold lower as compared to the vaccine strain, and that was also true as the serologies were done at the other laboratory in Australia.

Pardon me.

On page, let's see, 16, again, another study done in elderly in Virginia with an A/Nanchang

containing vaccine. In this particular instance, these serologies were done in Australia and at the Center for Biologics.

The difference between the vaccine strain and the Sidney or the Wuhan strain was not as marked in these elderly patients as it is in some of the other studies that were done, unlike the preceding study that was just shown.

Okay. To try to put it all together, and I did not mention, but you have also all of the raw information in the sense that it's the original tables that were put together by the individual centers. So you have the full information from each of the different institutions available to look at.

Trying to put it all together, there are some summary tables here to try to do what we did last year and to try to pull all of the information together in a more simplified form.

I'm showing here serologic panels that were tested that showed reductions of at least 50 percent or greater in the post vaccine geometric mean titers and showing the new virus strains that were being looked at, including B/Beijing 243/97, which is the B/Victoria-like strain, and two B/Harbin-like strains, B/Argentina 218 and B/Argentina 275.

And what you can see is that pretty consistently in the studies that were done, there was reduction of at least 50 percent or greater for the B/Beijing 243/97 strain, and that was quiet a marked difference on average, taking all of those studies and making a mean out of that, and in general, some of the studies were even as high as 90 percent lower. So it was quite a dramatic difference.

In contrast, the more recent strains that are similar to the vaccine strain really showed no difference at all.

On page 18, there's information for the H1N1 viruses, the same type of setup with 50 percent reductions. I think you can see from this that the Argentina 974/97 strain, which is quite similar to the H1 vaccine component, really showed -- and is representative of other strains -- really showed no difference in terms of the post vaccine geometric mean titers.

In contrast, again, the Beijing 262/95 strain pretty consistently demonstrated reductions that were as much as twofold or at least twofold or greater, and, again, there's a very substantial reduction when these studies are looked at as a whole.

And then finally for the H3N2 viruses, the

same type of setup, looking at the strains that are representative of the newer variants, including the A/Sidney 05/97 and the A/Wuhan 254/97. Although there was some variability in the results, again, there were reductions that were fairly obvious and very marked in some of the studies.

I will mention that in working with these strains, at least it appears to us that there may be some increased susceptibility to serum inhibitors, and it certainly has been true with working with strains like this to try to make reassort viruses, and I would suspect that some of these studies that do not show as much of a marked reduction, that may be part of what's going on. So that this total here possibly should be considered to be more than what is being shown here, which is about 50 percent of the studies showing reductions of 50 percent or greater.

But overall, there was still substantial reduction for all of these new strains that were seen as compared to the vaccine strain.

Okay. You can take that off. I'll stop there and ask if there are any questions.

(No response.)

DR. LEVANDOWSKI: And if there are no questions, then I'll ask Dr. John Wood from the

National Institute of Biological Standards and Control if he'll present his information on the clinical trial with the H1 deletion and the B/Victoria-like strain.

DR. WOOD: Thank you very much, Roland.

If I could have the first overhead.

As Roland explained, I'm going to present the results of an experimental study that was the result of a collaboration between three centers. The vaccine was made at SmithKline Beecham laboratories in Dresden in Germany. The serology was done at CDC here in States and NIBSC in the U.K.

Next.

Whenever the selection is made for new influenza vaccine strains, there's always some concern, first of all, whether you've got it right or not, but specifically, the concerns are whether the new strain is going to be as immunogenic as a vaccine as the old strain.

In the first case, if the new strain takes over and predominates, will the new vaccine stimulate protective antibody against that new strain when it circulates, or even of more concern, if the old strain persists and the new strain does not take over, will the vaccine made from that new strain stimulate cross-reactive immunity to the old strain?

The second concern is really a production issue. Will the new vaccine strain grow and process well? I'm not going to address that. I'm just going to address the immunogenicity issues.

Next one, please.

So as Nancy Cox described earlier this morning, for H1N1 and for B there were two different lineages circulating throughout the world. For H1N1, there's the A/Bayern 07/95-like strain in most parts of the world, and then the deletion mutant, Wuhan 371/95-like strains, last year in China, Hong Kong, Singapore. Senegal also we had, and then more recently isolates from Hong Kong, Taiwan, and Johannesburg, and now in Japan as well.

Then for influenza B, the B/Beijing 184 or B/Harbin-like variants in most parts of the world, and again, we have the separate lineage, the B/Victoria 02/87-like strains in China last winter, and then during '97 to '98, this has expanded a little bit, and it's spread to Japan and Singapore, but essentially two different communities.

So at the Geneva meeting last year, we thought maybe we could do something about this, to try and find out just how good these variants would be as vaccine strains.

So very kindly, the laboratory in Dresden offered to make an experimental vaccine from the deletion mutant, and the virus we chose for this, the H1N1 virus, was the Beijing 262/95, which was the X-127 reassortant.

The B virus was B/Beijing 243/97. This also had an H3N2 component, the RESVIR 9 vaccine strain.

The vaccine was made in Dresden and then standardized to NIBSC by the usual methods, and you see the vaccine contained essentially 15 micrograms of hemagglutinin per dose, which is normal vaccine concentration.

Next one, please.

SmithKline Beecham did two trials last year, first of all, a trial of their conventional licensed vaccine, which is 026, trial 026, and the strains in that were Johannesburg 82/96, the H1N1 strain, NIV 39; Nanchang, which was RESVIR 9 and B/Harbin 07/94.

They actually did these trials in 120 people, the adults and the elderly, but 30 of these were selected for comparative purposes across the age range.

The experimental vaccine was coded 029,

and as we just heard, it contained X-127, RESVIR 9, and B/Beijing 243/97.

Two study populations, one in the 18 to 60 year old and the other in the over 60 year old, 60 representatives in each of the two populations.

The serology was done at day zero and day 21 in three centers, CDC, NIBSC, and in the Dresden laboratory, as well, at SKB.

Next slide, please.

First I'll show the serology results to the conventional vaccine. This is the Johannesburg vaccine strain, the H1N1 strain, and as Dr. Levandowski has just described, there's the characteristic drop in HI reactive with the deletion mutant here.

And then if you look at the B viruses, again, a lower post vaccination GMT to the older B strain.

So it's important, I think, to bear this in mind to really form a baseline with which to judge the experimental vaccine study.

Next slide, please.

So now we come on to the H1N1 deletion mutant. These are the adult results, and these are the results in the elderly, and these are the

laboratories doing the serology: SmithKline Beecham, CDC, SmithKline Beecham, CDC, NIBSC.

Overall, the results from the two European laboratories, there was slightly higher HI titers than at CDC, but there were similar patterns of reactivity irrespective of who was doing the serology.

If we look at the prevaccination levels of antibody, you can see for H1N1 25 percent, zero percent, 20 percent, zero percent, 32 percent. Very low percentage of individual had antibody to the H1N1 deletion mutant before immunization.

Now, after vaccination we saw a very interesting result because the post vaccination GMT to the vaccine virus, Beijing 262, was lower than the post vaccination to the heterologous virus, Johannesburg 82/96. You can see this in each of the centers and in both of the populations.

You can think of possible reasons for this. One reason may be an anamnestic response that the deletion mutant is initiating in people who have been primed with Bayern like strains or before that Singapore 06/86-like strains. So it's stimulating immune response specifically to this lineage of H1N1 strains.

Possibly it's a technical problem, and

this particular virus is not very reactive in the HI test with human antibody, a similar story to the one we heard when Nancy Cox was talking about the ferret antibody responses to reassortants versus wild type. It could be the same phenomenon there.

To look at the anamnestic theory, I'll show the next slide, which is CDC's results where they broke down the serological data into two sets, first of all, people who have not had recent vaccination and people who had had vaccine very recently, within the last year.

These are the results to Johannesburg, results to the Beijing variant, and you see the post vaccination GMTs were reduce, again, to Beijing 262 in both populations. So if there was any convection in the theory that the higher heterologous titers were do to anamnestic response, maybe this would shed some light on it, but it's the same in both populations. So I think the jury is still out on that one.

What may be interesting to do is to look at the antibody responses to another representative of the deletion mutant to see whether this lack of reactivity could be due -- it may be strain specific particularly to the Beijing 262 strain, or it may be specific to the group of deletion mutants. We haven't

established that yet.

But the bottom line, I think, is that when you compare the conventional vaccine with the experimental vaccine, in both studies the results, the post vaccination GMT to Johannesburg were equivalent, but when you look at the responses to the deletion mutant, then with the experimental vaccine the response is higher even though we have some problems with homologous titers.

So I think despite the problems, the experimental vaccine did show greater cross-reactivity than the conventional vaccine.

Next slide, please.

Now we look at the B responses, and here the results was fair clear cut and easy to interpret. The B/Beijing 243 vaccine stimulated satisfactory immune responses to both itself and to the Harbin virus in all cases, in all centers, and in both studies.

So the B/Beijing virus acted very well as a vaccine that stimulated cross-reactive antibody against the Harbin group of viruses.

Next slide, please.

In this slide I've just shown the H3N2 responses in both studies, in the conventional vaccine

and in the experimental vaccine, and you can see the pre and post vaccination GMTs were very similar in both studies, which again helps to standardize the results from one study to another study.

And the next slide, please, the last one.

Just to acknowledge this very effective collaboration between three centers, but particularly the work of SmithKline Beecham in Dresden, Rita Beyer, Elizabeth Neumeier, Carmen Raderecht, Hans Engelmann, and Water Kuenzel; at CDC Nancy Cox and Sasha Klimov -- sorry, Sasha. I spelled your name wrongly -- NIBSC, Bob Newman, Ann-Marie Riley, and Una Dunleavy.

And just as a parting shot really, I think it does illustrate that this could form the basis for future evaluation which may help us when we have new strains emerging which have very limited geographic spread. Then we may have some time to make an experimental vaccine and just look at the immune response from those new strains.

Thanks very much.

DR. LEVANDOWSKI: Thank you, John. That's very interesting data.

Are the questions and comments from the Committee?

Dr. Couch.

DR. COUCH: Well, I'd like to give a strong endorsement to what's been done here, for one thing, and as Dr. Wood pointed out, this is the kind of data that might help us resolve some of the dilemmas we have on occasion.

I think because it would be sometimes difficult to get it on line and to get data and get analyzed with the time lines we're on, we certainly would never want to make it requirement, but we ought to strongly encourage this kind of data to help us in the responses that we want with a little less guessing.

The second is just get you to explain a little better for me now, now that you've got the data, and we've got data on two of the strains or types of strains that would be up for consideration, your view of whether the differences are significant.

I mean the homotypic responses are greater for both --

DR. WOOD: Yes.

DR. COUCH: -- of the newer antigens. The pretiters are lower. The magnitude of the response is greater if you add in the new antigens, although as you point out, the existing antigens do pretty well.

So --

DR. WOOD: You mean particularly the H1N1?

DR. COUCH: If we want the best Beijing 97 response that we can get and that it is important, should we switch from Harbin? It's a hypothetical question, if you would.

DR. WOOD: I think for the B responses, it provides some evidence that if the epidemiologic data were sufficient to make that vaccine strain change, then the vaccine would be effective not only against the B/Victoria type of viruses, but also against the B/Harbin group of viruses that are predominating.

I mean that's what these data suggest to me, although as a caveat, we don't have data from children who have no experience of these particular viruses.

DR. COUCH: As you point out, that's an important caveat.

And then the same question for the A strain, H1 strain.

DR. WOOD: That I'm not so convinced because there may be technical difficulties interpreting the data where you have low homologous titers. I would prefer to answer that question at a later date when we've had more time to look at other

deletion mutants, the reactivity with other deletion mutants.

DR. LEVANDOWSKI: Are there any other questions or comments?

(No response.)

DR. LEVANDOWSKI: In that case, thanks, John, for a very interesting presentation.

We'll move on and present some information about the availability of strains and reagents.

Just as an update about where things stand with materials needed for manufacturing, as you know, not only do the manufacturers need to have the actual strain available for inoculation of eggs, but they also need to have the specific reagents, and I would just mention that the reagents do need to be very similar to the strain that's in the vaccine.

If there are even modest differences, often that's reflected in difficulties in interpreting the information and assigning potency values because the zone sizes that occur in the test that's used for doing potency assignments, a single radial immunodiffusion, may be larger than they should be using a nonidentical reagent.

Anyway, what we have for influenza B vaccine strains, of course, the current vaccine

strain, the B/Harbin 07/94 strain is available, and it seems to be a reasonably good growing strain for most of the manufacturers.

In terms of the B/Beijing 243/97 strain, there's not a lot of information, although we have just heard that one manufacturer was able to make a vaccine with that strain, but in terms of the overall parameters and how that would function in large scale, I guess we don't really know.

Moving on, for the H1N1 strains, of course, the A/Johannesburg 92/96, NIB-39 reassortant virus is available. It is a very high yielding strain that is remarkably high yielding I would say compared to other reassortants that have been available for use in recent years.

There are other candidate strains for the H1 deletion mutants. There are two reassortants that are available. There's the X-127 reassortant from Dr. Kilbourne's laboratory, and that one has been described as being moderate to high yielding.

There's the RESVIR-10 reassortant from our laboratory, and that one is somewhat lower yielding, so that out of those it sounds like the X-127 reassortant might be the more desirable one for manufacturing if there were a use for Beijing 262 type

strain.

And the next one for the H3N2 viruses, of course, the vaccine strain, the A/Nanchang 933, RESVIR-9 reassortant is available. It's a moderate to high yielding strain.

There are other candidate strains. Although it hasn't really been discussed in great detail, there are reassortants that are available for the A/South Africa 1147/96 strain, which I guess could be considered to be an intermediate between the Nanchang 933/95 and the Sidney 05/97.

There are two reassortants that are available for that, X-129 from Dr. Kilbourne's lab and RESVIR-11 from our lab. What we do know about those so far is that at least what has been tested seems to be somewhat lower yielding.

The A/Sidney 05/97 strain from CSL, the IVR-108 reassortant is a moderate to high yielding strain, although there has been some variability in the description as to how high yielding it is. It is available and is being used for manufacturing vaccines in Australia and for Australia.

Okay. Next one.

The reagents which are available for standardization of the vaccines for testing potency,

currently all of the current vaccine strains we have reagents readily available for. However, for any of those other strains that we might be looking at, specific reagents will have to be developed, and these reagents at least for us may be available only in May. If we were starting to make reagents now, it typically takes six to eight weeks to have the reagents available so that the manufacturers and we can use them for testing potency.

I think I'll stop there with that. I don't know if John Wood would like to say anything about reagents in the United Kingdom or for WHO.

DR. WOOD: I'd just like to add that for the Sidney H3N2 variants we should -- we've actually preempted any kind of decision and decided to go ahead and make reagents for Sidney. So our reagents should be ready probably at the end of February. It is a gamble.

DR. COUCH: In adequate volumes to share with the FDA here?

DR. WOOD: Well, before the U.S. reagents were ready, I think that might be possible.

DR. LEVANDOWSKI: Okay. Are there other questions or comments about that?

DR. KILBOURNE: Yes.

DR. LEVANDOWSKI: If not, I'd like --

CHAIRPERSON FERRIERI: Dr. Kilbourne.

DR. LEVANDOWSKI: Oh, sorry.

DR. KILBOURNE: Do you want to get an update on the X-129, which I exhumed last week at your instigation? Further work has to be done. It's a moderate yielder, but it's not a 62 reassortant on the basis of our gels. So we're trying harder.

It also, incidentally, proves that the IVR-108 is not a 62 reassortant either. Part of the polymerase complex is mixed. So we're trying to re-reassort that with the hope that we can get a really high yielder from that.

DR. LEVANDOWSKI: Okay. That's very useful information.

At this time we usually reserve time for comments from manufacturers, and Dr. Ralph Vogdingh from Connaught Labs, Inc., represent PHRMA, the Pharmaceutical Manufacturer's Association, has agreed to give us some comments.

So, Ralph, you're not moving up here, but would you please come to the podium and give us your brief presentation?

DR. VOGDINGH: Good morning.

At Roland's request, the manufacturers

will briefly review the issues that are involved, particularly the logistics involved, in manufacturing influenza virus vaccine in the quantities and in the time frame that's required for distribution in the United States.

These are the three key issues that we have to deal with and that have to be considered by anyone involved in influenza, the influenza vaccine program.

Number one is egg supply. This is a logistical issue that we have to deal with every year, and the important point to remember about the egg supply is that it has a very long lead time.

The second issue is strain selection, of course.

And thirdly, reagent preparation.

The vaccines can't be standardized to potency or released by the FDA until reagents are available.

Dealing with the egg supply, just for your own information, this is how this works, and this is the procedure each year.

To begin with the egg suppliers that supply the embryonated eggs required for manufacturing the vaccine order their birds, and this is one year

before flu manufacturing begins. So, in other words, they're already making plans for next year.

The chickens are moved into the laying houses, and this generally occurs about three months before production begins. This is usually October and November.

And I should point out that this is the most critical time in the availability of eggs, and it should also be considered in any pandemic planning that occurs. During this period, there are no eggs available. So it is not possible to manufacture any influenza virus vaccine during this time period.

Then the next thing that happens is that reproduction begins in full scale, and we begin receiving eggs once we know the strains and begin inoculating eggs and producing vaccine.

And I can't stress the importance of this last point. In order for us to produce the quantity of vaccine that we need to produce, we need to begin producing vaccine now. That's why it's so critical that we obtain a decision on the strains as soon as possible, at least one strain in early January or in January.

And this is following it through with the process. In the past we've always had one strain that

was from the previous year's formula. That allows us to initiate our production cycle.

Associated with this, this is development of the Grow 3 assortants. Again, this is critical in order for us to obtain the yields necessary to produce the quantity or the doses of vaccine required.

This is the idea scenario that would be for us. The first strain selected in January, the second in March, and the third in early April.

A clarification on this. Again, the objective here or what's necessary is for us to distribute vaccine in October, and in order to do that, we began in January manufacturing the monovalents. By June usually we have a representative monovalent of each strain.

We compound bulk vaccines in July. Usually our license is issued in July, and we begin distributing vaccine in October.

And also I might point out in order for us to distribute vaccine, we have to work closely with the FDA in order to test each pool of monovalents. It gets tested by the FDA and released for the manufacture of bulk vaccines. Also, each bulk vaccine has to be approved for use by FDA.

Okay. Here's a few other points that you

should keep in mind. Number one, when these chickens being producing eggs, that egg production cannot be put on hold. The eggs can't be put on the shelf for later use.

Also, the timely strain selection is very important in the preparation of these reagents that Roland was talking about, and as he mentioned, there's a lead time that is required to have these reagents available.

Another important point is that -- and this first point deals with the interval between the selection of the first, second, and third strains. As an example, if you select a strain today, we'll manufacture that particular monovalent, but once we manufacture the quantities that we're going to require for the number of bulk vaccines, any additional monovalents manufactured are wasted, and if we don't manufacture vaccine, the eggs are wasted.

And this second point is also always very important, again, as it relates to the amount of vaccine that we can manufacture within a specified period of time.

So this last slide here is just to try to stress the complexity of the logistics involved in manufacturing influenza vaccine in the time frame that

is required for use in the country, and again, it relates to a very key issue, is the timing of the selection of the strains.

CHAIRPERSON FERRIERI: Thank you very much.

Are there questions from the panel?

Dr. Couch.

DR. COUCH: Well, first, a comment. Perhaps these dates that you just gave us have been known before, but they weren't to me, but I'd like to compliment the manufacturers, and I assume you are representing the group with these explanations.

DR. VOGDINGH: I'm speaking for all manufacturers.

DR. COUCH: We've always known about the pressure for that decision as soon as possible, to be able to make that with some specific deadlines I think will help and guide the Committee consideration, and that not to mean that the Committee will delay by your deadlines, but if two can be made at the end of January, then two would be made or all three, but to know what's being faced I think was very helpful, and I think you should be complimented for that.

DR. VOGDINGH: Well, thank you. It would be very beneficial to us.

DR. COUCH: I have two minor questions. It's almost informational.

Is Europe on approximately the same time frame?

DR. VOGDINGH: Pardon me?

DR. COUCH: Are the European manufacturers on about the same time frame?

DR. VOGDINGH: I would suspect so. I don't know that for a fact. Evans is representing -- he says yes.

DR. COUCH: And the second is, and again I don't know. I know Dr. Wood held a workshop, but if the manufacturers who are developing tissue culture substrates and are thinking about moving in that direction, will that provide us then, assuming it works as they desire, provide us advantages on this time frame?

DR. VOGDINGH: I think they would be faced with the same. They have the same -- I would think that they would have the same criteria because they are faced with lower yields per fermenter, and so they would have -- they would be fighting time the same as we are.

CHAIRPERSON FERRIERI: Dr. Broome.

DR. BROOME: I assume because of the

constraints on egg number that increasing valency of a vaccine wouldn't necessarily reduce the total number of doses that could be produced.

DR. VOGDINGH: That's correct.

DR. BROOME: Are there any other technical constraints on increased valency for vaccines? Have you ever made a four valent flu vaccine?

DR. VOGDINGH: Well, that would still be -- it would result in the same number of doses per -- well, that's not stated correctly.

We can manufacture so many, say, antigenic units whether that's divided into three valences or four, and then that equates to the number of doses.

CHAIRPERSON FERRIERI: You might remember that last year we discussed the possibility of a four valent vaccine for pediatric populations. Someone here representing the American Academy proposed that to us, and we strongly rejected that proposal.

Dr. Snider.

DR. SNIDER: Just a clarification. If I understood correctly, you indicated that the assumption was made that one of the strains was going to be the same.

DR. VOGDINGH: In the past such --

DR. SNIDER: Did you state that? And I

guess the question is if that's the case, what if that was -- if it wasn't the recommendation, if all three were changed, what impact would that have?

DR. VOGDINGH: Well, it would be a disaster.

(Laughter.)

DR. VOGDINGH: No, if our interest is to supply, you know, a good vaccine to immunize as many people who want to be immunized, that number of doses would be seriously reduced.

DR. EICKHOFF: Pat.

CHAIRPERSON FERRIERI: Yes, Dr. Eickhoff.

DR. EICKHOFF: Again, I appreciated your comments very much, too. Dr. Levandowski earlier today showed a slide that suggested we were beginning to approach a plateau in vaccine production somewhere on the order of 80 to maybe as high as 90 million units. Is that, indeed, in your judgment a plateau?

And if it is, what's the constraint or are there multiple constraints, but what are the major constraints that suggest that you can't readily go beyond that level of production?

DR. VOGDINGH: Well, maybe some of the other manufacturers might want to make a statement, but if there's a desire to go beyond that level, then

it would be necessary for the manufacturers to expand their manufacturing facilities.

DR. EICKHOFF: So that would take a major capital outlay?

DR. VOGDINGH: Yes, it would.

DR. EICKHOFF: Good enough. Is egg supply a constraint?

DR. VOGDINGH: It is for each year. Say like, for example, I mentioned that the birds have been ordered for next year, and that's based on an anticipation of how many eggs are going to be required. You know, we make contracts for that. You know, other manufacturers do, too.

So if we anticipate that we're going to manufacture more vaccine, say, for the next year, we have to make those arrangements this year.

DR. EICKHOFF: Thank you.

CHAIRPERSON FERRIERI: Dr. Estes.

DR. ESTES: We've heard that the plateau is about 80 million doses. Is that all really being used or are there excess doses that are made that actually are not being used every year?

DR. VOGDINGH: Again, I can't answer that. For our company we distribute almost all that we manufacture. I can't speak for the other

manufacturers.

CHAIRPERSON FERRIERI: Yes, Dr. Clements.

DR. CLEMENTS-MANN: Can you remind us how many doses are per egg are you getting normally?

DR. VOGDINGH: It depends with each strain of the virus, and the number of doses per egg is proprietary information.

(Laughter.)

CHAIRPERSON FERRIERI: Yes, Dr. Kilbourne.

DR. KILBOURNE: Well, I'd just like to comment on the question raised about what if three strains had to be changed simultaneously. It's a very good and appropriate question. I think it just goes back to the importance of John Wood's study that he reported.

We have to realize that these strain changes we've gotten into have a certain arbitrary character to them and make certain assumptions that are not always or invariably valid. Things are different. We want to change and have an exact match if possible.

But I think past experience, including studies Ted Eickhoff has done, would indicate that we can probably get fairly effective immunity among heterovariants so that a choice may have to be made

someday between the practical reality of production capacity and the scientific desirability of always having exact match.

So I think there's a little wiggle factor there that's important.

CHAIRPERSON FERRIERI: Dr. Levandowski.

DR. LEVANDOWSKI: I'd like to comment on that last point also. Some of how we got to the dose of vaccine that's being used today, the 15 microgram per dose, was based on the concept that that dose, an increased dose compared to what had been used after the clinical trials that were done in the late 1970s, would be better geared toward producing antibodies that would cross-react with other strains that weren't so closely related to the vaccine strain.

I just mention that because that is one of the considerations that we would have for strain selection under some circumstances.

CHAIRPERSON FERRIERI: Thank you, Mr. Vogdingh.

DR. VOGDINGH: Thank you.

CHAIRPERSON FERRIERI: We'll move ahead then with options for strain selection, and we're back to Roland Levandowski.

We will not take a break today. We will

continue to work through the discussion and recommendations that will require a vote, and then we will break for lunch as close as possible, if not earlier than, the designated time.

DR. LEVANDOWSKI: Okay. I'll try to be quick.

No, no slides yet.

So in terms of what's happening right now. influenza A viruses of the H1N1 and H3N2 subtypes and influenza B viruses continue to circulate in human populations. Therefore, it would be reasonable for the vaccine to continue to be a trivalent vaccine.

In terms of the influenza B viruses, we've heard a lot of information this morning. The strains of influenza B that are in the Yamagata 16/88 lineage predominate with strains that are similar to the current vaccine strain -- that's the B/Harbin 07/94 strain -- being isolated in the Americas, Europe, Africa, Australia, and Asia, essentially the whole world.

Strains of the B/Victoria 02/87 lineage continue to appear in Asia, which has been true for several years, with the limitations of spread of that strain for unknown reasons.

The sera from people who have been

immunized with the current vaccines inhibit the Harbin-like strains quite well, but as we've seen, they're less well inhibitory for strains in the B/Victoria lineage.

There is somewhat limited information at this time on the B/Beijing 243/97 strain for use as a vaccine candidate. Therefore, the options for influenza B -- and can I get the first slide -- the first option, of course, would be the maintain the current vaccine strain, and in favor of that, most of the strains worldwide are similar to the current vaccine strain.

The vaccines that are being used are immunogenic. The recent Harbin-like strains are very well inhibited by the post immunization antisera, and the manufacturing for this particular item is very well defined and predictable.

On the contrary side, the recent Victoria-like strains are not really well inhibited by the current vaccines.

The other option would be to change the current vaccine strain to a recent B/Victoria-like strain. In favor of that the vaccines would be more immunogenic for the B/Victoria-like strains, and as John Wood has pointed out, for people who are not

immunologically naive at least, it might be expected that antibody responses to the other lineage would be expected.

But contrary, there really is no predictable advantage in the presence of continued circulation of the B/Yamagata type lineage for the most part, and there's no superior alternate vaccine candidate strain that's identified at this point.

You can take the slide off.

The influenza A viruses, the H1N1 strains, the strains that predominate in human populations are antigenically closely related to the A/Johannesburg 92/96 vaccine strain. However, strains that are similar to A/Beijing 262/95, which is the HA deletion mutant, have now appeared outside Asia and have been seen in West and South Africa, which suggests that there's the very distinct possibility of future activity elsewhere.

Human serologic responses suggest that the current vaccines are highly immunogenic and inhibit current related strains very well, but the H1 deletion mutant strains are less well inhibited.

Studies done with an experimental H1 mutant containing vaccine indicate that the antibodies that are produced against both the H1 deletion mutant

and the non-deletion mutant strains may be expected, but the results actually are in some ways similar to the overall effect with the current vaccine.

The vaccine candidate strains similar to A/Beijing 262/95 are currently available, and there's some limited information about the manufacturing potential on a broad scale. So for H1N1 the options are to, first of all, again, maintain the current vaccine strain, and in favor of that would be that the current vaccines are really high immunogenic.

And in addition to that, these are strains that have manufacturing that are very well defined and predictable, and the yield is extremely good.

On the contrary side, the H1 deletion mutant strains have now been found outside Asia, and the horologous response to the H1 deletion strains is quite clearly reduced.

So the other option would be to change the current vaccine strain to an H1 deletion strain, and in favor of that, that might provide a better match with the H1 deletion mutants.

Contrary-wise, it's unclear that the antibody responses to the H1 deletion vaccine are superior in proportion to the current vaccine strain, and the choice of the strain could benefit from

additional epidemiologic, serologic, and maybe some manufacturing data.

Therefore, another option at this point would be to defer the decision on this particular strain to accumulate some more data, and as we've heard from some of the other speakers, it is likely that there may be some additional information in terms of epidemiology and probably serologic studies in the next several weeks, and those additional data might help to clarify the position.

In terms of the H3N2 influenza A viruses, there's considerable antigenic drift continuing among the H3N2 influenza strains, and new variants, such as the A/Sidney 05/97 which were previously identified for the first time in Australia in June of last year, are now appearing in the United States and elsewhere.

Strains similar to both the vaccine strain and the antigenically distinguishable variants are approximately -- well, they were equal and proportioned yesterday, but I guess today it looks like the overwhelming majority are Sidney-like.

In addition, serologic responses for these strains are reduced against most of those that have been identified and tested.

I would comment that at least in some

instances it appeared that the antiserum to the A/South Africa 1147/96 strain inhibits many of the older and the newer strains.

And finally, vaccine candidate strains and high growth reassortants for several different strains in addition to the vaccine strain are available.

So the options for the H3N2, the first option would be to maintain the current vaccine composition, and in favor of that, the manufacturing is well worked out.

But on the contrary side most recent strains are not well inhibited by the post immunization antisera. So I'm not saying much good about that.

The second option would be to change the current vaccine strain to a more recent strain, and in favor of that, the most recent strains are poorly inhibited by the post immunization antisera, and a change would, of course, achieve a much better antigenic match with the currently circulating strains.

And, in addition, there are what are probably suitable alternative strains for production available right now.

Contrary, the choice of the strain, again,

could probably benefit from some additional epidemiologic, serologic, and developmental information.

So, again, another option would be in this case to defer to accumulate some more data, and it's likely that there will be additional information on the H3N2 strains. It is changing by the day, and I would expect that we should have a much clearer picture of the overall appearance of these strains in a short period of time.

I didn't emphasize, but it's been brought up previously by many people that if we had the luxury of time to do this, that we would probably like to defer, and in view of last year's experience with the A/Sidney-like strains appearing very late in June, it would be nice if we could do that. Of course we can't.

So since the H3N2 strain is the one that's most likely to cause morbidity and mortality, we should make this choice very carefully, and that's another reason to perhaps defer to accumulate more information.

I'll stop there, and thank you.

CHAIRPERSON FERRIERI: Thank you, Roland.

Questions for Dr. Levandowski? Dr. Estes.

DR. ESTES: I have one question. Do we know that people that are getting the Sidney virus have been vaccinated this previous year? We didn't hear that data.

DR. LEVANDOWSKI: I think that's a question for Nancy Cox or somebody from CDC on surveillance.

DR. COX: We have heard of a number of outbreaks in nursing homes where they're highly vaccinated populations with the current vaccine, and outbreaks of disease.

Now, of course, this can also occur when there's a very close match, but I think we're having an indication that perhaps there is a bit more disease than usual in these kinds of highly immunized populations.

CHAIRPERSON FERRIERI: That seems to be the information emerging at various state health departments, as well, that I'm familiar with in our state.

Other questions?

DR. COUCH: Well, it's emerging elsewhere. I mean it's all anecdotal experience.

CHAIRPERSON FERRIERI: Right.

DR. COUCH: But, you know, how many calls

and how many colleagues, "This year's different than previous years." The vaccine is not as good is what they're saying. "I got my vaccine, and it didn't work."

CHAIRPERSON FERRIERI: Are there any other general points that anyone would like to bring up or the need for further information before we grapple with the precise questions that are in front of us to aid everyone who has presented today?

Yes, Dr. Huang.

DR. HUANG: I have a very general sort of question, and that is that when we look at the data that we have for the past few years and contrasting that to the amount of vaccination that we have been doing, we're still seeing the same sort of proportions of influenza coming every year, and in some years we're still seeing above epidemic -- you know, reaching epidemic proportions.

And I'm wondering if it isn't time for some of us to think a little harder, and are we doing this right? I mean we all have the same assumptions as we're coming here. We've been given some guidelines today about selection, and we're about to do that, and the issue really is we aren't affecting that curve very much. It is still happening, and I

guess if the vaccinations were working, I would assume that we'd stay below the curve. At best we would hope that maybe we would even keep it level.

So is that maybe too sanguine a wish?

CHAIRPERSON FERRIERI: Dr. Cox, would you like to address it? That's a very challenging question.

DR. COX: It is. It's a very challenging question and one we often get.

I assume that you're talking about the curve of pneumonia and influenza related deaths, and I think the only way really to assess what vaccine is doing is to have vaccinated an unvaccinated population.

When we're looking at the population as a whole, it's very difficult to assess what vaccine is doing. We have an aging population. We have more or less disease in different years. Some years when we have H3N2 activity, we really don't have a tremendous number of influenza related excess deaths. In other years, we do.

So we are trying to put in place methods and studies which will try to address this issue of vaccine efficacy on an annual basis.

CHAIRPERSON FERRIERI: It's very hard to

assimilate all of the serologic data that are presented on humans, but an impression that I get from some of it is that many of the very elderly or nursing home age patients tend to respond rather poorly at times, depending on the immunogens.

And have studies been done giving a series to the elderly, too, that would -- if their general immune system is waning, and this is true for other types of responses in general, would there be any merit in doing a two injection series in the elderly who are the most critical population with the highest morbidity and mortality?

DR. COX: That's another very good question. We have been using one nursing home population to look at the kinetics of response and the decline of antibody over time in order to try to determine if there might be rationale for immunizing people, the elderly nursing home, the most vulnerable individuals twice during the season. And we had limited data last year, which was developed as a result of the recall of vaccine.

I think that it's something that we're going to be looking at over time, but there isn't a tremendous amount of data that would support giving two immunizations, but we are looking at that

question.

CHAIRPERSON FERRIERI: Other questions?

Dr. Clements.

DR. CLEMENTS-MANN: Yes. I think one of the things that still plagues us is the optimal utilization of the vaccine because it still seems that only about 30 percent of the non-elderly high risk are actually being immunized, and of course, those individuals would be the ones that might show up on those surveillance records.

The other thing I think is that the health care workers often who are providing care and are perhaps part of the disseminators of the flu are not being optimally immunized, so that I think we have to take that into consideration before we view how effective the vaccine is or isn't.

CHAIRPERSON FERRIERI: Any other comments, questions?

Any of our nonvoting members at the table? Drs. Breiman, Kilbourne, LaMontagne, Webster? You haven't spoken quite as much. Would you like to add anything to the discussion?

John, we haven't heard from you.

DR. LaMONTAGNE: Well, I don't know whether this is going to help much, but, I mean, I

think the record of activated influenza vaccines is actually quite good, and the studies that have been done not only in health adults, but in the elderly, do confirm that the vaccine can provide protection and does prevent death and illness in that population.

Examining it at the macro epidemiological level, as Alice was posing, I think, is very challenging. I mean, the fact is that influenza is a very common infection, and even if we achieved immunization coverage levels in excess of 50 percent of the population, we'd probably still have a big burden of disease.

So I think having the expectation that we would lower that level, of course, is the dream that we all have, but it's going to be quite difficult to achieve, I think, under any circumstance.

CHAIRPERSON FERRIERI: Dr. Webster.

DR. WEBSTER: I'd just make a comment in the same vein. Alice and I were talking about this question before over the coffee break, and the question is what happens if you don't receive the vaccine. In the elderly if you take the vaccine and you still get infected, the complaint is the vaccine didn't work.

On the other hand, if you didn't take the

vaccine, you might die, at least fill the hospitals and cost the country vast amounts of money.

So in a sense maybe we're not measuring the right criteria for reducing this overall curve. I think that the vaccine by and large is very effective, and occasionally when variants occur in the season, like the Sidney did, we're still getting protection of the population.

CHAIRPERSON FERRIERI: Thank you.

Dr. Kilbourne, do you?

DR. KILBOURNE: Well, I think it's been said very well by John and Rod. The only thing I would add is just to remind people of the point John was making implicitly, and that is that the amount of immunity in terms of total immunity you'd have to achieve to wipe out influenza is really going to be very high, indeed.

So we don't want to do the experiment not vaccinating anybody next year and watching the PI curve I don't think, but short of that, there probably are ways to design more effective and better and wider scale clinical trials, but for that we need more money.

CHAIRPERSON FERRIERI: Dr. Breiman.

DR. BREIMAN: Well, I guess I've been

struck, having spent some time recently having to think about pandemic planning, more about the issues related to being able to stay ahead of the curve and still sort of reeling about by the recognition that we need to purchase birds, you know, a year in advance in order to be prepared.

And it makes we wonder. This is a different issue actually than what we're now talking about, but whether we should also, in addition to focusing on the importance of clinical trials be thinking about how we can push the timetable forward to a point where we're not relying on eggs, you know, to produce vaccine.

I think as we see sort of the pace of influenza even as demonstrated by H3N2, I mean, Sidney, it's going to make it tougher and tougher to be able to respond.

CHAIRPERSON FERRIERI: Other general points before we become very focused on each of the vaccines?

Dr. Apicella.

DR. APICELLA: Just a point of clarification. Is there an A/Sidney reassortant that can be used for production?

DR. LEVANDOWSKI: Yes, I can answer that.

Yes, there's the IUR-108 reassortant that I mentioned earlier that is available, and it is being used for manufacturing vaccines for Australia right now.

COMMISSIONER McCARTHY: Dr. Hall.

DR. HALL: Well, just going back to the point before that, I think still though that the bottom line of why this isn't working is we're not getting it to the right people in time, and that's what Mary Lou was saying also.

In children that are at high risk, it's estimated to be ten percent only that are getting this. So all of these other facts, we have to change our whole policy, and it's more of a policy decision at this point than an immunogenic if we really want to make a dent using the current vaccine.

CHAIRPERSON FERRIERI: What I would like to see in the way of epidemiologic data would be the number of doses distributed within states and then what the disease prevalence curves look like. This would really add punch to what you're saying.

I feel there's a very unfair distribution utilization. The vaccine is available, but there is different emphasis and the rigor with which it's recommended and used nationwide.

Dr. Couch.

DR. COUCH: I just wanted to go back and emphasize the point Dr. Huang started with, and that was that, gee, it's not being done perfectly, that there's still some deficiencies here, and we've heard about that nobody is proposing that we abandon inactivated vaccines, but we've heard about the problems of delivery and utilization in the elderly and so forth. They are not perfect instruments as we use them in our society right now.

But the goal is still, as you said, what we want to control. Actually I guess you suggest maybe we ought to look at alternatives. I think most of us have that in mind, but we're thinking about those alternatives as an addition as opposed to true alternatives to the inactivated vaccine.

But control is still a goal we ought to focus on.

CHAIRPERSON FERRIERI: Yes, Dr. Snider.

DR. SNIDER: Perhaps to take things even one step back, just to remind everyone that we have not -- if we want to talk about root causes, it's not easy to do that since one thing seems to lead to another, but we do have to acknowledge, I think, it's important to acknowledge in a setting like this, that we have not as a nation made the same kind of

commitment to adult immunization as we have to childhood immunization.

Consequently, a lot of the problems we've been talking about have not been as well addressed as they have for vaccine preventable disease in children.

CHAIRPERSON FERRIERI: Thank you.

Dr. Broome, and that will be the last comment before we embark on the precise question.

DR. BROOME: I just wanted to speak to the issue of what do we know about the actual effectiveness of the vaccines, and I think first you have to very carefully define what question you're asking.

One of them is certainly does the current vaccine work against A/Sidney, and I think there there's no way you're going to get any information with, you know, population-wide or ecologic analyses. You're going to need virologic confirmation of cases, and my guess would be efficacy studies in nursing homes. Formal efficacy studies would be the best way to get that data.

In terms of the general issue of, you know, can you say anything about the P&I impact, I think that's a perfectly valid question, but I think you can also -- I don't think you're going to get the

answer by ecological studies, but I think you can do admittedly large, well designed epidemiologic studies on impact.

CHAIRPERSON FERRIERI: Okay. We'll start with Dr. Levandowski's question, which is: which strain should be recommended for the antigenic composition of the new '98-99 vaccine based on the epidemiologic, antigenic characteristics of the strain circulating, serologic responses in persons immunized with current vaccines and availability of the suitable strains?

We'll start with influenza B, and the issue here is that we are seeing some recent Victoria-like strains of a different lineage. I'd like to pose to Dr. Couch how he responds to the possibility of retaining the current strain despite the recent strain isolation of the Victoria lineage, and how comfortable would you be with that?

And, by the way, this will be the easiest question we are facing perhaps.

(Laughter.)

DR. COUCH: Well, I came, as I was telling Roland earlier, with my usual little table of viruses, vaccines, epidemiology, and I added in the last two years a column for seed virus availability, and that

affect us a little bit last year.

But I don't consider BMH a problem. I've got good answers in all columns, and we've managed to studiously avoid the B/Victoria question successfully, and we continue to need to be worried about B/Victoria, but I think our decision ought to be to retain the B/Harbin component to the vaccine and continue to worry about B/Victoria while we do that.

CHAIRPERSON FERRIERI: Are there other opinions either in concurrence or divergent from what Dr. Couch has just said?

And we will take a formal vote, but I'd like to hear any other opinions from the panel for or against this approach.

Dr. Edwards and then Dr. Hall

DR. EDWARDS: I think the comments of the manufacturer are really very important, and if the questions are only going to get more complicated, maybe this is one that we don't have much choice in making.

CHAIRPERSON FERRIERI: Dr. Hall?

DR. HALL: I was going to say exactly the same thing. If we can't change all of them, this is the only one for sure we're not going to change.

CHAIRPERSON FERRIERI: Sounds good. I see

heads nodding around the table. So we'll move to a formal vote then. Yes or no, starting with Dr. Couch.

We will retain the current B vaccine strain.

DR. COUCH: Yes.

CHAIRPERSON FERRIERI: Dr. Clements?

DR. CLEMENTS-MANN: Yes.

CHAIRPERSON FERRIERI: Dr. Apicella?

DR. APICELLA: Yes.

CHAIRPERSON FERRIERI: Dr. Hall?

DR. HALL: Yes.

CHAIRPERSON FERRIERI: Dr. Poland?

DR. POLAND: Yes.

CHAIRPERSON FERRIERI: Dr. Edwards?

DR. EDWARDS: Yes.

CHAIRPERSON FERRIERI: Ms. Cole?

MS. COLE: Yes.

CHAIRPERSON FERRIERI: Dr. Estes?

DR. ESTES: Yes.

DR. HUANG: Yes.

CHAIRPERSON FERRIERI: Dr. Snider. That was Dr. Huang, yes.

Dr. Snider?

DR. SNIDER: Yes. That's why I asked the question.

CHAIRPERSON FERRIERI: I'm sorry. Dr. Karzon?

DR. KARZON: Yes.

CHAIRPERSON FERRIERI: And Dr. Eickhoff?

DR. EICKHOFF: Yes.

CHAIRPERSON FERRIERI: Dr. Broome?

DR. BROOME: Yes.

CHAIRPERSON FERRIERI: And then my vote is yes.

I don't think I've missed anyone. Ms. Cherry?

MS. CHERRY: No, that's it.

CHAIRPERSON FERRIERI: Okay. And I'm sure there's a feeling of jubilation from the manufacturers.

(Laughter.)

CHAIRPERSON FERRIERI: I see a big smile --

DR. COUCH: We've made the right decision.

CHAIRPERSON FERRIERI: -- from Mr. Fosden (phonetic) there. Yeah, great.

Well, then you'll indulge us for the subsequent discussion and decisions on the other A virus strains for the vaccine, and I don't want to always put Dr. Couch in a bad corner, but since you

are there --

(Laughter.)

CHAIRPERSON FERRIERI: -- you appear to have tabulated data and you've come with a table and so on --

DR. COUCH: I thought this was the end of the line, not the head of the line.

CHAIRPERSON FERRIERI: No, it's a very pivotal position here.

DR. SNIDER: I'm glad somebody else is in it, too.

CHAIRPERSON FERRIERI: Yeah, it's usually Dr. Snider. We're rotating that hot spot.

The A H1N1 is a more complex issue obviously.

DR. COUCH: Let's make that one last.

CHAIRPERSON FERRIERI: We've heard various information here today. We could talk interminably about the data we've heard. We have three options: retain current strain, adopt one of the new ones circulating, or with the deletion mutant being a very high candidate for the substitution, the third option is defer as we gather more data over the next few weeks, next several weeks.

Dr. Hall?

DR. HALL: Would it be possible to do that one last since --

CHAIRPERSON FERRIERI: The H1N1?

DR. HALL: -- that decision may be somewhat dependent on the H3.

DR. COUCH: If you're talking about level of difficulty, H3, I think, second and H1 is most difficult.

DR. HALL: Yes, I would say.

CHAIRPERSON FERRIERI: For us at the table? Fine. Would you like to start with the H3N2?

Again, the options are the same: retain, substitute, or defer, and the big player here that has emerged to shake us all up is the A/Sidney 05/97.

DR. HALL: I would think that we need to put in a change to an A/Sidney-like mutant. The problem is obviously which one and the availability.

Now, I understand that there is one that is the moderate to high yield. The question comes up, which was one of the options, which is whether we should wait. I'm not sure what data we could get in time by that manufacturer's line of the cross-reactivity or serologic response of these viruses.

And if somebody can answer that, it would be a little bit -- you would think that by waiting X

number of weeks, whatever we're allowed, that we will have enough data to help in that decision.

And secondly, is the current potential vaccine strain available now and in enough yield that it could be utilized?

CHAIRPERSON FERRIERI: Well, the IVR-108 that Dr. Levandowski mentioned has a moderate to high yield. He may wish to address your question first, and then anyone else.

DR. LEVANDOWSKI: Okay. Well, I suppose some additional information that we might get, there are other reassortants that are in the works, and they're not to the point where anybody could talk about them today, but it is something that has been looked at as a potential.

We have had feedback from the manufacturers that is a little bit variable, and of course, that is always true with new strains. When manufacturers get them, they need to have some time to take a look at the strain to know exactly how it's going to perform.

But we have had some sort of unusual events, I guess I would say, in working with the strain in the laboratory that's some variability up and down in terms of HA yield. I don't know what that

means. I don't know that it's not something that's just an event that happened that day in the laboratory.

But there has been some discussion about how high yielding this particular strain is, and I suspect that if we had one that were better, that were a higher yielding strain, that the manufacturers might want to use that, and experiences in the past are such that it is possible for them to get a strain at a later point if it is a very good, high yielding strain, and be able to manufacture a vaccine.

Now, this puts them in a very uncomfortable position, of course, but I guess the experience -- and I would say we had some luck in this last year -- is the experience that we had with the H1N1 component of the vaccine last year with the NIB-39 reassortant, which was an extremely good, high yield strain.

Now, those are somewhat unusual, but there is that possibility, and I think it's to the manufacturers' benefit to have a strain like that if they can.

There may be some other comments that others want to make, as well.

CHAIRPERSON FERRIERI: Dr. Cox, would you

address part of her other question though from an epidemiologic standpoint or some of these sequencing data? What more would you like to do over the next several weeks?

DR. COX: Right. I think that as you've seen from the data that were reported, influenza season got off to a bit of a slow start in the U.S. and certainly in Europe, and as usually happens, the states begin to send in the strains that they've isolated in November and December right after the Christmas holidays, and we have some 250 strains from the United States that have arrived just in the past couple of weeks, and we're pushing through the system as rapidly as we possibly can and expect to have data on a good number of during the next few weeks.

There also is sort of an intriguing intermediate that I really didn't point out when I was going through my presentation, but there are a couple of strains which are intermediate between the Wuhan and the Sidney viruses, and we'd like a chance to look at some of the strains from Japan, Hong Kong, and so on, and make sure that that's not an emerging group of viruses.

You know, from my perspective, I feel that we will have quite a bit of additional data that will

be generated over the next two and a half or three weeks.

CHAIRPERSON FERRIERI: And the Sidney-like viruses that you've sequenced, all are homologous in that HA-1 domain; is that correct?

DR. COX: They share some signature amino acid changes. Of course, there's some amino acid heterogeneity among them, but they share the signature changes, except for a couple of strains which only share a portion of those signature changes.

CHAIRPERSON FERRIERI: Thank you.

Well, with that information then, Carolyn, how do you feel about the three options then for the H3N2 strain?

DR. HALL: Given the expert's view of that, as I said, I would opt that we wait.

CHAIRPERSON FERRIERI: Okay. We have that on the table. Are there any divergent opinions from the panel members regarding deferral then?

Dr. Couch.

DR. COUCH: Well, I think it's always desirable to make the decision later because we always tend to get forced to make it for what most of us think is a little early, but in looking at this one, I mean, I think we all agree there needs to be a

change. Some of us have never been happy with Nanchang as an antigen. I don't know how much of that is host and how much of it is the antigen, but, see, they've always been sort of wimpy responses compared to some of the ones we've seen for antigens in the past.

Maybe Sidney won't be any better, but the bothersome thing about it is that this horse may already be out and we're chasing drift after the fact, so that you'd really like to have that herald wave, if you can put your finger on it, for the next H3, and I think that's what Nancy is suggesting.

But what happens to my thinking is that if you look at this time frame, if you identify, you know, what looks like a herald wave in the next two to three to four weeks, look at the time frame we've got. To take a virus out of that, to characterize it, to make a new seed, high growth, and to meet the deadlines of the manufacturers seem to me to be heading toward the highly unlikely.

So that I think the compromise I was kind of thinking about, and I might try you on that one, is that perhaps if we follow the time frame, I think it's always desirable to have more money -- I mean more time.

(Laughter.)

DR. COUCH: No question about that former one. You see what I had on my mind.

CHAIRPERSON FERRIERI: We agree with all of the above.

DR. COUCH: I know John LaMontagne was sitting over there, see.

(Laughter.)

DR. COUCH: That the Committee could make a tentative decision that doesn't require conference call follow-up unless new data develops.

CHAIRPERSON FERRIERI: I think that's a very good suggestion if we could all live with that. So that if new data emerges, then fine, but otherwise then we would go with the Sidney.

Shall we take a vote on that?

DR. HALL: Could I just ask?

CHAIRPERSON FERRIERI: Yes, Dr. Hall.

DR. HALL: Nancy, do you think there's really -- I'm concerned from what Dr. Couch said also that the A/Sidney may be a this year's virus and not next year's virus because it's out of the barn, as he says.

Is there a reasonable chance from your experience that it will still be the predominant virus

considering that it has rapidly increased to what, 61 percent at this point?

DR. COX: I simply can't say. I think it surprised us all in the rapidity with which it has spread, but you know, I have the same reservations that perhaps next year it wouldn't be the predominant strain, and we need to look carefully and see if there is something else, but of course, we do have a very limited amount of time.

I think that in the past when we've really had to pull out the stops and work together very hard to get a high growth reassortant at the last moment, we've been able to do it. So if something does emerge, we'd have to discuss it in the conference call or the follow-up and try to cover whatever newly emerging virus we were able to see.

DR. HALL: To phrase the question another way, in your experience a virus that has been in the current season at 60 or more percent, is that still at that level the next year?

DR. COX: We have seen H3 variants circulate two consecutive years. The Beijing 353/89, for example, circulated in two consecutive years.

DR. HALL: At over 50 percent or so?

DR. COX: Yes, yes.

CHAIRPERSON FERRIERI: Dr. Cox, refresh my memory. We're always told watch what comes out of China, and so there are some new isolates you have from China that you're studying now, will be studying soon, the H3N2 isolates.

DR. COX: We haven't -- Sasha, correct me if I'm wrong -- we don't have a shipment. I mean often we do have a shipment on the way or something. I think our colleagues in China have been preoccupied with H5N1 surveillance.

CHAIRPERSON FERRIERI: Okay. Well, we have on the -- sort of a --

DR. COX: Excuse me.

CHAIRPERSON FERRIERI: Yeah, go ahead.

DR. COX: What we do have in our hands and on the way is a large number of viruses from Hong Kong, which they have as a result of their enhanced surveillance activities.

CHAIRPERSON FERRIERI: Right. Well, we have on the table, Committee members, sort of an informal motion that we make a tentative recommendation to adopt the Sidney strain, the 05/97, pending any new information that will then lead to a conference call.

Are you comfortable with that

recommendation, Roland?

DR. LEVANDOWSKI: I suppose we could live with that.

(Laughter.)

DR. COUCH: Can the manufacturers live with that?

CHAIRPERSON FERRIERI: Can the manufacturers live with it? Well, I think that it's a better option. We have more information on this at the moment than we have about some new strains coming down the pike that may suddenly be put on their table.

It's not the best, but we've had other years where we've only -- last year I think -- was it last year we stayed with two, adopted one new one? The previous year we retained one and had two new ones.

And so I think that this is not the worst year, and this is a little bit better than two years ago. So we'll take a formal vote on this motion then, that we tentatively recommend the Sidney strain for the H3N2 component of the vaccine. This is a major change now, unless new information emerges with studies of strains that are coming in or under some study at the moment, and also based on what we think of the yield of the reassortant.

So we'll start again with Bob. Dr. Couch?

DR. COUCH: H1?

CHAIRPERSON FERRIERI: No. Yes or no on this.

DR. COUCH: Oh, this one. Yes.

CHAIRPERSON FERRIERI: I'm afraid we do have to take a vote.

DR. COUCH: Yes.

CHAIRPERSON FERRIERI: Dr. Clements?

DR. CLEMENTS-MANN: Yes.

CHAIRPERSON FERRIERI: Dr. Apicella.

DR. APICELLA: Yes.

CHAIRPERSON FERRIERI: Dr. Hall?

DR. HALL: Yes.

CHAIRPERSON FERRIERI: Dr. Poland?

DR. POLAND: Yes.

CHAIRPERSON FERRIERI: Dr. Edwards?

DR. EDWARDS: Yes.

COMMISSIONER McCARTHY: Ms. Cole?

MS. COLE: Yes.

CHAIRPERSON FERRIERI: Dr. Estes?

DR. ESTES: Yes.

CHAIRPERSON FERRIERI: Dr. Huang?

DR. HUANG: Yes.

CHAIRPERSON FERRIERI: Dr. Snider?

DR. SNIDER: Yes.

CHAIRPERSON FERRIERI: Dr. Karzon?

DR. KARZON: Yes.

CHAIRPERSON FERRIERI: Dr. Eickhoff?

DR. EICKHOFF: Yes.

CHAIRPERSON FERRIERI: Dr. Broome?

DR. BROOME: Yes.

CHAIRPERSON FERRIERI: And my vote is yes, as well.

So now we'll move to the H1N1, and we've heard data today about the two lineages that are present. The major one, that is, the Bayern 07-like that is represented by the current composition, the Johannesburg 82 strain, which was new last year, and we have the possibility of the mutant Beijing, the 262/95, the H1 deletion mutant.

So I'll entertain discussion on an option that we preserve, change, or defer a decision.

Bob, do you want to start?

DR. COUCH: I think this one's a deferral for sure for more data, and the question is: what's the -- what I had on my little table which I made out is the old vaccines are not very good against the new deletional mutant, and under epidemiologic significance the best I could do right now was

possibly, but if its worldwide epidemiologic significance and we had that nailed down, I don't think there'd be any question that we had to have an antigen that would adequately cover the new H1 strains.

That brings us back to the question that we have had before with B/Victoria. If that's a risk and an uncertain risk, should we give any consideration to two H1 strains, Bayern and adding this new one? And while I think that can be discussed, you already know that the manufacturers strongly discourage that thing, that sort of addition.

So I would think that we ought to be on very strong grounds before we propose that, and we're not on such strong grounds right now in my view.

So I think this is a straightforward deferral for more data, primarily epidemiologic significance of the strains.

CHAIRPERSON FERRIERI: Other?

DR. COUCH: The Bayern looks quite good for those strains.

CHAIRPERSON FERRIERI: Right. Any other divergent opinions from the panel, from the Advisory Committee or temporary voting members?

Is there a concurrence? And then we will

take a formal vote. Is there a general concurrence?

(No response.)

CHAIRPERSON FERRIERI: So we'll start taking the vote starting at this end of the table, starting with Dr. Claire Broome so that the vote is --

DR. COUCH: Why don't you push them a little bit first and see if anybody else wants to comment, including our nonvoting members on that one?

CHAIRPERSON FERRIERI: Great. What do you think of this decision before we vote on it? Dr. Kilbourne, what do you think about our deferring a decision on that one?

DR. KILBOURNE: Good decision.

(Laughter.)

CHAIRPERSON FERRIERI: You'll still get a lunch break even if you do --

(Laughter.)

CHAIRPERSON FERRIERI: -- even if you disagree with us.

Dr. Webster, how do you feel about this?

DR. WEBSTER: I concur.

CHAIRPERSON FERRIERI: Okay. John LaMontagne?

DR. LaMONTAGNE: And I.

CHAIRPERSON FERRIERI: Okay. That sounds

good.

Dr. Breiman?

(No response.)

CHAIRPERSON FERRIERI: Okay. We'll start voting then formally with Dr. Broome at this end and come around counterclockwise. The motion is deferral on the H1N1.

DR. BROOME: Well, I agree with deferral, sitting here trying to look at the studies of experimental vaccine which seem to me to be sort of critical to this decision, as well as information about what strains are circulating in the most up to the minute information.

So I mean the easy thing to say is just defer, but I think we should maybe look very quickly at what you can or can't conclude from the experimental vaccine.

CHAIRPERSON FERRIERI: Thank you.

Dr. Eickhoff?

DR. EICKHOFF: I agree with deferral pending further information.

CHAIRPERSON FERRIERI: Dr. Karzon?

DR. KARZON: I agree with deferral.

CHAIRPERSON FERRIERI: Dr. Snider?

DR. SNIDER: I agree.

CHAIRPERSON FERRIERI: Dr. Huang?
DR. HUANG: Yes.
CHAIRPERSON FERRIERI: Dr. Estes?
DR. ESTES: Yes.
CHAIRPERSON FERRIERI: Ms. Cole?
MS. COLE: Yes.
CHAIRPERSON FERRIERI: Dr. Edwards.
DR. EDWARDS: Yes.
CHAIRPERSON FERRIERI: Dr. Poland?
DR. POLAND: Yes.
CHAIRPERSON FERRIERI: Dr. Hall?
DR. HALL: Yes.
CHAIRPERSON FERRIERI: Dr. Apicella?
DR. APICELLA: Yes.
CHAIRPERSON FERRIERI: And Dr. Clements?
DR. CLEMENTS-MANN: Yes.
CHAIRPERSON FERRIERI: And Dr. Couch?
DR. COUCH: Couch.
CHAIRPERSON FERRIERI: Yes, I do know who you are.
DR. COUCH: Yes.
CHAIRPERSON FERRIERI: Thank you, and my vote is yes also.
If anyone would like to add to what we've just said before we break for lunch. Any response

from Dr. Levandowski or anyone else who wants to attach some caution on our decision making today and the time frame we're looking at?

Is there anything you would like to add, Roland?

DR. LEVANDOWSKI: I don't think there is anything I would like to add. I think that everyone has spoken, including the manufacturers, and I think the Committee are listening and assessing very carefully all of the information that's coming in and doing the best possible to give guidance. So I think that's what we are looking for, and that's what we're going to get.

CHAIRPERSON FERRIERI: Thank you.

I would propose we break for lunch and return at 1:15, and then we have the afternoon on avian flu.

(Whereupon, at 12:02 p.m., the meeting was recessed for lunch, to reconvene at 1:15 p.m., the same day.)

AFTERNOON SESSION

(1:23 p.m.)

CHAIRPERSON FERRIERI: Good afternoon everyone. We'll begin the open session now, if you could all take a seat, please. We have a very busy afternoon ahead.

We've all had a nice, leisurely time for lunch. So everyone should be in a good mood, tummies full.

This is the open session on the update on influenza A H5N1 subtype viruses, and everyone at the table is the same, except I thought we had sitting at the table then Dr. Wood and Dr. Fukuda.

Fine. Okay. Dr. Roland Levandowski will begin with the introduction of the subject.

DR. LEVANDOWSKI: Thank you, again, and welcome, everybody, back from lunch.

This afternoon we're going to hear information on the current situation regarding the H5N1 influenza viruses that were first identified to infect man in Hong Kong during 1997.

A great deal of data have been accumulated in what's really a relatively short period of time, and I'd like to acknowledge, in particular, the really heroic efforts of our colleagues from the CDC in

putting a lot of information together.

We're really glad that they're here today, and some of them have only come back into the country within the last day or so. So I really do want to thank them greatly for being here.

Several of them are going to provide some of the latest data on the characterization of the H5N1 strains and also on the scope and the nature of the threat that's posed by the H5N1 influenza viruses. This appearance of H5N1 viruses in man has come as what I'll call an expected surprise, and it reflects the great versatility of influenza viruses and their ability to cross the species barrier.

When such an event occurs, of course, we all think the potential for rapid spread of influenza viruses and the development of a pandemic exists, and just a brief reminder. The pandemics of 1957 and 1968 are known to have resulted from reassortment in nature of an avian influenza virus with the influenza A virus, which was then current in people.

In each of those instances there was substantial morbidity and mortality in all segments of the population, and although that was not really to the same extent as the pandemic of 1918, which was caused by a virus which now is thought to have been

derived from an avian strain, that possibly was transmitted through swine as an intermediate host without an intervening reassorting event.

Preparation for the next appearance of an influenza virus with the potential for causing pandemic influenza has been the subject of a lot of ongoing discussions in the United States and elsewhere. On several occasions in the past few years, the status of development for planning for a pandemic has been brought to the attention of this Committee, and that's in particular since this Committee has a key role to play in the selection of influence virus vaccine strains, and also in providing guidance on new vaccine products.

One of the primary assumptions of planning has been -- and this was mentioned this morning -- that currently licensed influenza virus vaccines will play a major part in any response strategy to either blunt or to prevent the impact of a pandemic.

I would like to remind you that there were extensive and comprehensive clinical studies done during 1976 and 1977 upon the reappearance of H1N1 strains in human populations, and that's really the basis for the formulation of current vaccines and also the basis for the things that we're doing these days.

Those particular clinical trials, which have all been published, establish a number of key parameters of immunogenicity and reactogenicity of inactivated influenza virus vaccines, and that includes the relation of immunogenicity to the vaccine dose, utility of the method that we call single radial immunodiffusion, which is used for measuring potency of vaccines and also the direct correlation of SRID, as I'll call it in acronym form; its direct correlation with immunogenicity; in addition, the need for two doses of vaccine for immunologically naive populations, and the frequency and severity of immediate type adverse events were all fairly well defined by those clinical trials.

The coordinated effort during those clinical trials of Public Health Service agencies, including NIH, CDC, and FDA, resulted in the establishment of the process that we're using today to prepare for the new influenza vaccines for next year.

Those efforts also resulted in the first versions of pandemic plans by the Public Health Service initially in the late 1970s, and then with later revisions in the mid-1980s.

We're fortunate that several of the scientists and physicians who were involved in those

efforts are with us today, and they will be able to provide us with some perspective, I'm sure.

As we mentioned earlier this morning, the trivalent inactivated influenza virus vaccines produced for the United States are made at approximately 80 million doses per year currently. If you extrapolate from that capacity a monovalent vaccine that contained 15 micrograms per dose, could be manufactured in sufficient quantity to produce what would amount to be around 300 million doses of vaccine.

But as we also heard this morning, and I'll reiterate now, the reality is that there's a finite capacity and a finite time for production of vaccines, and careful choices between components will probably be necessary because other viruses, such as H3N2 and H1N1 subtypes of influenza A, as well as the multiple lineages of influenza B are continuing to circulate in man and do not really show signs of leaving.

In addition, the assumptions on the potential for vaccine production depend directly on the ability to obtain a virus strain that replicates the high titer in eggs and goes through the production process with limited loss of immunogenic

hemagglutinin.

For this purpose reassortants are produced regularly using the A/Puerto Rico 834 strain, or as it's known to most people, PR-8, as the high growth, egg adapted donor. There are over 25 years of experience producing inactivated influenza virus vaccines with these kinds of reassortants, but there's really not very much or no experience with that sort of production using other reassorting substrates.

Therefore, a substantial effort in many laboratories, including our own, is directed to producing reassortant viruses to support a maximization of current vaccine production capacity.

So having said that, and in anticipation of the presentations that we're going to hear, I'd like to pose to the Committee two questions, and I'll just put those up here.

These questions are in the form of really stimulating discussion by the Committee. The first one is: please comment on the need for immediate production of H5N1 vaccines for general use and also in developmental clinical trials. Probably a typo here.

And the second one is: please comment on the nature and scope of the clinical trials that would

be needed to support licensing of H5N1 vaccines.

I'd say we're very fortunate to have the people that we have gathered here today, and I want to thank them all again for being here since almost everybody who's going to speak is critically -- I shouldn't say "almost" -- everybody who's going to speak is critically and actively engaged in the current efforts that surround the H5N1 influenza viruses.

So to begin, Dr. Keiji Fukuda of the CDC will present a summary of the epidemiologic investigations which have been ongoing since late 1997 in Hong Kong.

DR. FUKUDA: I'm going to start the session off going over two investigations which have been done. The first one was done in August of 1997, and the second one really is sort of ongoing right now, and I'll be focusing my comments on the field investigation part.

But before I start I really want to emphasize, and I can't overemphasize this part, that any type of investigation like this really draws upon necessarily a number of different organizations and a huge number of individuals, and amongst all of these organizations I really want to highlight the role of

the Hong Kong Department of Health. They have done an absolutely heroic job in getting the work done which needs to be done, and I think that's something that this group should take away with.

Influenza A H5N1 viruses have usually been found in avian species, and prior to 1997 they have not been known to cause disease in humans.

In May of 1997, a three year old boy, a resident of Hong Kong, developed fever, sore throat, and cough, and he was diagnosed on an out-patient basis as having pharyngitis and was treated both with antibiotics and aspirin.

On day six of his illness, he was hospitalized both for continuing high fever and also because the admitting physician just felt that something was wrong, although she couldn't quite put her finger on what it was.

His respiratory illness rapidly progressed, and by day ten he was intubated, and after intubation, a tracheal aspirate specimen was obtained, and a few days later the child died, and his cause of death was respiratory failure, secondary to ARDS.

In addition, he had some complicating complications. Reye's Syndrome was one, and on the ventilator he had multi-organ failure.

On the day that he died, he had an influenza A virus isolated at the department which could not be subtyped by existing WHO reagents.

That isolate in August was identified to be influenza A H5N1. The initial work was done at the National Influenza Center in Rotterdam, and it was confirmed a few days later at CDC. A few days after that, the Hong Kong Department of health invited CDC to assist in an investigation.

I won't go into too much detail on that investigation since it's already been discussed, but let me go over some of the key questions and the answers that we came away with at that time.

The first question was whether the virus showed any signs of reassortment, and work done by Sasha and others indicated that all the genes were avian.

The second question, and probably the leading hypothesis at the time, was whether the isolate was a laboratory contaminant, and again, based on some very strong epidemiologic and laboratory evidence, we quickly became convinced that, no, it was not a contaminate, but was a true infection.

The next question was whether the virus was related to the child's illness or perhaps simply

was in the child's throat for other reasons, and we quickly became convinced that it was the likely cause of the child's illness. The clinical course was consistent with viral pneumonia. The virus was identified in respiratory cells based on immunofluorescent antibody assays, and other pathogens were sought, but none were found.

Now, the source of the virus appeared to be infected poultry in Hong Kong. Just prior to the child's becoming ill, three outbreaks of influenza A H5N1 had been identified in chicken farms in Hong Kong, in the New Territory area. These outbreaks occurred toward the end of March up to the beginning of May, again, just before the time the child became ill.

And work done by Rob Webster's lab and at CDC showed that the isolates from the first chicken outbreak and from the child were virtually identical.

However, it was unclear how the child became infected. We believe that he was probably directly exposed to infected poultry feces through some exposure, but we could not detect what the exposure was.

Now, one of the first things that was done was to look for additional cases, and so all of the

hospitals in the area were alerted, and surveillance was increased, but no other active cases of disease were identified at that time.

As part of the study approximately 2,000 blood samples were collected, and these came from several different groups. The first group were people who had close contact with the case, and this included family members, health care workers, classmates, and so on, laboratory workers at the Agricultural Department and at the hospitals and at the virology laboratory who worked with the virus, poultry workers both on farms and retail stalls, and then from a number of so-called controls. These were healthy adult blood donors, health children in vaccine trials, and so on.

And I won't go over those results as part of the second investigation because that's when they became available, and so the real question at that time was: what was the virus' pandemic potential?

And at the end of that investigation in September, we thought that the pandemic potential at that time was relatively low and that this appeared to be an unusual infection that occurred for reasons we didn't understand.

However, being mindful that this was a new

virus appearing in the human, surveillance was increased both in Hong Kong, but also in south China in the cities of Shenzhen, Guangzhou, and also in Guangdong Province, and then the development of serologic assays was begun at CDC, and Jackie Katz's group started working on microneutralization assays and ELISA and a Western Blot.

Things were pretty quite except for in the laboratory for the next several weeks, and then on November 25th, the Hong Kong Department of Health notified CDC that a second case had been detected. This case occurred in a two year old boy who had an underlying ventricular septal defect.

On November 6th, he presented with an upper respiratory illness, and he was admitted to a hospital on the 7th, and two days later he was discharged doing relatively well.

As part of his admission work-up, a nasal pharyngeal swab was taken which grew out to A H5N1. On November 27th, CDC was invited by the Department of Health for a second investigation.

Now, when we got on the airplane, we knew of that one case. When we got off of the airplane, we were greeted with the news that there had been two additional cases.

Now, the main public health question at the start of the investigation, and the one which remains now, is whether the new cases indicate an increased likelihood of an H5N1 pandemic.

In order to answer that question, we broke it down into questions which could be answered perhaps a little bit more easily, and the first one was: is there evidence of increasing human-to-human transmission?

Two, were the viruses being transmitted more efficiently than before?

And, three, did they show any evidence of cumulative genetic changes or perhaps reassortment?

So to conduct this investigation the usual sorts of things were done. A number of people were interviewed, including cases whenever we could. Medical records were reviewed, and a number of different sites were visited.

In terms of analytic studies, several cohort studies were conducted basically looking at people who were exposed to or potentially exposed to virus and compared with people who were not, and then a case control study was instituted.

In addition, a group led by Ken Shortridge and Rob Webster, with the assistance of the Department

of Agriculture and Fisheries, conducted a number of animal studies, and I think that Rob will be discussing these later on.

Now, in the cohort studies, we were very focused on one question. Is there evidence of human-to-human transmission?

And in answering that question, the major confounder or the thing that we had to take into account was whether the degree to which people could have been exposed to poultry, and so we conducted approximately ten different cohort studies, and these revolved around -- well, family members were just tested as a matter of course, but the formal cohort studies revolved around health care workers who took care of the people when they were both sick and infectious. There were two school-based cohorts. There was a cohort based on co-workers, and then there was one of the cases had actually traveled with a group of people to another country, and so we studied that group as a cohort.

And then finally, there were a large number of people who were exposed to poultry that we also studied. These were retail stall workers who handle chicken on a daily basis, and then the second group were the personnel involved in the large culling

operations of chicken.

Now, in the case control study, we focused primarily on defining other risk factors, and primarily factors associated with poultry. Now, there were two major difficulties with this study. As in any case control study, selecting controls is really the heart of the study, and in this instance we selected two to four controls per case, and they were relatively randomly selected, and if anyone wants more details, I can go into that later.

They were also age, sex, and neighborhood matched to the cases, and one blood specimen was collected from each control.

Now, the real difficulty of this study was that most of the interviews were conducted with surrogates, and that's because most of the cases were either children or they had died or they were intubated at the time.

So between November 6th and December 28th, there were 17 additional cases of H5N1 related disease. Sixteen of these cases were confirmed by culture, and one was serologically confirmed. The ages of the cases ranged from one to 60 years, and they were approximately evenly divided between males and females.

Now, this slide here shows you a breakdown of cases by age group, and you can see that the first bar is the group one to four years of age, and you can see, by and large, these are relatively young people that became symptomatic from this infection.

Now, this slide here represents the epicurve of these cases, and it's a little bit different than the one, I think, in your handouts, but basically the same, and what it shows is that there were a few cases in November, and then the majority of cases really began taking off in December.

And you can also see from that line that on December 29th is when the large operations basically to kill all of the chickens in Hong Kong took place, and you can see that no additional cases occurred after that operation.

Now, I don't know how well you can see this, but the cases were spread out relatively all over the Hong Kong area. Hong Kong itself is an island, and then to the north is the Kowloon area, and both of those are highly, very densely populated urban areas, and then further to the north is the New Territory's part of Hong Kong, and you can see that up around here, this is the Yang He Lang area of the New Territories, and this is where about 90 percent of the

domestic poultry farms are located. And so, again, you can see that the cases are spread throughout the entire area.

Now, of those 17, of those cases that appeared, eight people required mechanical ventilation, and of those people that were put on a mechanical ventilator, six of them died. One person still remains intubated, and they may have suffered a fair amount of neurologic damage, and then one person, a 19 year old woman has been successfully extubated, and she should do well.

Now, one of the striking things about the case fatalities is when you simply eyeball the cases, you can see that they're really concentrated among young adults, and so in this graph here what we have are the people who are over 18 years of age, and you can see that of the people 18 years or older, six of them died. So six out of seven people who are over 18 who became infected and who became a case died. So about 88 percent of those people died as opposed to people under 18 years of age. Two out of 11 died, and that was very striking to us.

Now, again, during the middle of the current investigation is when the serology results surrounding the first case became available to us, and

basically you can see that in this first group over here, the case contacts, that none of four family members were seropositive, and these tests were based on the microneutralization assay, whereas about two percent of health care workers, less than one percent of classmates, and two percent of neighbors showed evidence of being infected by H5N1.

Also, among the laboratory workers we know of one person who was seropositive and who also was symptomatic.

These numbers stand in contrast to the poultry workers where you can see that five out of 29, about 17 percent of them, were seropositive for H5N1, again, in contrast to zero out of 18 swine workers and none out of the 419 controls.

So in terms of the cohort studies currently, we collected almost 2,900 questionnaires total and about 3,300 blood samples, and currently the serology are being run on these. We do not have results from those studies yet. We hope to have results on most of the cohort studies in about two weeks' time.

The same for the case control study. We were able to study 15 cases and enroll 41 controls, and again, we expect to have results in about two

weeks' time.

So I think at this point in terms of the field investigations, it's too early to draw conclusions. However, we can make a number of observations, and the first one, and the one which everyone here really ought to take home, is to remember that there is a six month period between the first case and the second case. There is really a long, quiet period in which no additional cases were detected.

The second observation is that the age distribution of people who became ill from this is quite unusual for influenza. The cases that we saw that were all hospitalized, except for one out-patient case, occurred predominantly in children and in young adults.

Again, the mortality pattern, at least among the disease cases, was unusual in that the overall mortality was strikingly high, and again, we saw that mortality was concentrated among young adults.

Now, based both on field evidence and laboratory evidence, there appears to be a quite close link between avian and human infections. Out in the field we saw that there was the occurrence of

contemporaneous disease in poultry and in humans. The molecular evidence from the laboratory studies indicates that, again, there is close relationship between the animal viruses and the human viruses.

And then the serologic studies from the first investigation suggest that people who are exposed to poultry were the group that by far was the most likely to be seropositive for H5N1.

And then finally, we see that there has been no additional cases after the culling operation, and so perhaps there was some effect there.

Now, in terms of transmission, at present it appears to be primarily from poultry to human, and it also appears to be relatively inefficient at this time, and we say that in part because we are dealing with 18 cases as opposed to hundreds or thousands of cases, as is typical with influenza.

However, in pointing this out, we also have to remember that the second appearance of this virus was associated with a cluster of cases as opposed to another single case, and also the data that we have now, even though it suggests that poultry-to-human transmission may be the predominant mode of transmission, indicates that human-to-human transmission clearly is possible and is probably

likely in a few of the cases that we know about.

Hopefully, the data which will be available within the next few weeks will shed further light on this.

And then the last point is that the current studies may clarify these points. They may not clarify these points, but one thing that they will do is help to establish some baseline data so that if additional cases appear in the future, we'll really be able to get a better sense of whether the kinetics of the transmission are changing more quickly.

So I think that I will stop at this point. I don't know if there are any questions at this point or if you want to just go on to the next talk.

DR. LEVANDOWSKI: Dr. Hall?

DR. HALL: Yes. I just noted that at least in the 18th case there that there was isolate still available after 12 days or so of illness. Has this been a characteristic also, that they seem to shed this virus for a longer period than what would be expected for a 34 year old woman?

DR. FUKUDA: Yeah. Case 18 is a very confusing case in many different ways. I think that there was another case in which we know that virus was shed for ten days, and so I think that -- and that

happened in a child, and so that gives some indication of how long these viruses may be shed.

Case 18 was a 34 year old woman who had an underlying history of lupus and quite severe lupus. She had been treated for nephritis in the past, and at the time she became ill, she was not on any immunosuppressive drugs, although she had been on both steroids and azathioprine in the past.

She lived by herself, and she didn't have any family members, and she came in paraplegic for unclear reasons, and she also had large decubiti on her body, and someone had sort of mysteriously telephoned the hospital that this person was sick, and apparently she had been in bed for about ten days, but there were no family members, and there was no other person to speak to to corroborate any history, and so it was very unclear when she became symptomatic.

If she was infected, it either had to have happened at home in some way that we don't understand or it had to be a nosocomial infection, and so this is part of the investigation which is still ongoing, to try to find out whether there is any possibility that she could have been infected in the hospital by another person that we don't know of at this time.

Otherwise we were not able to gain access

into her house because there were no family members to get permission for that, and so she will probably remain quite enigmatic as to what really happened and whether she really was a case or not, although she clearly had a lot of respiratory disease, but again, the respiratory disease was complicated by congestive heart failure.

CHAIRPERSON FERRIERI: Dr. Clements and then Dr. Edwards.

DR. CLEMENTS-MANN: I was just thinking that with this kind of virus that adults and children would be probably the same in their shedding pattern and that they wouldn't have prior immunologic background to be able to control the virus replication.

Sometimes in children they shed for, you know, for two weeks or so.

CHAIRPERSON FERRIERI: Dr. Edwards.

DR. EDWARDS: The association of the pneumonia presumably from the influenza and Reye's Syndrome is quite different than what one generally sees with Reye's Syndrome where it comes after an event of an influenza illness that has clearly been finished and is not ongoing. What evidence do you have from the liver involvement whether was it fatty

infiltration which was compatible with Reye's or is there evidence to suggest that this virus may not be restricted simply to the lungs, but may indeed have grown and caused cytopathic changes in the liver that are distinct from Reye's Syndrome?

DR. FUKUDA: Sure. Those are good questions.

I think that in reviewing his medical records, it was really clear to me that his predominant pathology surrounded his viral pneumonia and his inability to ventilate or to oxygenate, but in terms of the Reye's Syndrome, he was noted to have some central nervous system changes. His personality was different than it normally was in the emergency room, and this had just been noted, and he gradually became somewhat lethargic during the course of his illness before becoming intubated.

There were biopsy specimens available both from liver and from kidney, and there were vacuolated changes on the liver biopsy, and there were similar changes on his renal biopsy, again, consistent but not pathopneumonic of Reye's Syndrome.

And so I think that it would be a secondary diagnosis, but it did seem to have occurred early in the course of his illness.

CHAIRPERSON FERRIERI: I asked this question the last time we talked about avian flu here, about the pathology in the chickens, and I didn't feel I got a straight answer about that, the liver involvement in particular.

Are there pathologic changes in the chickens who are infected with it or are they asymptomatic?

DR. FUKUDA: Well, Dr. Webster would be the preeminent person to speak on this, but this virus is highly pathogenic for chickens, and when you do an autopsy on the chickens, you see evidence of widespread hemorrhaging and necrosis in many if not most organ systems.

CHAIRPERSON FERRIERI: Yes, Dr. Karzon.

DR. KARZON: Was there opportunity to look for viremia or virus in visceral organs?

DR. FUKUDA: Dr. Sharif Zaki has some specimens, biopsy and autopsy specimens, at CDC and hopefully additional ones will be coming, and I think that he has done some staining studies looking for antigen and also will be doing additional ones and probably some in situ studies, and so we don't have evidence right now of antigen in other organs, but that's something that will be sought.

DR. KARZON: Amongst other things, I was thinking about the possibility of whether or not the H5 required exogenous protease for splitting the hemagglutinin.

DR. FUKUDA: Boy, I wouldn't be the right person to ask about that. I think Nancy maybe would be able to.

CHAIRPERSON FERRIERI: Dr. Cox or Webster or Dr. Kilbourne?

DR. WEBSTER: All of these viruses with the series of basic amino acids at the cleavage site in the hemagglutinin are cleaved by the furin series of enzymes that are found in chickens and are ubiquitous, and it's one of the properties of these viruses, and in human. I'll deal more with that later.

CHAIRPERSON FERRIERI: Thank you.

Other questions from the panel? Dr. Couch?

DR. COUCH: Maybe a question for Rob, but maybe Keiji knows. Were there further outbreaks recognized in the chicken farms between May and November? I know the virus was there. I think Rob's going to tell us, but were there further outbreaks recognized?

DR. FUKUDA: Well, there were additional chickens that were known to be infected, and I think Rob will probably discuss this in more detail, but, yes, there were a number of other chickens that were identified.

CHAIRPERSON FERRIERI: Yes, Ms. Cole.

MS. COLE: Have any of the wild bird populations been looked at at all? Because I know, you know, that the -- my understanding is influenza can be spread even from feathers on infected birds.

DR. FUKUDA: Right. I think Rob will be discussing that, and I'll leave that.

MS. COLE: Okay.

CHAIRPERSON FERRIERI: Others? Yes, Dr. Hall.

DR. HALL: Has there been previous outbreaks identified in the poultry farms of this particular virus, the same virus?

DR. FUKUDA: Not that I know of. I think that before the March to May outbreaks, I don't know that it had ever been identified in Hong Kong poultry before.

DR. COUCH: Well, I had one other question, and maybe Rob wants that one as well.

No outbreaks recognized was my

understanding, but does Ken Shortridge know that the chickens in Hong Kong were actually free of avirulent H5? Was that known, preceding the first outbreak?

DR. WEBSTER: Preceding the first outbreak there was no evidence in Hong Kong.

DR. COUCH: No evidence of H5, and the test --

DR. WEBSTER: But unfortunately an important point that I'm going to make and repeat, there was no surveillance done in this part of the world.

DR. COUCH: That was my next question.

DR. WEBSTER: How would anyone know?

DR. COUCH: So we don't really know for sure.

MR. WEBSTER: Either for nonpathogenic or pathogenic. So that's the problem. We weren't doing the surveillance. There were irrelevant viruses, and so we're left with nothing to work on.

CHAIRPERSON FERRIERI: Roland, will you proceed then with the program?

DR. LEVANDOWSKI: Okay, sure. If there are no other questions or, I guess, questions could come up later that Dr. Fukuda would need to respond to, we'll move on, and Dr. Klimov from the CDC will be

speaking about the antigenic and molecular characterization of the H5N1.

DR. KLIMOV: And I'm going to start with antigenic analysis of the strains isolated from humans, and totally we have in the lab right now 15 viruses. Virus number 16 is in progress, and this table presents the hemagglutination inhibition test data for all 15 viruses I mentioned before, and this is one particular test, the data from one particular test.

And from this table you can see, first of all, that H3 viruses -- I mean H5N1 viruses could be clearly distinguished from the H1 or H3 viruses using the sheep antisera compared against H5 virus A/South Africa, and I should tell that this serum was developed, produced by Dr. Webster's group, and it's, you know, extremely useful in whole story of investigation of H5 viruses appeared in Hong Kong.

Secondly, you see that we used two ferret antisera prepared to the very first virus isolated in Hong Kong from the child, Hong Kong 156, and also we had another ferret antiserum prepared against another virus called Hong Kong 483, and both sera, you know, produced titers like 160 in this test.

As the second observation -- I mean the

next observation we can make from this test is that it looks like we have two antigenic groups of viruses circulating among humans, and this is especially clear from the comparison of the inhibition data using the Hong Kong 156 serum.

You can see that this group of viruses including, you know, we could call this group of viruses Hong Kong 156-like viruses. They have titers indistinguishable from the homologous titer, but another group of viruses have fourfold or higher decrease in titers, and we could call this group Group 2 or group of Hong Kong 483-like viruses.

Next slide, please.

Here summary of data obtained by sequencing. This is phyllogenetic tree for H5 hemagglutinins, HA-1 domain, major antigenic domain of hemagglutinin, and the Hong Kong viruses are in color in this overhead.

First of all, we can see that all Hong Kong viruses belong to so-called Eurasian group of avian viruses, but not to the so-called North American group of avian viruses.

Second conclusion from this picture is that the closest relative to the Hong Kong viruses is the H5N1 virus isolated from goose in 1996, a year

ago, in Guangdong Province of China.

This genetic data also supports the idea that there are two genetic groups of viruses circulated in Hong Kong. This is Group 1, the Hong Kong 156-like viruses, and the second group is Hong Kong 483-like viruses.

Also, important to notice that each of these groups have genetically close chicken viruses within the group, and this data came from Dr. Webster's group, and again, you know, the collaboration with Dr. Webster's group is extremely important for understanding what the relationships between avian and human viruses.

Second group also has representatives of chicken viruses which are extremely genetically close to the human viruses.

I should mention that those groups, Group 1 and Group 2, have major difference in terms of glycosylation sites. Group 1 does not have a glycosylation site at the position 156 of the hemagglutinin, while the representatives of Group Second have this glycosylation site at this position.

Next, please.

This chart just shows that representatives of both genetic antigenic groups circulated

simultaneously after November of 1997, and actually evenly caused the fatal cases. Three fatal cases were caused by representatives of Group 1 and three fatal cases were caused by representative of Group 2 of the human influenza viruses.

One essential feature, characteristics of the hemagglutinins of all these viruses is that all of them, all 15 at least we were able to analyze, have multiple basic amino acids at the cleavage site between the HA-1 and HA-2 domains of hemagglutinin, and this feature is associated with highly pathogenic H5 avian viruses.

And the group in Athens in the South Poultry Laboratory of FDA, and Michael Perdue is here, has shown that, indeed, all those viruses isolated from humans are highly pathogenic for chickens.

As to the neuraminidase, at this moment we have eight viruses sequenced, neuraminidase general sequence for eight viruses as related in Hong Kong, and you can see that all the viruses are pretty close to each other, from one to a few nucleotide differences between the viruses.

Also you can notice that the neuraminidase of the goose Guangdong virus is not as close to this group as in the case of the Cheng Xiowenian (phonetic)

gene. Unfortunately not too many neuraminidase sequences are published, but I repeat all the human cases are very similar in this gene.

All the viruses have 19 amino acid deletion in the stalk region of the neuraminidase, and this situation wasn't known before the human viruses in Hong Kong and chicken viruses in Hong Kong.

Just to summarize, you know, genetic analysis of internal genes, and Keiji already mentioned this, I should notice that all human viruses contain all eight avian-like RNA segments in their genus. In other words, all the viruses are pretty similar in all genes to the chicken viruses of H5N1 subtype.

Also, there is a very close homology between all the viruses we were able to sequence, and here is the data for nine viruses for internal genes. Four viruses were sequenced completely in internal genes -- I mean including Hong Kong 156. This is comparison of all other viruses with Hong Kong 156, and for six viruses this comparison is done based on partial sequence data.

And you can see that there is extremely high homology between all those viruses from 1980, .4 percent to 100 percent, but nonetheless I should

notice that the viruses are not absolutely identical. There is some variations.

Also, I have to say that there is no visible evidences of accumulation of mutations. Usually when viruses are circulating within a population, especially human population, we always see the accumulation of some, at least some nucleotide changes, but we don't find this yet at least in the group of human H5 viruses.

And this last overhead shows the data about the geometric mean titers in neutralization tests using, you know, using some sets of sera from children and young adults, and a group of sera from elderly people is in progress. This part of the study was done by Jackie Katz and group.

Actually this table just to show what is the sort of base level of H5 specific antibodies in the last population, and you can see that this is actually bottom line of the H5 antibodies among children, among young adults. At the same taste -- in the same taste you can see that there is definite level of antibodies against control H3N2 virus.

Thanks.

And as a summary, I'd like to say that there were two genetically and antigenically close

groups of human H5 viruses, genetically close, but nonetheless still visibly different, and those groups are different by glycosylation site, deposition 156 of the hemagglutinin.

Those groups are similar to two genetic groups of chicken viruses isolated approximately at the same time in Hong Kong. Both groups circulated simultaneously, since November, and caused the same number of fatal cases. In other words, they're probably equally pathogenic for humans.

Genetic analysis reveals that all human viruses of H5N1 type have multiple basic -- I mean acids -- at which sites of the hemagglutinin. All are high pathogenic for chickens. Are viruses have 19 amino acid deletion in stock region of the neuraminidase. All viruses have internal genes close to the avian, but not to the human viruses, and all internal genes of those human viruses are pretty close to each other while being not identical.

Thank you very much.

DR. LEVANDOWSKI: Thank you, Dr. Klimov.

Are there questions or comments?

Dr. Kilbourne.

DR. KILBOURNE: In view of that 19 amino acid deletion in the neuraminidase, do you have any

evidence that that's functionally important in terms of reactivity with antisera or activity in cell detachment or anything like that?

DR. KLIMOV: We don't have our own data about this, but according to Dr. Alan Hey, the N1's neuraminidase from the H5N1 viruses is quite different from human N1 neuriminidases in the neuraminidase inhibition tests, quite different. That's probably the only information we have about.

DR. KILBOURNE: How different antigenically?

DR. LEVANDOWSKI: Dr. Couch?

DR. COUCH: I wanted to ask you. It wasn't clear to me whether we can label or should or should not label the Hong Kong Group 1 and the Hong Kong Group 2 as antigenically distinct.

DR. KLIMOV: At least according to the data we have this moment, there is evidence that at least with the ferret antiserum to Hong Kong 156 there is fourfold or higher decrease in the hemagglutination inhibition reaction, and also, as I mentioned, those groups --

DR. COUCH: There is in those two ferret sera, except that the ferret sera did not distinguish,

I mean, the human strains very well.

DR. KLIMOV: Yeah, in this particular case it does distinguish.

DR. COUCH: We've raised that question here before as to whether some selection of the ferret sera might have skewed the results a little bit. So that's a more direct way of asking the same question.

Do you have several ferret sera, more than one ferret serum?

DR. KLIMOV: We have, at this moment, we have only two of them available. We are working; we are obtaining other ones.

DR. LEVANDOWSKI: Dr. Hall, another question?

DR. HALL: I just wanted a clarification on your last table there about the level of H5 antibodies, and I assume that ten is your lower limit.

DR. KLIMOV: Actually it should be lower than ten, yeah, of course, yeah.

DR. LEVANDOWSKI: Other questions or comments?

(No response.)

DR. LEVANDOWSKI: If not, we'll move on, and Dr. Nancy Cox from CDC is going to give a report on a recent trip to southern China for investigation

of activity with H5N1 viruses.

DR. COX: Thanks very much.

During the time that cases were being reported in Hong Kong, there was considerable interest in and speculation about whether H5N1 viruses might also be causing illness in south China, and the World Health Organization put together a mission which occurred from January 16th to 24th basically with the following objectives.

First of all, to review disease and virologic surveillance information that was available from south China and to determine just how surveillance was being conducted;

To enhance surveillance for influenza A H5N1 viruses both in hospitals and in out-patient clinics in Guangdong Province in south China;

Third, to enhance collaboration and rapid information exchange among the existing surveillance sites in south China and among WHO collaborating centers and with the WHO regional offices in headquarters in Geneva.

We also hope to strengthen influenza surveillance efforts in China as a whole and to convince authorities in China that influenza surveillance is something that needs to be supported

with additional resources by the Chinese authorities.

And we also hope to strengthen communications between animal and human influenza surveillance experts and ministries responsible for animal health and human health in China.

Our team was actually fairly large compared to some of the other missions, WHO missions, I've been on. There were 14 mission members, two from WHO headquarters in Geneva, two from the western regional Pacific office. There were two U.S. representatives, Dr. Couch and myself, and perhaps Dr. Couch will make some comments when I'm finished.

Dr. Kuniaki Nerome, who's also here, was a team member, and he might also like to make some comments when I've finished.

The other Japanese team member is an epidemiologist, Dr. Hirota, who was a very valuable member of the team.

We had two extremely valuable members from the special administrative region of Hong Kong, Dr. Margaret Chan, who's the Director of the Department of Health in Hong Kong, and Kay H. Mak, who's one of her key staff members.

In addition we had Dr. Guo Yuanji, who's the head of the National Influenza Center in Beijing,

the WHO collaborating national lab in Beijing, and Dr. Huang Hui, who is a member of the Ministry of Health in Beijing. These two individuals here are responsible for surveillance in Guangdong Province and in Cheng Xiowen, respectively.

I thought I should first orient you a bit so you would know where we were when I'm mentioning some of the places that we visited. This is a map of the influenza surveillance sites that are currently being supported financially and technically by CDC funding, and Hong Kong is about right here.

There are two surveillance sites in Guangzhou, which is the capital city of Guangdong Province. One of the sites is in the municipal antiepidemic station, and the second site is in the provincial station. So it's sort of the equivalent of a city health department and a state health department site.

The other place we visited was Dongguan, which is sort of halfway between Guangzhou and Shenzhen, and then we also visited Shenzhen, which is in one of the new economic zones, and it's really quite an interesting place to visit because of the development that's occurred there on a very rapid timetable, and it is reflected in the health care and

so on that you see there.

Next slide, please.Now, I wanted to remind you that since the technical and financial support and collaboration has been occurring with Dr. Guo Yuanji and the network of influenza laboratories in China, the number of influenza viruses from China that have become available for analysis by the WHO collaborating centers has increased quite dramatically so that during calendar year 1997, we had over 225 isolates to look at.

This is in contrast to the very small number of isolates that we were receiving prior to putting in place this collaborative work.

This program has been incredibly important to us because it has provided vaccine strains. I've shown here the recommended vaccine strains from 1988-89 season to the 1996-97 season, and strains which have come out of the China surveillance program are shown in red, and you can see that they've been very important in our vaccine strain selection over the past few years.

Okay. So back to the China mission. We visited a total of five laboratories while we were there. Some of them are very well equipped. For example, the Shenzhen municipal antiepidemic station

is extremely well equipped and well organized and staffed.

In contrast, the Dongguan municipal antiepidemic station is just getting set up to do influenza surveillance and will need some new equipment and so on.

We visited five hospitals as well, and we were actually allowed to delve into medical records, both computerized records and paper records. We also were able to go onto the wards, and Dr. Couch may want to make some comments about that.

There was a great deal of openness and hospitality shown to the WHO mission, and I feel like we learned quite a lot during this time.

We also visited a number of poultry facilities, and first on the list is the Guangzhou animal and plant quarantine station, where we learned about the ongoing surveillance that occurs among poultry that are being exported to Hong Kong and elsewhere.

And then we visited two chicken farms, but I must say that these were extremely well run, high tech chicken farms, and it really wouldn't be expected that one would see any problems in these particular chicken farms.

We also visited a live chicken market in Shenzhen, where chickens were being sold while we were there. It was extremely clean and well run.

I wanted to emphasize that we had contacts at the very highest level of the Health Bureau of Guangdong Province and also at the Ministry of Health in Beijing.

We presented recommendations both to the Ministry of Health in Beijing and to the Guangdong Bureau of Health. The Vice Minister of Health was there for our briefing where we gave the recommendations, and then the Chinese Minister of Health flew back into Beijing to host a reception for us the evening after our briefing.

Our recommendations, I've tried to sort of condense our recommendations and point out the ones that I thought were most important here, and again, others who were on the trip may wish to add to this list.

We recommended that there be integration of virologic and disease based surveillance for influenza, including some mortality studies if possible.

We recommend that they include culturing of hospitalized patients with severe respiratory

illness. They had in the past been culturing mainly patients who were seen in out-patient clinics. Because of their interest in -- the Ministry of Health -- in this problem with H5N1, they had already issued directives to culture hospitalized patients, and our mission emphasized that this was absolutely crucial for identifying cases.

We recommended that they increase from 20 to 40 per month to approximately 100 per month the number of cultures taken from patients with respiratory illness in each of the sites.

We recommended that this enhanced influenza surveillance continue for at least six months.

We recommended that they increase staffing levels to handle the increased number of specimens, and that they properly equip the start-up laboratories that were doing influenza surveillance for the first time.

We recommended that technology that had been developed specifically to detect antibodies to H5N1 viruses be transferred to laboratories in south China, and that this technology transfer be coordinated very carefully by WHO.

We recommended that all efforts be made to

decrease the interval between the collection of specimens and the receipt of isolates at the National Influenza Center in Beijing and then subsequently at the WHO collaborating centers. We're trying to just simply speed up the flow of information and specimens from the point of isolation to the point where the information is centralized and so on.

We recommended that there be increased coordination of influenza surveillance at the municipal, provincial, and national levels, and once again, that there be a free flow of information.

We recommended that all influenza surveillance sites be linked through Internet or Intranet as resources could be made available.

And we also recommended that there be increased communication between officials and scientists responsible for human and poultry health.

So in conclusion, I'd like to say that there was recognition at the highest level in the Chinese Ministry of Health of the importance of surveillance for influenza H5N1 viruses and disease. There was an infrastructure already in place mainly because of some resources that had been put in place in the past, and this infrastructure was really critical for this rapid response that was initiated by

the Chinese government to the H5N1 situation.

There was a very positive reception of the recommendations made by the WHO mission from the Ministry of Health in China, and finally, I believe that there is a need to review the efforts that are now being put in place for enhanced influenza surveillance in about a six month time period. So I'm hoping that it will be possible to have another mission return to south China and see what has come out of these efforts.

Okay. I think that concludes my talk, and I'd like to open the floor for questions.

DR. LEVANDOWSKI: Thank you, Dr. Cox.

Are there any questions or comments?

DR. COUCH: Would you like to add?

DR. COX: Certainly.

DR. COUCH: And maybe Kuniaki would have comments as well.

No, I enjoyed the meeting. It's the first time I've ever been to China. Interesting.

I described to my friends what did we learn about influenza, and this is perhaps a little bit too strong, but mainly we learned a great deal about what they don't know about influenza, and I think that partly is explained, as contrasting my

experience with having the opportunity to go to the Soviet Union a couple of times back in the '70s, is that influenza was a very high disease on the priority list for emphasis in the Soviet Union, and it clearly is not and has not been apparently in China.

So that there has been some surveillance going on. It's in the level of what they call a Class 3 disease, and that's among transmissible diseases.

So that that is the major thing that I think explains the lack of the kind of quantitative data that we hoped we'd be able to see, but certainly you should say, to second what Nancy said, that I think we all had the perception that we were greeted openly. We could ask to go anywhere. They showed us a very fancy breeder farm that replaces all their chickens once a year with chickens imported from Arkansas.

(Laughter.)

DR. COUCH: And two people take care of 10,000. It's all mechanized, you know, and so a great deal of the poultry industry is obviously very well done and very efficient, but you can't see all of the poultry industry in a very short period of time, and it was difficult to get a complete feel for the absence of H5N1, except that the poultry industry

people who spoke with us were very strong.

In fact, I was looking to see in my notes if I had brought this quote. This is directly out of one of their handouts they gave us. This is in the poultry industry.

"H5N1 subtype of influenza A virus has never been discovered in chicken flocks here, nor have we ever encountered avian epornitic" -- I don't know what that is unless it's an ornithine epizootic or something. It's a new word for me -- "never introduced by highly pathogenic virus."

So they deny ever having seen it at any time in the past, and the way the descriptions they make of the monitoring of the poultry industry would make it highly unlikely that they would miss it, but then that assumes that the level of monitoring the poultry industry is of the high level that they describe it to be and hope it would be, and of course, nothing is ever 100 percent perfect. So you have to leave a little bit of qualifiers, is that maybe something was there and they didn't know it.

Certainly I don't think any of us had the perception -- I certainly didn't -- I don't think anyone did that information was being suppressed, but it's quite possible with regard to the poultry

industry that something's down there and they simply didn't know about it.

But at any rate, they are very attuned. That poultry industry is very attuned toward now upgrading things and being sure that something that's obviously of very great importance economically to south China maintains itself clean and doesn't develop any kind of a bad reputation that would affect not only its domestic use, but the exportation industry.

So they're really responding and were responding before we got there in the poultry industry.

With regard to the hospitals, I was the one doing most of the running around the wards, as Nancy indicated, and we sort of learned on the trip as to how to get a little bit better at the data and might have profited a little more in the first couple of hospitals if we'd have had ourselves in gear for the last ones where we broke up in teams, and one group went to the record one, which she's indicated to you they opened up their records.

In opening up the records, we started trying to check. One of the things, the perceptions, that we picked up on the wards earlier is that they simply are not having children or adults die of virus

pneumonia or acute respiratory disease on their wards, and you reel off the numbers, you know, and they could say one virus pneumonia death in the last year.

How many have diagnoses made? And they'll reel off one and two cases with beds (sic) that contain 1,000 beds and 500, 400 children's beds, and things like that.

And the people who were going to the records rooms were pulling the computer records, and the discharge diagnoses were not there. I was on the floor, and the patients were not there.

So we were a little confused as to where the cases were that were certainly in our pediatric wards and our adult wards at any time of the year to some extent, and we don't have a clear explanation for that.

An explanation that was given by some of the people who know the WHO well in Beijing was suggested that a great deal of that kind of disease is maintained on an out-patient basis and with home care, and the descriptions -- see, this is a little bit anecdotal information -- the description was that the pattern of care, much like we're developing in our country now, is to focus on keeping people out of the hospital.

Well, as a result of that focus, why, I don't think there's any question that -- let me not say completely across the board because the pediatric hospital was attuned to acute respiratory disease -- there's no diagnostic virology unless the specimens are picked up now -- excuse me. I should say that now they're studying in-patients, but in the past, no studying of in-patients. It's been an out-patient disease, no diagnostic virology, no orientation toward this kind of cause for disease of a patient that would have been admitted.

So that while I think they are correct in saying that they have recognized no clinical cases of H5N1 in patients in the out-patient or in their hospitals, I came away feeling fairly strongly that if we're talking about a sporadic disease, 18 cases and a mini outbreak in Hong Kong or one or two or four sporadic cases that might have been seen in south China if this has been an ongoing thing, they would have missed it. The system was just not attuned to picking up an etiologic cause like that with a sporadic disease.

But again now, the surveillance is going up at a higher level. Now it's including in-patients. So now a great deal of effort is being made to try and

improve that circumstance.

As Nancy said, one of the hopes out of the team is that the whole perception of surveillance for influenza and being attuned to influenza in in-patients and out-patients will now go up to a higher level that can be maintained.

The six month figure was sort of a compromise. You know, we were talking about a year or so, and then there was, well, that's not realistic at their level, and so forth, but they were talking about three months. So I don't think there's any question about the fact that they will accept the six month reputation -- recommendation, rather, and if H5N1 should be identified, we were pretty strong about saying it should go longer than that.

So I think a lot more is going to be done to be looking in south China, without question. We came away with some reassurance, well, certainly a reassurance that there's no major 1918 flu or disease going on in south China. There's no question about that.

The sporadic H5N1 also in south China, they don't know, but now they might be able to find it out, although the level of sensitivity with populations that big is still going to be relatively

low compared to the way we might be looking for it in this country.

But I think progress has been made. I think I enjoyed the trip. I think it was worthwhile.

CHAIRPERSON FERRIERI: Thanks.

One question, and then we'll hare to move on because I'm going to lose some of the virologists on the Committee before we get to discussion, and that won't be very good.

Dr. Hall.

DR. HALL: I just wondered if they have a vaccine for the chickens. I guess there was a vaccine that was utilized at some point in Mexico; is that correct?

DR. COUCH: I don't think so, but, Nancy or Rob, do you know about that? The Chinese have never had a vaccine for H5, have they?

DR. WEBSTER: The Chinese don't, but Mike Perdue might want to comment on that. There is a vaccine that was used essentially effectively in Mexico, and there are much more up to date vaccines available, recombinant vaccines, and we're going to hear very shortly about other vaccines.

So I'll leave that until later.

CHAIRPERSON FERRIERI: Thank you.

DR. LEVANDOWSKI: Okay. Thank you.

We'd better move on because we are getting somewhat behind.

Dr. Robert Webster from St. Jude's Children's Research Hospital will give us a summary of surveillance of H5 viruses in animals, and I'd like to especially thank Dr. Webster for being here because I didn't know until this morning that he was actually going to be able to make it because of his other activities.

So please, Dr. Webster.

DR. WEBSTER: Thank you.

I'm honored to be invited to this important meeting for the first time. I'm pleased to see that this panel is interested in animal influenza for the first time, and I would encourage you to be interested in animal influenza in the future. So that's my bottom line.

(Laughter.)

DR. WEBSTER: And so if I could have the first slide, please. If someone could switch on the -- how do I switch this light on? I can't seem to switch it off. That's okay.

I'd like to take a couple of steps back and just to remind you that there are 15 subtypes of

influenza A viruses that exist, and these 15 subtypes of influenza viruses occur in aquatic birds of the world. They're perpetuated there, and these viruses are divided into two clades, if you like, those in the Americans and those in the Eurasia.

So when we think about surveillance, long term surveillance, which I would encourage you to put into place throughout the world, it should be done in Eurasia and in the Americas.

I'm just going to share a little bit of surveillance that's been done on a year-to-year basis on this population of birds that maintain influenza viruses. These are the birds, the red knotts and the ruddy turnstones that migrate annually from South America to the north slopes of Alaska. They stop off in Delaware Bay, and they poop out their influenza viruses on a yearly basis.

And this is the slide that I tell my students you should never show, but I'm showing you anyway, to give you some idea of the scope of influenza viruses that these little birds poop out each year.

And so we're interested in this meeting on H5 viruses. We see that in 1991 there was H5N2, '92 H5N9, '93 H5N9, and we haven't time today to deal with

it, but this H5 virus found its way into the live bird markets in New York City, found its way into the poultry in Delaware, Del Marva, and also into the chickens in New Mexico, and caused a severe pandemic in chickens.

I also would like to draw your attention to this group of viruses H2N2. Where have we seen those before? In 1994, these birds were carrying H2N2, and from year to year they carry these viruses.

I can't get any interest in the Public Health Department around the United States to look for evidence of antibodies to these. Maybe now we'll get that done.

I'll stop preaching and move on.

(Laughter.)

DR. WEBSTER: So I want to introduce the players in Hong Kong. You'll notice that they're bright red in color, and these birds talk to each other, and they say things like this.

"Now we're famous," and the press giving them enormous attention. In the time I was in Hong Kong they didn't come off the front of the newspaper for about four weeks.

And so what was the source of this H5N1? We've actually heard quite a lot of this information.

So I'll go over it rather quickly.

The virus was first detected in the New Territories between March and May 1997, when three farms were affected with a highly pathogenic influenza virus. Six thousand eight hundred birds were involved, 70 percent mortality. Agriculture and Fisheries identified it as an H5 virus, and it was sent by Ken Shortridge to United States through Ames to be studied, and Dennis Senne showed that it was a very highly pathogenic virus.

In fact, this is one of the most pathogenic avian influenza viruses. It kills chickens inoculated in one day, and as we've heard from Dr. Klimov, it has a series of basic amino acids in the cleavage site of the hemagglutinin, which is absolutely critical for highly pathogenic viruses, and this permits passage from the respiratory tract and for the virus to become systemic and the virus to spread to every tissue in the body, and so the virus essentially caused leakage through every blood vessel, and the virus causes generalized paralysis and hemorrhage and death.

And we've heard most of these properties of this virus, and so I'll pass on. A very small number of changes between the chicken virus and the

human virus I think is the important point to make here.

The other point is that the chicken virus maintained its receptor specificity. The hemagglutinin of avian viruses differ in specificity from human viruses. Chicken viruses preferentially combined with alpha 2-3-6, alpha 2-3 terminal sialic acid, the human viruses with alpha 2-6.

Even after passage in the human, the viruses still maintain this binding characteristic of avian viruses.

And if we look at the hemagglutinin, and this is the top of the trimeric hemagglutinin, this is the groove that the sialic acid is bound in, and the chicken viruses had a carbohydrate attached to residue 158, and this is diagrammatic. If we attach this carbohydrate sitting on here, we're going to influence the binding and probably the antigenicity, and as we've heard, this is an important difference between these viruses. This carbohydrate sitting at these three binding sites is an important difference.

And the other difference we've heard is the deletion in the stork, which is a useful marker, and time will tell whether it plays a role in pathogenicity.

And so to Hong Kong. For those that have been to Hong Kong, this is a typical picture of the Hong Kong island, looking at this huge, modern complex of buildings, and right in the middle of this we have a live bird market, not one live bird market, but in the whole of Hong Kong something like 300 live bird markets, big ones, small ones, and ones that have a few birds to those that have hundreds of birds.

And time will only permit me to briefly deal with some of the findings in Hong Kong. As mentioned in conjunction with Dr. Shortridge, we established an international group at the University of Hong Kong to study influenza viruses. We got started on the 23rd of December, and all of the birds were killed on the 29th of December.

And the markets in Hong Kong at that time contained all of the different species, pigeons, chickens, geese, ducks, Silkie chickens, pheasants, wild ducks. You name the kind of bird; it was there.

And I'll give you the take home message, is that each one of these markets that we examined contained H5N1 influenza viruses. Approximately ten percent or more of the chickens in those markets were shedding H5N1 influenza viruses.

And there was a number -- we have not

processed all of the information yet -- there's quite a number of uncharacterized hemagglutinating agents. Maybe they're bacteria. We don't know at this time. The important feature is that each and every one of those markets had H5N1 in them.

And we'll go on.

And as I said, on the 29th-30th of December, the decision was taken to slaughter all of the birds in the markets and on the farms. All of the chickens were disposed of, and this happens to be a Silkie chicken they're disposing of at this time, these chickens that have the black meat.

And I'll just give you a couple of pieces of information about properties of these viruses found in the laboratory. Since they may originate from wild ducks or migrating birds -- and I would answer this question that was asked a moment ago directly. Hong Kong has a very high number of migrating birds. It's on the flyway between Siberia and Australia, and there is a large number of birds that over-winter there.

In the last week we studied, in conjunction with Professor Shortridge, large numbers of those birds, and in the middle of this time of the year, in the winter, we wouldn't expect to find many viruses. We found on H5N1 in hundreds and hundreds of

samples collected.

So that doesn't mean to say that those birds didn't bring the viruses in because during migration, even in Delaware Bay, you'll only find the viruses there in May. If you look in other times, you won't find them.

So these migrating birds probably played a role. If we inoculate these viruses into ducks, the original Hong Kong human strain and the chicken strain, they barely replicate it in ducks experimentally. There was the original chicken virus, gave 1.5 logs of virus in the trachea. The others, barely anything.

So these suggest to me that this virus came from ducks. It's been out of ducks for quite some time, and I would suggest that if it came from the wild birds, it's probably been in the domestic poultry for some time because it takes some time to accumulate those mutations leading up to a very, very pathogenic virus.

So the chances are it's been out of the migrating birds for quite a long time, maybe years.

Another question is what about pigs. Pigs are looked upon as the intermediate host between avian species and humans, and so we inoculated pigs under

quarantine conditions in laboratories and looked for the replication of the human and chicken virus. Both of them replicated, not to tremendously high titers, but it is important that these viruses replicated immediately in pigs.

So the potential is there for these viruses to spread to pigs if pigs and infected poultry are raised together.

And we've already heard that all of the viruses isolated, H5N1 viruses isolated in Hong Kong belong to the Eurasian lineage, and all of the avian viruses that we've characterized so far all belong to this Eurasian lineage, which says that it certainly wasn't brought in with those chickens that came in from Arkansas, Bob. These are viruses belonging to the Eurasian lineage.

And so in conclusion, this is where we stand. Chickens, the chicken ban is to be lifted. On the 7th of February, chickens will be reintroduced into Hong Kong. There are going to be some changes.

The majority of chickens eaten in Hong Kong come from the mainland, and so the questions are going to be answered now. Did any viruses of the H5N1 come in from the mainland? Probably not.

There's going to be enormous surveillance

now to find out if this occurs. The structure of the markets in Hong Kong are going to be dramatically changed. So far the decision has been taken to reintroduce the chicken. No decision on reintroducing anything else, and I think there will be very careful thought given to the ducks and the geese and the other species that have H5 and, in theory, any other subtype of influenza.

So maybe separation of these species will play an important role in the introduction of viruses from avian species into humans.

So I think that was my last slide. Yes, indeed. I'd just like to conclude by saying that I think the Hong Kong authorities who decided to depopulate the markets probably prevented the next pandemic because if it had been allowed to continue, being an RNA virus, sooner or later it would have acquired that mutation to pass from human to human.

We can't give it up yet. It's going to take months and maybe a year before we can relax because this virus could still be taking over in the human population in Hong Kong.

And I'll stop there.

DR. LEVANDOWSKI: Thank you, Dr. Webster.

I think we have time probably for just one

question because we're really behind, and maybe we'll have to save the other questions and comments for the end and the discussion.

I'm not sure who's first. Dr. Estes.

DR. ESTES: Rob, it's been unclear to me. Were the poultry sick? You said about ten percent of the animals you could isolate virus from. Were those animals sick?

DR. WEBSTER: A very key question. In the markets we were studying, there was no disease. You know, when you have markets with hundreds of thousands of birds in them, you're always going to lose a small number, but, no, there was no evidence of excess mortality in these markets, and that's a key issue.

This virus that will kill a chicken in one day is not killing the chickens in those markets, and so there was no warning that these markets were infected with these viruses. In fact, these markets in my opinion are breeding places for influenza viruses, between the ducks and the geese that are transmitting them to the chickens, and even in the United States it's known very well that the live bird markets in New York City are also breeding places of influenza viruses.

But I can't answer you question. I do not

know why the chickens were not dying.

CHAIRPERSON FERRIERI: Is the practice not to bring a live chicken home and slaughter it at home rather than have it slaughtered at the market?

DR. WEBSTER: I'm sorry. I missed your question.

CHAIRPERSON FERRIERI: Is the custom to bring a live chicken home in Hong Kong and slaughter it there usually rather than in the market?

DR. WEBSTER: Most of the chickens are slaughtered in the market, but you do have the option. If you want to do your own and have it really fresh, you carry it on home, but most of the chickens are slaughtered in the market by the butcher as it were and you carry the freshly slaughtered bird home.

I think it's important to realize that essentially the whole of the population of Hong Kong was being exposed to this virus at any time, and you really couldn't rule out the possibility that this person or that person wasn't exposed.

Right around the corner from the Ramada Inn where I first stayed, there was a little stall, and certainly there was H5N1 in that stall.

DR. NEROME: Did you isolate the virus in the market?

DR. WEBSTER: Yes, to Dr. Nerome, to answer the question directly, yes, we isolated H5N1 from every market that we examined, every market that we examined.

DR. LEVANDOWSKI: Okay. Thank you.

We were scheduled to have a break.

CHAIRPERSON FERRIERI: We can have a five minute break perhaps. I think that would be fair. Five minutes, please.

(Whereupon, the foregoing matter went off the record at 2:58 p.m. and went back on the record at 3:06 p.m.)

CHAIRPERSON FERRIERI: Could we all take our seats so we could resume the afternoon meeting, please? Could we please take seats at the table?

We're running a very tight schedule, and what makes it particularly difficult is that there are several people with burning questions, but it's not compatible with other members saying they need to leave by 4:30. So something has to give here, and so I vote in favor of your asking your questions, that we maximize the worth of our being here this afternoon or there's no point in having convened this session.

And so in order to have full participation and be able to respond to Dr. Levandowski's questions

for us from CBER, everyone has to feel fulfilled that their probing questions have been answered, and so we'll start then with Ms. Cole. You have some questions, and hopefully the responses will be very focused.

MS. COLE: The first question is do they use chicken manure fertilizer in China, and couldn't that spread the influenza?

DR. WEBSTER: They do, indeed, use chicken fertilizer in China, but an important piece of information I didn't provide you with is that we've done the destruction of this virus in feces from markets, and in one day as soon as it's dried the virus is destroyed.

So feces, dried, are not a real source of this virus.

MS. COLE: Okay. I've got one more, real quick.

CHAIRPERSON FERRIERI: Yeah, please. Go ahead.

MS. COLE: The H5N1 in China wasn't really noticed, I'm assuming, until a human was affected. Have any of our poultry workers in the United States been tested for seroconversion?

DR. COX: WE have not collected or tested

serum from poultry workers in the United States recently.

CHAIRPERSON FERRIERI: Any other questions?

DR. WEBSTER: We did look a number of years ago during the chicken Pennsylvania outbreak of H5N2 of humans that were working in those houses, and at that time we did not detect antibodies. Whether we were using the most sensitive techniques we're not sure. We need to go back and look again.

CHAIRPERSON FERRIERI: Thank you, Dr. Webster.

Dr. Clements-Mann.

DR. CLEMENTS-MANN: Yes, I'm just wondering if you know anything about the Mexico outbreak of H5N1.

DR. WEBSTER: H5N2. What was the question?

DR. CLEMENTS-MANN: H5N2. I was just wondering if there was any information whether there is any similarity of the H5.

DR. WEBSTER: The hemagglutinin is very similar, but it belongs to the North American lineage of H5 viruses, and that virus has essentially been taken care of in Mexico. There is still potentially

residual virus in Mexico, but by vaccinating with just a crude inactivated vaccine, they essentially controlled it.

CHAIRPERSON FERRIERI: Other questions for Dr. Webster or anyone else?

I mentioned earlier as I opened the session that several of you have burning questions, and you have to make the decision. Is it compatible with your concomitant desire to leave here at a certain hour?

(Laughter.)

CHAIRPERSON FERRIERI: Seriously, I want you all to feel that you've had a chance to get all of the information you can today from our experts here joining us.

Other questions? Otherwise I'll turn it back to Roland.

DR. LEVANDOWSKI: Okay. We have more information for you. The next section, we want to give some information about activities that are being done in relation to vaccine development, and first on the agenda is Dominick Iacuzio from NIAID. Dominick is going to talk to us about some vaccine trials that are planned with purified hemagglutinin vaccines.

DR. IACUZIO: Thank you, Roland, for

inviting me to be here. I know I don't have much time. So I'm going to try to move quickly through this.

My first slide is -- I apologize to those who know us very well, but for those I feel who are not very familiar with the NIAID and what our role is, we have a long history of supporting influenza and related viral respiratory disease research, both through intramural laboratories on the NIH campus, especially in the laboratory of infectious diseases with Dr. Robert Channick and Brian Murphy, and also through our extramural research facilities, through mechanisms of direct funding of grants for basic research and for clinical research, through various groups of mechanisms, including contracts and CRDAs, for example.

Over the years, the institute has supported various types of influenza research, and I just wanted to preface this because I thought that I need to explain why we chose the route that we did.

When the H5 was first isolated, only one company that I was aware of had an experience of preparing an H5 recombinant antigen. It was the Mexican Jalisco strain, which was just recently, you know, mentioned here, and back in August when the

first report of an H5, we realized that protein sciences at this time was probably the only choice. So we moved quickly.

Next slide, please.

Moved quickly to initiate a contractual agreement with Protein Sciences Corporation to accomplish a couple of goals.

One is to provide GLP grade recombinant HA, and the O stains for uncleaved HA antigen for our colleagues at the CDC, FDA, and USDA. I also learned some of the material was also shipped to our overseas colleagues at WHO and the NIBSC.

Also part of this contractual agreement, we decided that we needed to go ahead at this time since there were no available candidates to make a reassortant strain. Since this H5 was identified to be lethal, pathogenic to the avian, the poultry industry, the USDA had restrictions on working with this to provide -- which is through the, you know, traditional means of reassortant for inactivated vaccine.

The recombinant technique that Protein Sciences Corporation has pioneered allowed us, we felt, a quicker way under these circumstances to at least initiate an experimental recombinant HA H5

vaccine, and we also -- we decided at that time that we would move ahead and take this opportunity under this urgent and compelling need in December after we learned of additional cases, not knowing what would happen in the weeks to come. We would plan a Phase 1 clinical study.

Next slide.

Part of the justification to even proceed was, like I said, our previous experience in working with Protein Sciences and with this particular product. A few years back, we were pursuing with Protein Sciences a different path. The experience was with H3N2 -- excuse me -- an H3 HA antigen, and we had actually five clinical studies that were conducted.

In addition, as you can see, the third one down, we also started the clinical work with an H1 antigen, and so for a total of these, I guess, five studies over those I believe it was two years, over 500 subjects were immunized with the recombinant HA vaccine.

So we had some idea of previous safety immunogenicity in young adults and in elderly and at various doses, 15 through I think we had gone up to -- the highest was 135 micrograms.

Next slide.

A lot of this data I don't have time to summarize, except stating that all of this information has been published. There are four publications which are listed here regarding the various studies. Dr. John Treanor, who was here earlier in this room, had participated in several of these studies, as did Doug Powers from St. Louis.

Back to what this recombinant HA influenza vaccine is. It's a purified recombinant hemagglutinin monovalent Type A, and the Protein Sciences has worked with the CDC to correct HA genes cloned from CDC material, and that information was just recently published by the CDC in Science.

This recombinant protein vaccine is produce in a bacolovirus expression vector in serum free spotopetera frugiperida insect cells.

For this particular H5, since this has only recently been manufactured, we have this information that's been shared by Protein Sciences, that initial analysis has shown there's full length glycosylated, uncleaved. I guess there is a portion of the recombinant HA, that is, that has recently been identified as also being cleaved with this H5. It may be something unique with this, but Bethany Wilkinson from Protein Sciences is here, and she could answer

more technical questions.

The molecular weight is 68,000. It's I think much greater than 95 percent pure, but that's for the specs. that they have written. It's trypsin digest resistant. It agglutinates red blood cells, induces hemagglutinin antibodies, and there is actually preclinical data on this particular H5 recombinant HA that Dr. Mike Perdue from the USDA has recently completed some studies, and I believe he's here in the audience also, but because of time restraints, I really didn't have the time to get him up here to talk about his data.

Since the decision had to be made early, we learned of the additional three and four cases on December 6th, and quickly we decided that as apparently as the cases started to be tallied, that something had to be done.

We at that time decided, based on the capabilities of scaling up of the recombinant HA and conferring with Protein Sciences and also reviewing the data I had just passed in front of your eyes quickly on the HA H1 and H5, that we decided that a ten micrograms per half a mil dose would be appropriate for a Phase 1 type study.

The company, of course, in filing their

master file with the FDA, which they recently, I believe, have just submitted, will include -- has included -- is including, I believe, the final sterility testing and animal safety test and identity test.

Now on to what we want to do with this material. The NIAID is sponsoring a multi-center trial, and primarily it is for the adults and laboratory workers and health care personnel.

Again, to go to the top, we decided on two doses of a ten microgram per half a mil dose. The two doses are separated by a three week interval. That's a compromise, and I could discuss that later on if possible, the decision why we went ahead with that.

The primary endpoints, of course, for this Phase 1 would be safety and immunogenicity, and we would assay the immunogenicity by the gold standard being, of course, discussing this with Nancy Cox, the virus neutralization assay, but also, we would also conduct ELISAs, and Protein Sciences, I think, is working with Mike Perdue on working out the problems with the HA1 assay.

Currently we started off with two sites, to immunize the workers at the CDC and the FDA through the NIH site, but since that time, there have been

additional inquiries to also have the laboratory workers immunized with this experimental vaccine.

So we're up to five sites now, and there are two or more international sites -- actually there are two sites that we have contacted or been contacted by who are interested in participating in this study, and we're working out the details.

We realize that this is an opportunity to gather information on a novel antigen which hasn't been seen in the human population before with a two dose regimen, but we also recognize that it's also an opportunity to gather more information than what can be gathered in a simple Phase 1 type study.

So there are plans, and we are working with John Treanor and others in our vaccine evaluation units to design a Phase 2 sort of study. Basically what the idea is is to vary the concentration of the primary dose, vary concentrations of the boosting dose, and also to look at the intervals between the two doses.

And that's all I have to say right now.

DR. LEVANDOWSKI: Okay. Thank you.

Is there time for a question? Shall we take questions now, Dr. Ferrieri? I'm asking you for advice.

CHAIRPERSON FERRIERI: Yeah, I think --

DR. LEVANDOWSKI: The time is very short.

CHAIRPERSON FERRIERI: I think that would be appropriate, you know, a question or so.

Mary Lou.

DR. CLEMENTS-MANN: From what I remember about the previous vaccine trials, the dose required to induce a good immune response I thought was around 45 micrograms, and also alum was required as an adjuvant.

DR. IACUZIO: In the first study, alum was used with a 15 micrograms and then without, and actually in that study the alum was not -- you know, we didn't see a difference, and the decision was, you know, not to go with alum anymore, except for that first study.

The 45 microgram dose, I believe, looked as good as or better than the current inactivated vaccine, but we also recognize that that was a single dose regimen. I guess the rationale here is that this would -- a novel antigen, that we would need two doses, and that subsequent studies, I believe, show that 15 micrograms was as equivalent.

Is that true, you know, Bethany, from what I remember?

So that was sort of our decision. Yes.

DR. LEVANDOWSKI: Dr. Huang.

DR. HUANG: Has it been done or are you planning to use this to protect chickens against the human isolate that killed a chicken in one day?

DR. IACUZIO: Actually that has been done, and Mike Perdue has actually done that clinical study. Mike, do you want to?

DR. PERDUE: I'll say something quickly.

Yes, a single does in two week old birds of about six micrograms was 100 percent effective at preventing disease and death in these birds, but I would echo what Dr. Webster referred to earlier, that vaccination of chickens is actually pretty easy against these subtypes. Within the H5 subtype, you can protect against lethal disease very readily by a variety of activation techniques.

DR. LEVANDOWSKI: Would you please identify yourself for the recorder?

DR. WILKINSON: Sure. Bethany Wilkinson from Protein Sciences.

And we are, in fact, trying to license this for immunization of chickens throughout the world, and we were trying to emphasize in China and Hong Kong and wherever we think this might be a

problem, but possibly the U.S. There are some questions and recommendations for vaccinating chickens in the U.S. just as a potential insurance against any kind of problems here.

DR. COUCH: What kind of vaccine is being used in Mexico? Just an egg grown vaccine in a conventional way?

DR. WEBSTER: This was an inactivated allantoic fluid.

DR. COUCH: Allantoic fluid inactivated?

DR. WEBSTER: Purified, treated, and not standardized and used.

DR. LEVANDOWSKI: Okay. I think -- oh, Dr. Poland, do you have a question?

DR. POLAND: I may have missed this, but I heard a description of two different clades of the virus. Does this particular recombinant -- would be sufficient for either of those or is it directed more toward one?

DR. PERDUE: Mike Perdue again.

Probably so. I think Dr. Webster would agree. Actually we've done some studies with turkey, Wisconsin 68, a North American lineage sort of prototype, and it protects against the Hong Kong 156 quite adequately in a kill vaccine, as does Dr.

Webster's original turkey RM-83 construct, I think, in the fowl pox regular vaccines.

So within a subtype they're probably going to protect very well against lethal disease. Now, replication of the virus in shedding is a different story. You would certainly want to be as close to the original isolate to vaccinate it as you could.

DR. WEBSTER: This raises a very important question. I mean if we're thinking of vaccines for H5N1, there's a difference in protecting people from death and from infection. Please have to keep that in mind as the dose that may be considered in the face of pandemic.

DR. LEVANDOWSKI: Okay. Thank you.

We're going to move on now and talk about some of the other activities that are going on in terms of reassortants and reagents that are being produced to try to support vaccines, and first Dr. Nancy Cox is going to speak about what's going on in CDC.

DR. COX: Now, I'd like to start by saying there's really a lot of work on vaccine development going on in many laboratories around the world, and I'm going not to steal anyone else's thunder. I'm just going to go through some of the special

considerations for vaccine candidate development that we have for these H5 viruses.

First of all, we must consider safety of laboratory personnel and the environment. We wanted to do everything we possibly could to protect laboratory workers and to eliminate the possibility that the virus could get out and infect birds in the United States.

There are strict USDA regulations requiring Level P3 plus containment for working on these highly pathogenic or influenza strains that are highly pathogenic for birds, and the P3 plus simply means that in addition to the regular P3 requirements, you have to shower out.

We have been, first of all, attempting, and many other people around the world have been attempting, to identify surrogate apathogenic avian viruses that could be used either without modification or after reassortment with APR-8 or other strains and would make suitable vaccine candidates without any further manipulation.

We also and many other people have been working on strategies to remove the multiple basic amino acid cleavage site in the hemagglutinin. This cleavage site, as we've heard, is associated with

these highly pathogenic strains, and we would then be trying to rescue that modified hemagglutinin gene back into an appropriate genetic background.

In addition to the usual testing that goes on, we feel that testing potential vaccine candidates for pathogenicity in animal models will have to be done this year, and we would expect that any potential vaccine candidates might be well tested in chickens and mice and possibly ferrets.

Of course, in addition, we need to consider that the growth and processing characteristics of these vaccine candidates need to be suitable for vaccine production.

So first of all, I mentioned that we were looking for related apathogenic avian viruses that were antigenically as similar as possible to the recently isolated human strains, and the one that has been explored in greatest detail is the A/duck/Singapore 97 H5N3 strain, and in many respects it does look like a suitable candidate, except that it has the wrong neuraminidase.

I would say that the studies are still preliminary. We're trying to get antiserum with a high enough titer to this duck/Singapore virus ferret antiserum so that we can do cross-tests, and we have

had a bit of difficulty, as have other laboratories, in getting a good ferret antiserum for these studies.

The second approach I mentioned was that we would make a human avian or a human or an avian-avian transfectant after modifying the HA cleavage site. So what we're trying to do is to rescue the N1 of the Hong Kong strain into a PR-8 background or into the mallard background.

And if we go on to the next overhead, what we've actually done at CDC to date is by using the X-31 H3N2 Aichi PR-8 reassortant and crossing that with a Hong Kong 156, we've made a 7:1 H3N1 reassortant, which will have a suitable genetic background for rescue of the modified HA gene from the Hong Kong 156 or Hong Kong 483 prototype strains.

We've also used the A/mallard/New York 78 H3N2 reassortant which we received from Brian Murphy, and this virus contains its internal genes -- its internal genes are avian genes, and we've reassorted that with the Hong Kong virus and have a 7;1 H3N1 reassortant, which also would be a suitable genetic background for rescuing the modified H5 HA genes.

Next, please.

Using site directed mutagenesis, we've actually altered the multiple basic amino acid

cleavage site, and I won't go through all of the details here, but we're modifying it in a couple of different ways, actually three different ways, but I've simplified it here so that we're converting this site to the avirulent cleavage site and also to the cleavage site typical of those found in human strains.

We now have PCR products with T3 promotor sequences and restriction enzyme sites, which have been constructed from cloning and generation of transcripts for gene rescue.

We have been working fairly closely with Averon in discussions of strategies for altering the cleavage site and rescuing the HA genes, and in the future we will be trying to rescue the modified HA genes using our 71 reassortants and anti-H3 antiserum to select the H5 HA and will be using qualified cell lines, and hopefully they would be suitable for vaccine manufacture.

Again, we would need to test the candidate vaccines for attenuation, and we are continuing our assessment of the duck Singapore virus as a candidate vaccine strain.

And what we've also been trying to do is to provide nucleic acid to companies and other interested parties who would have alternative

strategies for vaccine development. So we provided the PCR product or the full length H5 HA gene to Protein Sciences and will be providing similar materials to Drs. Harriet Robinson and Dick Compans. We provide also nucleic acid to Averon for their work, which I think will be discussed a bit later.

So probably unless there are any pressing questions, we'd want to move on and maybe questions on vaccine development could be handled at the very end of the presentations to save time.

CHAIRPERSON FERRIERI: Thank you, Dr. Cox.

DR. LEVANDOWSKI: Okay. Thanks.

Next, John Wood from NIBSC will speak to activities that have been going on in England.

DR. WOOD: I apologize that this is a handwritten overhead, but I only found out it was on the agenda yesterday afternoon.

The activities at our institute, first of all, to make ferret antisera for strain characterization, and as Nancy indicated, this is no mean task. It's quite difficult with these pathogenic viruses to produce good antisera. So we have produced three reasonable antisera so far, and also we have a high premium in our sheep serum against chick/Scotland 59, which is an H5N1 virus, and this is really broadly

reactive against all of the H5s that we've examined. So it's a very good diagnostic reagent.

In terms of vaccine strains, we are trying to produce a reassortant between the duck/Singapore 97 virus that Nancy just mentioned, the H5N3 subtype, and a swine virus, swine/Eire 97, H1M1.

Can I just have the next overhead, please?

This just shows phyllagentic tree of the H5 hemagglutinin gene, and here we have the Hong Kong 156 and chicken/Hong Kong HAs here, and here we have duck/Singapore, which is genetically quite closely related antigenically with the ferret sera from NIBSC and from Millhill, is also closely related to Hong Kong 156.

The next one, please.

The N1 neuraminidase, these are the N1s from a variety of Hong Kong viruses. This is an N1 from turkey/England, which is a pathogenic strain. So we couldn't use this virus to donate the N1, not easily anyway.

And these are swine viruses isolated from Ireland, and these are H1M1s of avian origin. So the N1 is quite close to an avian N1. So we're taking one of these viruses to donate the N1.

Could I go back to the first one, please?

Now, we've been trying since the beginning of January to do this, and it has proved to be quite difficult. One of the difficulties is that the swine virus grows nearly as well as PR-8, and the duck virus is really very bad. So you have an unbalanced ratio of virus infectivity, and we don't have very good antiserum reagents to inhibit the -- sorry. The N1 should be underlined there -- to inhibit the H1 hemagglutinin, which is of avian origin, and the N3 neuraminidase from the duck/Singapore virus.

So it has proved to be quite difficult. We've seen PCR evidence that we have an H5N1 reassortant, but actually getting that to clone out has been quite difficult.

Moving on to reagents to test vaccine potency, and this is for the future, we've used the Protein Science bacolovirus H5 hemagglutinin to immunize sheep, and we have one sheep that's actually being let out this week back in England, and this has very good antibody against H5 hemagglutinin and could be a very useful serum reagent in the SID test.

Obviously the antigen we would use depends upon the vaccine that's used in the future because the antigen has to be antigenically a very good match with the vaccine.

And then finally, serological tests. You've heard that HI tests are -- there are difficulties measuring antibodies in human sera to H5 using the hemagglutination and inhibition tests, and the virus neutralization test is the one that's been used routinely, but the problem with that is that you need a containment lab to do this in. We would really like to have a serological test that you could do easily.

And one possibility is to use the single radial hemolysis test. We have some provisional data that this works with H5s. What we have to do is to establish without question that it's measuring specifically antibody to the hemagglutinin and not to internal proteins. So this is ongoing work at the institute.

Thank you.

DR. LEVANDOWSKI: Thank you, John.

I'm next on the list, and I'm going to be extremely brief about our activities. Many of the things that have been mentioned already are activities that we will be involved in also, including work to develop reassortant viruses.

One thing that has not been emphasized, but probably should be, the laboratories that are

involved in producing reassortants every year, multiple sites are involved in this process, and one of the reasons for that is that often time is very short to try to produce the reassortants, and a little bit of luck is involved in it.

But in addition, the reassorting process itself is somewhat different at different locations and for reasons that aren't entirely explained. Reassortants that result sometimes are somewhat different in their antigenicity.

So we think it's probably important that multiple laboratories are involved in this kind of activity in order that at the end of the day at the time that we'd like to have it, we do have something we think is antigenically appropriate, not to mention the fact that it can be useful for vaccine production.

Our own experience has highlighted something that perhaps needs some further discussion in the influenza community generally, and that's the difficulty in finding laboratory space that may be considered appropriate for working with some of these different types of strains in order not only to protect the laboratory workers, but also to protect the environment.

And in that regard, I think that in

discussions that we've had going on that are related to the development of reassortants, some considerations have been expressed that we need to think about what's happening in terms of the producers of the vaccine and their needs as well in terms of these strains and how they will be -- how the workers in their facilities may be exposed to working with them.

In terms of other things that we're doing, we are doing -- we also are making reagents for the H5. As Dominick indicated, he's made available; he and NIAID have made available to us the purified hemagglutinin from Protein Sciences, and we, too, have immunized sheep and have sheep that are ready for bleeding probably within the next week.

Those reagents will be very useful not only for the purposes of making vaccines, but as they have been used in the past, they can also be used for surveillance purposes. So it may support that.

Our concerns overall are that this may be a reagent that's useful initially, but we're not really certain whether it will be the final reagent that needs to be made and will want to continue to observe closely, and as other strains come up, we'll probably want to get some experience with those, as

well.

I think I probably won't say anymore than that at this point because the time is so short, and we do want to have some discussion from the Committee on the comments.

Before going to that, there is a section that we have reserved here for comments from manufacturers, and I do know that we have one of the manufacturers. Averon are very interested in giving a brief presentation about their activities with H5 strains, and I'm not sure who's doing it at this point. I think it will be Dr. Sing Chung Lee from Averon.

DR. LEE: In collaboration with CDC, Averon is developing vaccines against the posigenic H5N1 virus. In our studies to fulfill the pandemic preparation we tried to complement CDC and the FDA's strategy by preparing live attenuated vaccine candidate which could be other used for -- also safe substituted for manufacturing of the inactivated vaccine.

Also, Dr. Cox just mentioned we are collaborating with CDC, particularly Dr. Sabraro (phonetic) and Dr. Cox, also Dr. Klimov (phonetic).

CDC has provided us materials, sequencing

information which we need for our approach. In return Averon is providing materials and reagents to CDC which may help CDC to develop their recombinant vaccine.

In addition, we have also collaborated with Dr. Adams and Dr. Hietala from UC-Davis, and Dr. Perdue from USDA for P3 plus containment and for animal intestine.

We've taken two approaches to develop the vaccine candidates. The first approach is based on using antigenic, and very similar, but not pathogenic avian strain, as Dr. Nancy Cox just mentioned to you, which is A/duck/Singapore 97 virus.

What we are doing there is we take this virus and try to reassort it into our stable attenuated code adapted influenza virus master strain vagrant to generate candidates which bearing HA agent from the low pathogenic avian strain and the remaining genes from the code adapted master strain.

The similar approach which we are taking is based on also -- similar also Dr. Cox just mentioned -- to mutate the HA gene <u>in vitro</u> and then use the recombinant technology to transfect the mutated HA gene together with the latent for NA genes into the code adapted master strain vagrant.

Our rationale behind our approach is based on our experience with reassortant vaccines based on code adapted influenza virus. We have generated more than 30 vaccine candidates, and we show they are safe and efficacious in human. They are known transmissible. They are genetically very stable, and importantly, they are capable of indicating higher titers in eggs and the chicken (inaudible).

And in addition, reassortant vaccine were prepared from both avian and human isolates.

I will briefly describe to you about the recombinant approach and how we use this technology to generate the reassortant virus. Basically it is a two stage transfection of the HA and the NA agents of wild type virus into the code adapted virus vagrant.

So initially we have a 7:1 intermediate and subsegment (phonetic) of wild type gene where it is transfecting to the 7:1 intermediate to generate a 6:2 master strain, which we occur (phonetic) just for our testing.

Averon has quite a bit of experience with this recombinant approach for generation of vaccines. In fact, we were able to generate five different recombinant candidates from both type A and type B wild type viruses in three different master donor

virus strains that included a code adapted type A and type B master strain in the PRA virus that could be used for the inactivated vaccine.

The recombinant approach is rapid, controllable process, and it is important in pandemic situation that timing may be an important issue, how fast we could prepare the vaccine.

In addition, the recombinant approach require on work with RNA template. So we don't need to work with the infectious virus. That could reduce the risk of contaminating with the higher pathogenic H5N1 virus.

Dr. Cox just mentioned we have quantified vaccine cell line capable of transfecting the influence of also RNP, and in addition, we also have experience on the code adapted recombinant reassortants in Canadian (phonetic) trial.

Let me briefly discuss with you about our mutagenesis strategy, which is kind of identical or similar to what Dr. Cox just mentioned to you. Basically, also you know we have two subgroups from the Hong Kong isolate. We prepare three candidates from both subtypes -- subgroups. I'm sorry.

So in the candidate one, basically we need the five basic amino acid, and then we can decide. In

the candidate two, we are adding one serum in bag, into the construct of candidate one. So the candidate two, we are looking like no pathogenic H5 cleavage site.

In candidate three, we totally change the cleavage site of the high pathogenic H5N1 HA into our H2 subtype cleavage site like sequences.

All construct was carefully designed based on attenuation, based on stability, and based on viability of the construct.

Let me give you an update of the progress which we made and the fact that we were able to use the P3 plus facilitated the use of Davis one week or so ago, and we made some progress there. I just want to single out we were able to transfect the modified HA into the code adapted virus background to generate a 7:1 intermediate. I think this is nice correlation with CDC's colleague, CDC about their approach. In fact, they were also able to make a 7:1 virus, and I think together we will be able to make any recombinant vaccine.

In addition, we also been able to transfect the NA into the code adapted virus background. Right now what we try to do is to take the 7:1 intermediate and try to transfect the second

wild type of gene into this construct to make candidates, which we plan to test in animal, first in chicken and in ferrets for its safety before we could consider it for testing safety in human.

The first approach I just mention to you is, in fact, what happens is we are applying our USDA permission to work with low pathogenic A/duck Singapore strain. However, the permit is still pending, and we're hoping we could get the permission as soon as possible so we could start the first approach.

Thank you for your attention.

DR. LEVANDOWSKI: Okay. That concludes our presentations, and I will turn the rest of the time over to you, Dr. Ferrieri.

CHAIRPERSON FERRIERI: Thank you very much, Roland.

Is there anyone else from industry who wanted to make a statement at this time?

Protein Sciences has been adequately represented or not? Any further comments?

DR. WILKINSON: I'm sorry?

CHAIRPERSON FERRIERI: I said do you feel that you've been adequately represented or do you have any other comments from Protein Sciences?

DR. WILKINSON: I think we've been adequately represented, but if there are anymore questions, we could address those.

CHAIRPERSON FERRIERI: Thank you.

Any questions? Dr. Couch.

DR. COUCH: Well, maybe we know the answer, but we've heard a good bit about the ongoing efforts of Protein Sciences and Averon. Do any of the manufacturers have any involvement so far in the laboratory at even early stage of thinking and looking at H5N1 possibilities? The current manufacturers.

DR. VOGDINGH: No, we don't.

DR. COUCH: Zero.

CHAIRPERSON FERRIERI: Well, I'm quite impressed with what we've heard from these other two firms and the progress that has been made.

Yes, Dr. Levandowski.

DR. LEVANDOWSKI: Could I just mentioned that in response to that question I think there is some progress that has been made in the sense that there are ongoing discussions as there always are with the manufacturers so that they understand where things stand in terms of what might be required of them when the time comes.

This goes on all year long, and it's part

of our regular interactions with manufacturers. They need to be in the loop, so to speak, on all of the issues.

DR. COUCH: Could I ask another question then? It might be a little bit more specific.

CHAIRPERSON FERRIERI: You bet.

DR. COUCH: I assume that the manufacturers, and as we would, are committed to preparing the trivalent vaccine that will be available for the market this fall. If we should make a decision that we'd like to have trial vaccines for development purposes, how much lead time to do have to have for ordering the egg to make additional vaccine, or is that feasible at the present time?

CHAIRPERSON FERRIERI: Would one of you like to --

DR. COUCH: Well, Bill points out it kills eggs, but you'd have to tamper with that, an earlier harvest or altered antigen to prevent that. That would be a qualifier for the vaccine preparation.

CHAIRPERSON FERRIERI: Yeah, that's quite a qualifier.

Yes, Dr. Edwards.

DR. EDWARDS: how widely available are these strains? Are there restrictions placed on who

you will send these strains to and how are they being managed?

CHAIRPERSON FERRIERI: Good question.

DR. COX: That's an excellent question, and there have been very extensive international discussions about the distribution of these particular strains, and the discussions were important because not only is there a danger to human health, but there's a very well defined danger to animal health.

And so it was decided that the strains should be distributed to only those laboratories that get a USDA permit and have the proper facilities for containment.

So that's part of the equation and part of the reason that the manufacturers haven't been sent these strains in advance. They simply don't have P3 plus level containment to be able to work on these strains.

Roland, would you like to add anything to that?

DR. LEVANDOWSKI: No, I think that sums it up. I guess that's something that I should have been saying, but I'm sort of assuming this, being a little bit -- what should I say? -- sleepy right now.

(Laughter.)

DR. LEVANDOWSKI: From all of the preparations that have been going on, but, yes, that's true, and I think I alluded to that. I maybe didn't make it direct enough in my other comments.

There is a concern about containment for these strains, and that would be a reason that the manufacturers would not be working with these unless there's a serious intent to do something and we know they can do it safely and they know that they can do it safely.

CHAIRPERSON FERRIERI: We have two critical questions to address today, but before we start on that, I might say we're only five minutes off from the schedule that was prepared for us, and there are some of you who think I prepare the schedule. I don't.

But this is an opportunity for those of you who have felt that your questions have not yet been delivered to do so. Dr. Broome, would you care to open up a few? You had some questions on your mind. Do you still have them?

DR. BROOME: Well, one question I'd like to pursue a little further is a question that Bob had raised earlier as to the magnitude of the difference between Group 1 and Group 2 human strains of Hong

Kong, and I'm a little puzzled by the ferret antisera results because it appears that the Group 2 antisera titers are higher for the Group 1 strains than the Group 2.

I just wondered if someone could explain that to me.

DR. COX: We have very little experience with ferret antisera to these strains. Ferrets are having to be boosted. So in other words, a single intranasal infection doesn't produce a high enough titer.

It does look like the antiserum to the Hong Kong 483, which is a representative of Group 2, does a better job in inhibiting all of the viruses both in Group 1 and Group 2. So we have to explore that further with additional antisera.

We also need to have, as I mentioned before, the ferret antisera to the duck Singapore strain and see if its antigenic profile matches well enough and if the antiserum to it will inhibit viruses in both Group 1 and Group 2.

I think that some animals experiments would be very useful in looking at cross-protection. Although they might not be definitive for humans, they certainly would be very interesting, and I think those

experiments will be ongoing.

CHAIRPERSON FERRIERI: Anything else, Claire, you can think of at the moment?

DR. BROOME: Well, I have lots of questions about the animal epidemiology, but maybe it would be helpful to just try --

CHAIRPERSON FERRIERI: Well, I like that --

DR. BROOME: -- to sort out the -- you know, is there anything further that can be said about the antigenic similarity or dissimilarity of Group 1 and Group 2 because I think that's absolutely key in sort of saying whether we know what candidate you would even propose?

CHAIRPERSON FERRIERI: Dr. Cox, do you want to address that?

DR. COX: We have gone ahead and modified. Because we don't have a definitive answer at this time, we're pursuing prototypes of both Group 1 and Group 2, and I think that's about all I can say at this time.

We will have additional ferret antiserum within the next couple of weeks, and hopefully those sera will help answer the questions, but we are pursuing prototypes of both groups so that we'll have

them available.

DR. APICELLA: Which one --

CHAIRPERSON FERRIERI: Dr. Apicella?

DR. APICELLA: Excuse me. You know, which one is the strain that the gene has been sent out on? Is that 156 or 483?

PARTICIPANT: One, fifty-six.

DR. APICELLA: One, fifty-six?

PARTICIPANT: Are you talking about the Protein Sciences'?

DR. APICELLA: Yeah.

PARTICIPANT: It's 156 or 157.

DR. COX: One, fifty-six.

DR. APICELLA: And Averon also, I assume, the same.

CHAIRPERSON FERRIERI: The same strain, Dr. Cox?

DR. COX: They have 156 and 483.

Dr. Apicella, and then we'll get back to you, Dr. Couch, or did you want to pursue that point now?

Mike.

DR. APICELLA: This is maybe a naive question from a pathogenic bacteriologist, but this is for Dr. Webster. If I was told that I had a strain

that killed an animal in a day, I'd be thinking about a toxin. Has anyone looked at these strains for super antigen production or some other antigen that could act as a toxin in the animal?

DR. WEBSTER: No. The actual mechanism of death in the chicken is not well established. There are lots of things to be done. Whether a cytokine induced or -- no, I can't answer the question.

CHAIRPERSON FERRIERI: Patients who have died have not had hemorrhagic diathesis, have they?

DR. COUCH: No.

CHAIRPERSON FERRIERI: Have they had hemorrhagic diathesis, all of them?

DR. COUCH: Most common virus disease leading to disseminated intravascular coagulation is influenza.

CHAIRPERSON FERRIERI: And you think that prevails here in these patients, as well?

DR. COUCH: Well, apparently the first case also had DIC, in Reye's Syndrome, DIC.

CHAIRPERSON FERRIERI: They're complicated by the other problems going on.

DR. FUKUDA: Actually, you know, several of the cases have had coagulopathies associated with their case. They haven't had overt bleeding, but

their PTA PTTs have been off and low platelets.

CHAIRPERSON FERRIERI: Could we pursue a couple of quick animal questions, Dr. Webster? I didn't quite remember whether or not ducks were positive and were susceptible to these strains, and they were not sacrificed in the first tier of what's been going on, the massacre going on in Hong Kong, the chicken massacre.

DR. WEBSTER: You ask a very important question because when these highly pathogenic chicken viruses are put into ducks, there's no pathogenicity at all, but the ducks usually shed. Experimentally the ones that were inoculated shed very low titers, but there's differences in breeds of ducks.

The important thing is both ducks and the geese can be infected totally nonpathogenic. Part of the history of these pathogenic avian influenza viruses where the ducks is not a figure.

CHAIRPERSON FERRIERI: Because --

DR. WEBSTER: A wonderful passenger in these markets for having the virus.

CHAIRPERSON FERRIERI: Well, we're interested in reservoirs that might persist after the chickens have been eliminated. The chickens will continue to be monitored, but many of us can't help

forget the photos of chickens who had managed to survive the first attempt to eliminate them and ran around Hong Kong, and they were sick.

The potential was there perhaps to infect other animals. Do you know if rodents have been cultured? Are rodents susceptible to the virus?

DR. WEBSTER: There has been surveillance done in conjunction with Dr. Shortridge. Mice and rats and dogs and cats have been tested, and there is no evidence at this time that they're susceptible.

So I would like to comment on this infected chickens running around Hong Kong. I think the press was rather irresponsible. I think the authorities in Hong Kong did a fantastic job in getting rid of the chickens in the markets in a very short time, and if you can imagine trying to get rid of 1.6 million chickens in one day and to train people to do that and not have a few misfortunes, then you're just God-like, and it can't be done.

There were very few incidences of chickens running around Hong Kong. I can assure you there weren't, and they have very successfully removed infected chickens from Hong Kong.

There are chickens on the ground in Hong Kong. They are not infected as far as we know with

H5N1.

CHAIRPERSON FERRIERI: Thank you. That's very reassuring, Dr. Webster, and I agree with you that unfortunate photos got into the newspapers.

Other comments from the panel or shall we move on?

Dr. Broome, yes.

DR. BROOME: I just wondered if you could clarify how a virus which resulted in 70 percent mortality in the chicken farms would be found in all of the bird markets with no apparent illness.

DR. WEBSTER: That's a question that we have to resolve scientifically over the next several months. There are several possibilities.

We're talking about a different breed of chickens. We're talking about the -- you saw the pictures of the chickens. These are red chickens. We use white chickens in the United States to determine pathogenicity.

There are genetic differences between these birds. I can't give you an answer at this time, but I think within a matter of months when we resolve the complete picture of what was going on in these markets we will come up with an answer on that subject.

CHAIRPERSON FERRIERI: Dr. Clements-Mann.

DR. CLEMENTS-MANN: Yes. I just was wondering, given -- I mean, just in the preparedness spirit, wouldn't it make sense to go ahead and prepare the reassortants or at least to make a prototype inactivated vaccine and do some clinical testing just to be that far ahead while we do have time?

I just wondered what the real plan is there.

CHAIRPERSON FERRIERI: Who wants to take that one on? Dr. Cox looks interested, but --

(Laughter.)

DR. COX: We're asking for advice from the Committee actually no that. I think that there's a general consensus that this would be a prudent thing to do, and we hope that there is agreement here in this room that we should proceed with the preparation of suitable vaccine candidate strains and they should be used in clinical trials.

CHAIRPERSON FERRIERI: This is a great entre then for us to move directly to the level of urgency, three words of the day, the rest of the day.

Number one, please comment on the need for immediate production of H5N1 vaccines for general use or for use in developmental clinical trials.

Who wants --

DR. WEBSTER: I have to leave to catch a plane.

CHAIRPERSON FERRIERI: Sorry.

DR. WEBSTER: I would urge you to go ahead immediately with the preparation of vaccines. You have no assurance that these viruses are not still in Southeast Asian, either in human or in the duck population. So you have a window of opportunity to do it. Do it now.

CHAIRPERSON FERRIERI: Thank you, Dr. Webster. We appreciate all of your contributions today.

How do you feel about this, Dr. LaMontagne?

DR. LaMONTAGNE: Well, I think it's actually important to try to develop some of these vaccines. That's why we took the steps that we took in December to get at least a purified HA vaccine produced.

I think there are logistic problems, some of which Nancy mentioned a moment ago, which the manufacturers are quite sensitive to and the USDA is quite sensitive to in terms of making an inactivated influenza vaccine in the conventional manner.

So I think working through around the strategies that were described by the Averon group and by the Protein Sciences group and also by the CDC and FDA groups, I think we will be able, one hopes, in the next several weeks to really make a decision as to whether or not we can make a conventional inactivated vaccine along the lines that Dr. Clements-Mann was suggesting.

I think we do need to do that, and we're fully prepared to try to do whatever we can to see that that happens.

CHAIRPERSON FERRIERI: Dr. Kilbourne, what is your reflection on this point?

DR. KILBOURNE: Well, I agree absolutely with both Dr. Webster and Dr. LaMontagne. I think that what always happens and what's happened in the past every time we have this kind of pandemic alert is there's an enormous amount of interest by everybody in the situation, and the minute it starts to ebb away, the interest ebbs away and the momentum.

I would urge even if somebody promised you there was never going to be another case of H5N1, that this should be a paradigm for doing some of the kinds of clinical trials that I think were mentioned by others.

You have the opportunity to put a potentially dangerous antigen which need not be in dangerous form when it is used in trial by the methods we heard about and put it into a completely susceptible population, immunologically virgin, and find out how they will respond, and we can bring other changes on this.

So I would think not only should a vaccine be made, but there should be clinical trials of this vaccine.

CHAIRPERSON FERRIERI: We'll get to the second point in a moment.

Dr. Karzon, what are your thoughts on this?

DR. KARZON: I would like to commend the early entry into this project on the part of the NIH with a new actor in vaccine development at the operational level at any rate, if I remember, and the CDC, and what I would like to ask, if I vote for progressing, which I will, I'd like to know how long it's going to take.

There are so many if, buts, and ands in the development of this process which are unknown. It would be very useful to be able to project what we will learn in trying to do something about it if we

wish to.

CHAIRPERSON FERRIERI: Nancy or John, would you like to respond?

DR. LaMONTAGNE: Well, David, that's very difficult to predict. I mean if your question really relates to whether or not we can go ahead and make a conventional inactivated vaccine of the traditional formulation that we've been using in the United States for the last 20 years or so, I think that's going to depend on which antigen one selections, and the choices are limited and perhaps not ideal if one were to go ahead today.

I mean, you're either going to have to use something like the A/duck/Singapore strain or another A virulent virus of that type.

So I think once that decision on what antigen to include, I think it could move fairly rapidly assuming that we could get it produced in a reasonable way. I don't see that that would be necessarily a problem.

But I think you're talking about months rather than weeks or days before one would have such a vaccine.

CHAIRPERSON FERRIERI: Nancy, do you have a little comment on that?

DR. COX: Yes, I agree. It will be months before we can get appropriate candidates, get them tested for safety, and actually get some clinical trials underway.

CHAIRPERSON FERRIERI: FDA has not asked us for a formal vote on this, but I really feel that it would be important for us to get the sense of the Committee. The strength of our thoughts on this could give a great deal of impetus and support to all of the federal agencies involved, and I would like a show of hands of the Committee members and the temporary voting members who are moving ahead for immediate production, appreciating what "immediate" means, that it's not going to be days or weeks.

Could I get a feeling for the support of moving ahead with the production of the H5N1?

(Show of hands.)

CHAIRPERSON FERRIERI: That's superb. It's unanimous, and we'd like to convey the strength of our thinking on this point.

This is not an impetuous approach. I think we've got to be prepared. Our thinking reflects the considerable data we've heard at this time and some of the preliminary information we heard back in December.

I'd like to -- yes, Dr. Eickhoff.

DR. EICKHOFF: Could you sort of put a qualifier around this, or at least I would like to put a qualifier around this?

CHAIRPERSON FERRIERI: Sure. Let's hear it.

DR. EICKHOFF: First of all, I think this is a golden opportunity in many ways for us to learn a great deal. I absolutely think we should go ahead, find a suitable candidate or two, make vaccine for clinical testing, test it, determine the safety and efficacy in humans, and come to a point of being ready to go if there should be a pandemic. We're all set and ready to make vaccine for public use.

We'll learn a whole lot in the process, but I don't -- I mean, the qualification that I would put on it was that I don't think we're anywhere near making a decision to make a vaccine for widespread use in the population.

CHAIRPERSON FERRIERI: That is implicit in our thinking, in our recommendation, but I value your having brought that up.

No, it's not a push to do anything impetuously at all, but to be prepared.

Shall we move on then to the next

question? Dr. Snider?

DR. COUCH: Well, I'd like to say, Pat, if I could, I think an important component of that is not waiting for each step to get completed before we take the next step. We need a time frame that's out here which might commit us to the Singapore or the recombinant out of Britain or the best one that's come out of the current effort, you know, as we go ahead, and when the time frame is there for preparing what we want to call something like a conventional vaccine for these trials.

CHAIRPERSON FERRIERI: Yeah.

DR. COUCH: That needs to be set up, and the manufacturer certainly needs to be a part of those discussions.

CHAIRPERSON FERRIERI: Yes, absolutely.

Dr. Snider.

DR. SNIDER: Well, I just wanted to make explicit what I think other people were implying, and that is that when we say we'll learn an awful lot, we don't mean just in terms of scientific information, but in terms of pandemic preparedness. So I think it's important to move forward for what we will learn hopefully in time to allow us to move more knowledgeably, more rapidly to deal with an actual

pandemic situation.

So it's not just adding to the body of scientific knowledge.

CHAIRPERSON FERRIERI: Well, that's true, and I wonder if you could expand upon that point, how you would view the nature and scope of any clinical trials that would be in the future. This is premature for us to discuss it in the kind of detail we're used to hearing, but perhaps we could open up the subject at least, and it would be helpful for CBER.

What would be your notion of the nature and scope of this to move forward in a bigger way towards ultimate licensure? What would your requirements be?

DR. SNIDER: I think there are a lot of things to tease apart, but let me just start with some basic assumptions.

That we were to move forward with developing vaccines that we determine were safe and immunogenic in the experimental animals.

Subsequently we would move into Phase 1 trials in humans, to look at safety and immunogenicity in humans.

Whether we move further in this particular setting, I think it's difficult right now to say. It

will depend upon further developments. If the question is that we believe that in a risk assessment that there still remains a significant risk that, let's say, H5N1 is likely to present a threat, if that further information unfolds, then we clearly have to move to the point of doing the Phase 2 and Phase 3 trials.

And one of the questions would be how many people need to be included. It seems to me -- and what kinds of people need to be included. Certainly we need to think about all the different age groups. We need to be sure the children are included, that young adults, and the older adults or elderly are included because we all know they respond differently to the vaccines or potentially could.

CHAIRPERSON FERRIERI: What about occupational risk? Should we think that one of the natural groups to focus on as we move forward would be poultry workers?

DR. SNIDER: Yeah, I think in terms of thinking about who would be suitable candidates, clearly one would think in terms of those who are most likely to be exposed, and in the end I think you're going to talk about at least several hundreds if not maybe a few thousand people.

CHAIRPERSON FERRIERI: Right.

Dr. Couch, do you have some reflections on this particular point?

DR. COUCH: No, I think I've heard everything Dixie was saying and I agree that the kind of trials we're talking about were the model for those trials I think Roland alluded to earlier, that a lot of us were in the middle of, the swine trials and followed up by the USSR trials, and the dose responses, the two doses, the different age ranges are an essential component of that, and that both is a scientific exercise, but it's a very important prelude, public health exercise to where we might go.

And I guess I have to view my view. Rob's not here. As Dixie says, what is the assessment of the risk? We can't assess that risk. We actually don't know what it is, and that makes the decision for us, I think. It's because we don't know that that risk does, indeed, exist, and therefore, we have to move forward with preparation and hope that it disappears.

But at the present time we don't know.

CHAIRPERSON FERRIERI: Right.

Dr. Clements-Mann.

DR. CLEMENTS-MANN: I was just also

wondering and thinking ahead of some of the approaches that will put us in the question of whether to move forward with, that it also might be prudent to get some proof of concept with, for instance, the bacolovirus expressed recombinant, you know, with a different -- you know, with an acceptable virus for challenge or, you know, to get some efficacy data just so that one could extrapolate from a vaccine that has been shown to be protective with a different hemagglutinin, you know, into future use.

CHAIRPERSON FERRIERI: Other points? Yes, Dr. Kilbourne and then Dr. LaMontagne.

DR. KILBOURNE: I think there's a much larger issue at stake here. I'm a little concerned that the conversation right now perhaps rightly is focusing on H5N1, but actually in 1971 right after the ability to transfer high yield characteristics to vaccine viruses was discovered, it was suggested that we prepare a bank or library of all the existing finite, non-Andromeda strain antigens which surround us in animals and prepare high yield reassortants in advance.

It's a little frustrating for some of us to see us going through these motions now in 1998. We could already have such a vaccine.

I think the kind of evidence I've heard this morning from Dr. Perdue and others of the cross-antigenic relationships within subtype is a critical thing to appreciate because one of the criticisms of this kind of approach has been that you always have to have the exact match.

I think in terms of the safety considerations of personnel, laboratory workers, and everything, you don't have to have the exact match. As Dr. Webster himself pointed out before leaving, there may be enough heterovariant relationship to prevent death or serious illness.

So I really hope that -- and I mention this because the Pandemic Planning Committee, which has been leading a life of quiet desperation now for five years and is now getting a gleam in its eye with this revival of interest, has been considering these things very seriously. I think ultimately this group is going to have to think about this and advise us.

CHAIRPERSON FERRIERI: Thank you.

Dr. LaMontagne.

DR. LaMONTAGNE: I was just going to add basically the following thought, and that is that I think I agree totally with Bob and his conclusion that we don't know what the risk is. So as a consequence,

I think we have to proceed along two pathways.

One of them is the recognition that the reliance is, in fact, the worst case scenario ensues, and that is we have H5N1 coming back. The public health reliance will be on those interventions which have been certified and with which we have experience, namely, the conventional inactivated influenza vaccines that we all know and use.

So there has to be an effort to try to produce that kind of vaccine, and in parallel, I would go along very strongly with what Dixie and others have said, and that is including Ed's recent comments, about looking at other approaches, but I think we have to recognize that the major tool we will have will be the inactivated vaccines that are currently licensed, and that has to be reflected in our priorities.

CHAIRPERSON FERRIERI: Dr. Broome.

DR. BROOME: I agree with what John's saying, but I guess I'm still remembering our sort of egg dilemma from the morning, and it seems to me that, yes, we need to go ahead with candidate vaccines through production and Phase 1 and 2 testing, but that still doesn't address the time delay if, in fact, a worst case scenario ensues in terms of large scale production.

I'm certainly not an influenza virologist or vaccinologist, but it just occurs to me whether we shouldn't also be investing substantial efforts in tissue culture alternatives or other ways in which you could avoid the egg dilemma.

CHAIRPERSON FERRIERI: Any scientific response to that latter point?

No one would disagree with you, Claire. What do we have cooking?

Dr. LaMontagne.

DR. LaMONTAGNE: Well, I mean, obviously if we have alternative sources, that would be wonderful, but I just remind the group that the production of influenza vaccines and embryonated eggs is a long, established, and quite well developed industrial process, and that if you're really talking for large amounts of vaccine that might be required to counteract a pandemic event, I think this is what you're going to -- you're going to have to deal with this one, I think, in eggs unfortunately.

DR. COUCH: Yeah, I think Mary Lou emphasized that a minute ago. This is an opportunity for new approaches to be in the comparative database, and that's how you develop your credibility for the future.

CHAIRPERSON FERRIERI: Well, I'm very impressed today with what we've heard, the cooperation that's been international, bringing together data from many, many sources, the U.S. cooperation among at least three federal agencies, the interaction with industry. It is all very impressive and has taken place over a short time.

So on behalf of the Committee members, I want to thank you all for educating us superbly today and, again, congratulate you for all that you've accomplished under enormous stress and time deadlines.

I think we'll be hearing more from all of you in the relatively near future.

I'd like to now turn the meeting over to Ms. Cherry for the open public hearing.

MS. CHERRY: At this time we will see if there is anyone in the audience that wishes to make a statement.

Yes, would you come forward and state your name.

MR. PETERSON: Paul Peterson from Biochem Vaccines in Canada. We're producer of about half of Canada's vaccine using the traditional egg approach.

I just wanted to make a comment on Dr. Broome's comments earlier about alternative

approaches. We're pursuing tissue culture technology for inactivated vaccine. We're in late stage trials right now for this process.

We don't know where we're going with the H5N1, but everyone in this room knows of the potential of where this could go. So I just wanted to say that we have initiated a program to evaluate growth potential and possibility of vaccine production for an H5N1 vaccine using our tissue culture technology.

So we all hope that the traditional egg approach and attenuated strains that could be used in the traditional way will be successful, but I just wanted to state that as an approach to have a Plan C if things go wrong or to remind everyone like with the situation with not only the egg supply and the logistics of egg supply, but also to remind everyone that our egg supply is also susceptible to this virus.

If something really bad happens, I just wanted to make people aware of that. So we are trying to do our best to pursue, you know, Plan D if something really bad happens.

Thank you.

CHAIRPERSON FERRIERI: Thank you very much.

MS. CHERRY: Is there anyone else who

would like to make a statement?

(No response.)

MS. CHERRY: If not, then I'll declare the open public hearing closed.

CHAIRPERSON FERRIERI: Thank you, Ms. Cherry.

Again, I want to thank the Committee members and also for the leadership displayed by Dr. Roland Levandowski, and we'll adjourn for today.

(Whereupon, at 4:30 p.m., the meeting was adjourned.)