UNITED STATED OF AMERICA

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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101st MEETING

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WEDNESDAY,

FEBRUARY 16, 2005

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The Advisory Committee met at 8:30 a.m. in the Versailles Room of the Holiday Inn Select, 8120 Wisconsin Avenue, Bethesda, Maryland, Dr. Gary Overturf, Chair, presiding.

PRESENT:

GARY D. OVERTURF, M.D., Chair

ROBERT COUCH, M.D., Temporary Voting Member

NANCY COX, Ph.D., Consultant

WALTER DOWDLE, Ph.D., Temporary Voting Member

PRESENT (Continued):

THEODORE EICKHOFF, M.D., Temporary Voting Member

MONICA M. FARLEY, M.D., Member

RUTH A. KARRON, M.D., Member

PHILIP S. LaRUSSA, M.D., Member

DAVID MARKOVITZ, M.D., Member

PAMELA McINNES, D.D.S., Temporary Voting Member

ARNOLD MONTO, M.D., Temporary Voting Member

STEPHEN PHILLIPS, D.O., M.P.H., Temporary Voting Member

CINDY LYN PROVINCE, R.N., M.S.N., M.A., Consumer Representative

BENJAMIN SCHWARTZ, M.D. (CPT)

STEVEN SELF, Ph.D., Member

WALTER ROYAL III, M.D., Member

MELINDA WHARTON, M.D., M.P.H., Temporary Voting Member

BONNIE M. WORD, M.D., Member

CHRISTINE WALSH, R.N., Executive Secretary

FDA REPRESENTATIVES:

KAREN MIDTHUN, M.D.

NORMAN W. BAYLOR, Ph.D.

FDA REPRESENTATIVES (Continued):

ROLAND A. LEVANDOWSKI, M.D.

ZHIPING YE, M.D., Ph.D.

ALSO PRESENT:

LINDA C. CANAS

KEIJI FUKUDA, M.D., M.P.H.

ALBERT THOMAS

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P R O C E E D I N G S

(8:34 a.m.)

CHAIRPERSON OVERTURF: I'd like to call the meeting to order and turn it over first to Christine Walsh.

MS. WALSH: Good morning. I'm Christine Walsh, the Executive Secretary for today's meeting of the Vaccines and Related Biological Products Advisory Committee.

I would like to welcome all of you to the 101st meeting of this Advisory Committee. Today's session will consist of presentations that are open to the public. Tomorrow's meeting will consist of both open and closed sessions.

I would like to request that everyone please check your cell phones and pagers to make sure they are either in the off or silent mode.

I would like now to read into the public record the conflict of interest statement for today's meeting.

The following announcement is made part of the public record to preclude even the appearance of

a conflict of interest at this meeting. Pursuant to the authority granted under the committee charter, the Director, Center for Biologics Evaluation and Research, has appointed for the discussions on February 16th the following participants as temporary voting members:

Dr. Robert Couch

Walter Dowdle

Theodore Eickhoff

Pamela McInnes

Arnold Monto

Stephen Phillips

Benjamin Schwartz

Melinda Wharton

For the discussions on February 17th, the following participants have been appointed as temporary voting members:

Drs. Pamela McInnes

Stephen Phillips

Benjamin Schwartz

Melinda Wharton

Based on the agenda for February 16th, it

has been determined that the topic being discussed by the committee on the strain selection for influenza virus for the 2005-2006 season is a general matters issue. The committee will not be providing advice on specific firms or products on this day.

To determine if any conflicts of interest exist, the agency reviewed the agenda and all relevant financial interests reported by the meeting participants. The Food and Drug Administration prepared general matters waivers for participants who require a waiver under 18 USC 208.

Because general topics impact on so many entities, it is not prudent to recite all potential conflicts of interest as they apply to each member. FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussion before the committee, these potential conflicts are mitigated.

We would like to note for the record that the agency is in the process of selecting a nonvoting industry representative for this committee. On February 17th, the committee will hear updates on

FDA's critical path initiative and will hear a presentation on the Laboratory of Biophysics and the Laboratory of Pediatrics and Respiratory Viral Diseases.

Meeting participants were not screened for potential conflicts of interest for these updates and overviews.

We would like to note for the record that Dr. Nancy Cox is serving as a consultant for this meeting, any speaker making a presentation. She is Chief, Influenza Branch, Center for Disease Control and Prevention in Atlanta, Georgia.

With regards to FDA's invited guest speakers, the agency has determined that the services of these speakers are essential. The following interests are being made public to allow meeting participants to objectively evaluate any presentation and/or comments made by the speakers.

Ms. Linda Canas is Chief of Diagnostic Virology, Epidemiological Surveillance Division, U.S. Air Force, San Antonio, Texas.

Dr. Keiji Fukuda is Chief, Epidemiology

Section, Influenza Branch, Center for Disease Control and Prevention, Atlanta, Georgia.

In addition, Mr. Albert Thomas is an industry speaker making a presentation. He has financial interests associated with his employer and regulated firms. He was not screened for these conflicts of interest.

Members and consultants are aware of the need to exclude themselves from the discussions involving specific products or firms for which they have not been screened for conflict of interest. Their exclusion will be noted for public record.

With respect to all other meeting participants, we ask in the interest of fairness that you address any current or previous financial involvement with any firm whose products you wish to comment upon. Waivers are available by written request under the Freedom of Information Act.

That ends the reading of the conflict of interest statement. Dr. Overturf, I turn the meeting over to you.

CHAIRPERSON OVERTURF: The entire first

day will be contributed to the issue of strain selection for influenza virus for the forthcoming season, 2005 through 2006, and the first speaker is Dr. Roland Levandowski.

DR. LEVANDOWSKI: Thank you, Dr. Overturf.

Good morning, everybody. Welcome to Bethesda. Actually I see there's lots of room left at the front. So those of you who are sitting at the back are welcome to come up a little closer and the slides will be a little bit better, I think, for you.

I have been reminded by a friend that this is the Year of the Rooster, and if I can get this up here, this is the rooster family, and they're all smiling because they know it's time to get started making influenza vaccine again this year. So I don't really know who to attribute this picture to. It was sent to me by a friend who found it on the Internet, and if you like it, you may be able to find it, too. I couldn't, but I got the picture from the friend.

DR. COUCH: I thought you were going to say it's our new susceptible population image.

DR. LEVANDOWSKI: Well, it could be. This

is the red jungle fowl here.

All right. Let me get down to business though. Okay.

As Dr. Overturf said, the reason that we're here today is for the committee to make recommendations for selection of the influenza virus strains, the A(H1N1) and A(H3N2) and B viruses that should be used for the influenza vaccines to be prepared for the 2005-2006 influenza season in the United States.

Why do we change the strains in the influenza vaccines? We do that because it's really important for vaccine efficacy. We know that vaccine efficacy relates to a couple of things, one of which is the potency of the influenza vaccines, but from a lot of experience, it has become very clear that the match of hemagglutinin and neuraminidase of the vaccine strains to the wild-type circulating viruses is important for vaccine efficacy.

And the first evidence of that for reduced vaccine efficacy was apparent two years after the first vaccines were licensed for use in 1945. Within

two years, it became clear that antigenic draft in influenza viruses could reduce the vaccine effectiveness.

The questions that the committee needs to consider answering in order to make the recommendations are listed here and we'll be presenting information that covers all of these areas during the course of this meeting.

The first and most important questions is from Surveillance and Epidemiology: are there new influenza viruses that are circulating that have hemagglutinins and neuraminidases that appear to be different from the current vaccine?

And if the answer to that question is yes, we also want to know: are these new viruses spreading in people? Are they in wide geographic locations or are they just from one location?

Occasionally we see viruses that look extremely different, but it turns out that they're one off, and they don't seem to spread anywhere. So this question two, if it's answered yes, are those viruses spreading, we also want to know whether current

vaccines can induce antibodies that will recognize those new viruses.

And if the answer to that is no, then we want to know further are there vaccine strain candidates available that would be suitable for large scale manufacturing of inactivated and live attenuated influenza vaccines.

I'd just like to go through a review of what the committee considered last year and what the questions and the sort of resolution to the questions was. First of all, for the current vaccine that we have now last year, the question was were there new strains of Influenza A(H1N1) circulating, and at that time you might remember we also had some reassortant viruses that were H1N2. Last year there really weren't strains that were antigenically different from the current vaccine strain. All of them were very much similar to what was in the vaccine.

The same question for the H3N2. Last year the answer to that question was yes. There were A Fujian-like viruses that we had known about since February of 2003. As you might recall, the first

season that those were identified it was not possible to make a change in the vaccine, but those strains continued to circulate widely around the world in people.

And by 2004, although early on those were more or less in the minority or fairly quickly they became the majority and by 2004, those were the main strains that were circulating in the world.

For Influenza B, the question was asked: are there new strains present? And the answer was yes, and in 2004, the majority of the viruses were similar to a strain called B/Shanghai/361/2002, which is from the so-called B/Yamagata/1688 hemagglutinin lineage.

That lineage was not the one that was being used in the vaccine that was current last year. In a minority of the strains that were found during the epidemiologic studies were similar to the strain that was in the vaccine for last year, which was B/Hong Kong/330/2001, which belongs to the HA lineage that we represent with the strain B/Victoria/287.

In answer to the question were these new

viruses spreading, the answer, of course, is definitely yes. The Fujian-like viruses had become widespread around the world and were predominant everywhere, and these B/Shanghai-like strains at the time we were holding this meeting in February were predominant not only in North America and the United States, but also in Asia and Europe.

Were the new viruses that were identified and spreading, were those inhibited by the current vaccines? And this question, as it sometimes is, was not a very definite no or yes. It was a little bit difficult to interpret, but it seemed like man of the A/Fujian-like viruses were not well inhibited by the current vaccines, although some of them were.

For the B/Shanghai-like strains, of course, we've known for a long time that these two divergent hemagglutinin lineages are not that well inhibited one by the other, and as time has gone on and antigenic drift has occurred in these strains, that has become truer.

Generally we also know that for the B/Yamagata-like strains and the B/Victoria-like

strains, that very young children and people who haven't been immunologically primed, exposure to one of these does not seem to immediately give antibodies that cross-react with the other HA lineage.

So were there strains that were suitable for manufacturing? And the answer was yes. Of course, we all know that for inactivated vaccines and for live attenuated vaccines manufacturing depends on having egg adapted strains, either the wild-type or reassortant, and in the case of the live vaccine, of course, it has to be a reassortant for the attenuation phenotype.

But there were A/Fujian-like strains that were available, and there was a high growth reassortant that was being used in manufacturing for the Southern Hemisphere already, the A/Wyoming/3/2003 X 147 reassortant.

For the B strain, there were a number of wild-type isolates that seemed to be suitable for manufacturing, including B/Jilin/20/2003 and B/Jiangsu/10/2003, in addition to the B/Shanghai/361 strain itself.

So based on that, the strains that were selected for this year include A/New Caledonia/20/99-like strain, which in this case really is A/New Caledonia/20/99.

For the B/Shanghai/361/2002-like recommendation that was made, there were all three of these strains, B/Shanghai, B/Jilin, and B/Jiangsu.

And for the A/Fujian/411/2002-like recommendation that was made and the A/Wyoming/3/2003 strain was chosen or is the one that has become widely used for vaccine preparation.

Now, the implications of the strain selection were that preparation of the vaccines was on schedule throughout the year. All of the strains seemed to be typical and easy to adapt for manufacturing purposes, and going into the summer, the supply of vaccine was expected to match the demand predicted by previous years' experiences.

But what happened was that we ended up with a vaccine shortage at the end of the summer, and just to try to put that into a little perspective, from January until August, manufacturing had been

progressing on schedule even including these two new strains that were recommended for use in vaccines, and it was anticipated there were going to be about 100 million doses of vaccine from all of the manufacturers combined for this year.

In August of 2004, Chiron notified regulatory authorities about a sterility issue and indicated that investigation to identify the cause and the implementation of corrections was underway, and at that time Chiron made a public announcement indicating that there would be a possible delay in distribution and possibly a reduction in the amount of vaccine that would be available.

You also probably all know that in early October of 2004, the MHRA, the U.K. regulatory authority, announced that they were suspending Chiron's license to manufacture inactivated influenza vaccine for three months, and that was based on the issues that have previously been identified and were in investigation and correction by Chiron.

Subsequently, over the next few weeks and certainly by November of 2004, it became clear after

consultation between FDA and MHRA that the vaccine that Chiron had planned to make was not going to be available for us in the United States.

In response to that, there were a number of things that happened within the Public Health Service, and I'll just very briefly indicate some of those. At FDA there was a lot of work done to evaluate manufacturers who were not licensed in the United States to identify whether their vaccines could be used under IND.

There was consultation with manufacturers to discuss regulatory mechanisms going forward from this time for getting approval of new products in the United States. That includes accelerated approval, fast track and priority reviews to facilitate those new licenses, and all of these things actually have been continuing.

CDC had a number of roles to play, and I'm not indicating everything here, but certainly there are some very prominent roles in the public health response to what was happening with loss of some of the vaccine that was anticipated.

CDC immediately reviewed and communicated the use recommendations that would be appropriate for this reduced amount of vaccine that was anticipated. It worked very diligently in terms of coordinating distribution of the existing vaccine supplies and were very closely linked and working with manufacturers and FDA in terms of acquisition and use of vaccines under IND in the United States.

National Institutes of Health also as part of the Public Health Service responded to this and were able to provide support for a number of clinical studies that might be done for vaccines under IND-made commitments to help manufacturers and their interests in doing clinical studies that would be useful for IND and possibly later on for vaccine license approvals.

And of course, they've been giving continuing support for development of new vaccines. This is something that was ongoing already at NIH, but have continued to try to facilitate development of new vaccines, tissue culture vaccines, recombinant DNA, and also adjuvanted influenza vaccines.

And the Public Health Service and HHS

generally underwent a global consultation with other partners, including national regulatory authorities, but certainly also with manufacturers to try to find where there might be additional vaccine supplies and to acquire those for use here.

Currently there still is vaccine that's available, and I guess the most recent recommendations that I have seen on use of vaccine for late season use are on the CDC Website, and I would anticipate that those are continuing to be updated. So anyone who is interested in them should certainly check -- interested in vaccine supply and maybe how to obtain additional vaccine -- should continue to check the CDC Website and see what the latest information is.

There still, as of the time I was putting these slides together, was inactivated and live attenuated vaccine available for use, and I think we would all like to make sure that the vaccine that has been produced is used effectively.

And finally, there are also IND vaccines that are available during this year from both GSK and Berna Biotech.

Now, switching gears a little bit and thinking about where we are and where we're going from here for this year. We're in February so there are a lot of things that are happening. So there are a lot of things that are happening. Obviously I've put this together as a kind of a pyramid, and the most visible part of the influenza vaccine, of course, is the vaccine use that occurs in the fall months and into the winter, but you'll see that there's a lot of activities that have to go on before that can happen, including preparation of the vaccine shown in blue here and all of those bars, and all of the support activities that are required for the manufacturers to know what strains that they're going to be using, acquire the reagents and the materials that they need to permit them to go ahead with manufacturing.

So we're here in February. I don't have a pointer. I don't know if I can get the arrow to show up here on the -- I don't see one, but we're here in February, and we're right at the point of recommendations being made both by this committee and by other national health authorities.

Obviously surveillance continues throughout the year. Development of seed viruses and reagents and reference materials, that goes on throughout the year as things become apparent and become available, and it's based on all of those underlying activities that the preparation of the vaccine can start.

Now, I showed this slide last year, but I wanted to show it again to talk about what happens when there are new viruses that are added to the vaccine. It's quite a challenge for manufacturers to get everything together in the relatively short period of time that they have, and even a simple strain change, we're talking about work that requires many, many weeks, somewhere in the order of between 12 and 20 weeks in order to accomplish all of the tasks that need to be done.

In order to have any change in the vaccine, of course, there have to be reference viruses that are obtained. Those come from surveillance, and it is not always easy to get those. As you might recall, it was difficult to isolate some of the H3

viruses in eggs, and as you're going to hear, CDC has been putting in a lot of effort into making sure that egg isolates, appropriate egg isolates, are available for manufacturing. I think Nancy Cox will talk about that a little bit later.

Once those reference viruses have been acquired, then that's not the end of the job because each of the manufacturers has to take the reference virus and develop a working seed virus from that. This is not something that is done in a day. It takes several weeks' worth of work to identify the strain that seems to be appropriate for the manufacturing process and also to make sure that all of the quality control issues that need to be handled and addressed for those new viruses have been done.

Thank you.

So once that's accomplished there still need to be reference reagents that are produced for the reference virus as well, and that can be a rate limiting step. Once the virus has been identified or it's in our hands, then we can start to work on getting those reagents made, but it takes a period of

about three months actually, well, six weeks to three months to have everything prepared because it requires both an antigen and an antibody that's made in sheep, which is a biological system that's not always readily controllable.

Generally though manufacturers are already for the strains that aren't changed can start working and keep working on preparation of materials for vaccine, and when it's time, they can start manufacturing the third strain so that they can formulate the trivalent vaccine, fill it, and then distribute that vaccine hopefully in time for use in the fall.

There will be a presentation later by our industry representative who will go into more detail about this, but I wanted to mention it also that it's a fairly complex set of activities that need to be undertaken for implementation of any strain change, and it is a kind of a stressful situation for all parties that are involved to first make sure that their reference virus is present, make sure that the reagents get produced and make sure that the

manufacturing can go forward.

I'll end up here with some bits of information from WHO recommendations during the past year. These are the recommendations that WHO made for the Southern Hemisphere, and you can see that the strains that were selected for the Southern Hemisphere, which were based on information much like what we'll be discussing here this morning, it was to keep the A/New Caledonia/20/99 strain as the vaccine virus and it actually was to include now a B/Shanghai/361/2002-like virus for the first time in the Southern Hemisphere, but it was a continuation of what had already happened with recommendations in the Northern Hemisphere in February last year.

However, there was a recommendation for a change in the A/Wyoming strain to an A/Wellington/1/2004-like virus, and that was based on the fact that the H3N2 viruses were undergoing antigenic drift.

And finally, these were the recommendations that have been published on the WHO Website for this coming year, and you'll see that

although the H1N1 and the B strain are the same as what they were for the Southern Hemisphere, the WHO recommendation for the H3N2 virus is for another different strain, the California/7/2004-like virus. And we'll be presenting information that will probably make that understandable.

So the question for the committee that we would like to have addressed, the specific question that we're asking the committee this morning is what strains should be recommended for the antigen at composition of 2005-2006 influenza virus vaccine, and this recommendation should be based on the epidemiology and antigenic characteristics of the circulating influenza viruses.

On serologic responses, people have been immunized with current vaccines and the availability of candidate strains, and I guess I can stop there and see if there are any questions or comments.

CHAIRPERSON OVERTURF: Other questions or comments for Dr. Levandowski? Dr. Couch.

DR. COUCH: Haven't the WHO recommendations for the Northern Hemisphere for 2005-

2006 already been made? Haven't they all? They were on the Website at any rate.

DR. LEVANDOWSKI: That's right. That's what I showed.

DR. COUCH: But you didn't include them. Won't you tell us what those are?

DR. LEVANDOWSKI: Right there. Isn't that it? Do I have it mislabeled?

DR. COUCH: No, that's fine.

CHAIRPERSON OVERTURF: Dr. Markovitz.

DR. MARKOVITZ: Yeah, thank you.

I wanted to ask. You showed something about the Berna Biotech vaccine in IND, and we're going to hear about the GSK tomorrow, but what is the Berna Biotech vaccine?

DR. LEVANDOWSKI: It's an inactivated influenza vaccine.

DR. COUCH: Aren't there other candidates for the IND or there was or what's the status of other manufacturing candidates for interest in our country? I guess that's the question.

DR. LEVANDOWSKI: Okay. Well, of course,

I'm not going to talk about any INDs that are, you know, confidential information, but there is a lot of interest; there has been ongoing interest. There was interest even before this from a number of manufacturers to bring their products to the U.S. market, and those are all things that were in the works and are continuing.

So I guess what I can say generally is that there are a number of manufacturers that are interested who are pursuing avenues toward getting approval for their products in the United States, and they're multiple. It's not just one or two. It's multiple.

CHAIRPERSON OVERTURF: Any other questions?

(No response.)

CHAIRPERSON OVERTURF: We'll go on then. Dr. Fukuda is going to give us the U.S. surveillance data.

DR. FUKUDA: Good morning. I see that I'm allotted more time than I really need. I'm only going to spend a few minutes talking about surveillance in

the United States, and then Dr. Cox will be covering some of the events going on in Asia related to H5N1.

So normally I just talk about the activity that's going on in the United States, but I thought I'd take a minute or two and go over some of the changes affecting how we're doing surveillance in the U.S. because they really have been quite substantial over the past year or two, and I think it's changes that the committee should know about.

So over in the left-hand column you can see how we've done surveillance in the United States for several years, and for quite a long time we've monitored viral activity through the WHO nerve laboratory system in the U.S., which is largely a group of Public Health laboratories, plus university laboratories. We've monitored influenza-like illness visits to a group of sentinel physicians scattered throughout the United States.

We've monitored mortality from influenza using two different systems. The 122 cities systems collects data from vital registrars' offices in 122 cities, and then the NCHS data set is the large data

set reflecting all deaths in the United States which are analyzed a couple of years afterwards.

And then we typically get state activity assessments from the state epidemiologists every week, and so this is basically the information that you've seen for year in and year out.

Now, there are a couple of things which are really driving changes in surveillance. One of them is that since really the mid-1990s we've been trying to strengthen surveillance as much as possible, recognizing that there are a number of limitations.

A second thing is that there has been a great deal of concern about pandemic influenza, and I think this concern continues to rise, and so that's another driving factor for enhancing surveillance in the U.S.

And then the third thing is that there has been directives from the Director's Office at CDC really to strengthen surveillance so that the data comes in a little bit more quickly and so that it's more broadly representative of the country geographically.

So based on that, there have been a number of things done to enhance the systems on the left, and I'll go over one example, which is the sentinel provider system. There have been a number of new systems which have been added.

We are now monitoring pediatric influenza related hospitalizations through two different networks, the NVSN and the EIP Programs, and this largely comes out of last year's experience where we had so many pediatric deaths and so many severe illnesses reported in that age group.

And then also as part of that, we have begun -- we worked with CSTE, the Council of State and Territorial Epidemiologists, to institute national pediatric death reporting for death related to influenza.

So these are new systems, and then because of concern of H4N1 and the initial cases that were reported back in 2003, we have been, in essence, at a state of heightened alert in the United States where state health department and hospitals have been on the lookout for H5N1 cases among travelers returning from

Asia. So these are new systems which have been added over the past year or two.

Then in addition, there are a large number of systems, and I'm just giving two examples here which are under evaluation. Biosense is a large conglomeration of data sets which are collected from groups such as the Veterans Administration, DOD, pharmaceutical industry, and so on. These are being evaluated for the potential value when conducting influenza surveillance.

And then we also will be talking with the Council of State and Territorial Epidemiologists later this year about whether influenza laboratory confirmed illnesses should be a national reportable disease, which would probably profoundly affect how we do surveillance. It would probably be the biggest change of all if we go in that direction.

So this is the effect of some of those changes. You can see on this slide here that this represents the numbers of sentinel physicians in the country and then the number of visits that are made to those physicians for influenza-like illness.

So back in 19 96, which is the column over on the left, you can see that we probably had somewhere between 50 and 100 sentinel physicians reporting these data, and then if you go up to 2004, we have over 1,000 physicians reporting on a regular basis, and so this represents an increase of less than a million patient visits to about five to nine million patient visits per year.

Now, these physicians are scattered in the United States and these dots represent where they're located, and you can see that, in general, they're distributed in the way that the population of the U.S. is distributed, and typically when we've analyzed these data, we've shown you curves like this, which shows you the percentage, the cumulative percentage of visits for influenza-like illness on a week-by-week basis, and you can see in different years that percentage increases as we go into the influenza season, then comes down.

What we're trying to do, we're testing a couple of other ways of analyzing these data, however. This map here represents the application of the so-

called outbreak detection algorithms to each physician, and so, in essence, each physician is treated as a sentinel for detecting outbreaks or increases in activity.

And so using certain statistical methods, what we do is look for an increase in visits for influenza-like illness for each of the physicians, and you come up with maps like this, this sort of speckled map where the red represents increases and the black do not.

I think right now what we're mostly struggling with is whether this kind of analysis adds anything substantial to what we already have, but anyway, so that work goes on.

So let me go into the current season now. So you can see, and this updates the report to the committee. I think the committee has surveillance data up through week four, and this goes into week five. So these numbers will be a little bit different from what you have.

So basically you can see that this year it has been a mixed Influenza A and B season, but

predominantly A. To this point there have been about 65,000 specimens tested by the laboratory system and about 11 percent of those have been positive for influenza.

And of those which have been positive, about 85 percent of the isolates have been Influenza A and about 15 percent have been Influenza B.

Now, of the Influenza A viruses, about a third have been subtyped, and you can see of those that have been subtyped almost all of them have been Influenza A(H3N2) viruses, with a few H1N1 viruses or a few H1 viruses.

And so Dr. Cox will be going much further into these data in a few minutes, and so this graph here represents the same data shown somewhat differently, and so these stacked bars represent Influenza A viruses and B viruses, and the numbers that have been identified as we've gone into the influenza season.

Now, one of the important things to see here is this black line. This represents the percentage of specimens which are positive for

influenza, and in many ways it's often the earliest indicator of how the season is going.

So right now you can see that approximately 23 or 24 percent of specimens coming into the system are positive for influenza viruses.

Now, if you look in the past of the past several seasons, you will see that this percentage typically peaks somewhere between a quarter and a third of specimens testing positive for influenza viruses when we reach the peak of the season. So right now this curve looks like we've reached the peak, but this was probably somewhat of an artifact, or we're not sure if it's an artifact right now. It may represent a bit of a reporting lag.

So based on this curve right here, it still looks like that we're going up in the season and we haven't quite peaked yet.

Now, this slide here represents the visits for influenza-like illnesses to sentinel providers, which I showed you a few minutes ago. The red line represents the pattern for this year, and the green line represents the pattern that we saw last year when

we had that early season.

Now, these are curves which you wouldn't have seen last year. So these are laboratory confirmed hospitalizations, and these are hospitalizations coming into the NVSN system, and so these represent hospitalizations of children zero to four years of age, and you can see the blue line represents last year when we were hearing about so many reports, and the red line represents what we're seeing this year.

Now, these are similar data coming into the EIP system. I won't go into the details. The NVSN system and the EIP systems identify hospitalizations in somewhat different ways, and so the absolute rates are somewhat different, but what they show, in essence, is fairly comparable.

And I want to point out one thing though. The blue lines here, again, represent what we saw last year. The solid blue line represents hospitalizations that we saw in children zero to four years of age, and then the dotted or the broken line, blue line, represents the hospitalizations that we saw in

children five to 17 years of age.

And so you can see that there was a quite large difference in rates of hospitalizations depending on age.

Again, the red line represents the hospitalizations that we're detecting this year. So, again, you can see there's a substantial difference between the experience this year and last year.

This curve here is the familiar pneumonia and influenza mortality curve which comes out of the 122 cities system, and so far this year we have not detected an increase in excess mortality.

I was looking at this slide this morning. So I'm struck that we have red states and blue states, and there are more red states than blue states.

(Laughter.)

DR. FUKUDA: But all things change. So anyway, these are activity levels represented by the state and territorial epidemiologists. The red, in essence, report reveals or indicates the highest level of activity in a state, and then the blue levels represent a somewhat lower level of activity.

So this is the last slide here. I think that what we can say is that in comparison with last year, this season has been relatively moderate. It has been dominated by Influenza A(H3N2) viruses. I didn't go over these data, but so far there have been six reported pediatric deaths associated with laboratory confirmed influenza. This is in contrast to 153 laboratory confirmed deaths reported last year for the entire year.

But then, again, this season clearly has started later than last year. We are in a period of ongoing activity. We cannot say that activity has peaked in the country yet, and so we still don't know what the full impact and what the full numbers will be.

So I'll stop there.

CHAIRPERSON OVERTURF: Just one question. You had that slide that looked like four curves or four seasons with pediatric hospitalization rates.

DR. FUKUDA: Yes.

CHAIRPERSON OVERTURF: What is the quality of the data for the two prior seasons?

Obviously we really didn't have a surveillance system that was looking at pediatric hospitalizations that I know of prior to last season; is that correct?

DR. FUKUDA: Well, this system, the NVSN system, has been in place since 2000, and so this actually represents now five years' worth of data.

I would say that the quality of these data are excellent. You know, this is a system which was set up by the National Immunization Program in Rochester and in Tennessee, Rochester, New York, and then in the Vanderbilt area, and then more recently they've added a third site.

And in essence, it's an active system where all children coming in meeting a certain case definition are then tested for influenza and other viral respiratory illnesses, and so it's a pretty labor intensive system, but the data themselves are quite excellent.

CHAIRPERSON OVERTURF: Other questions? Dr. Couch.

DR. COUCH: I wanted you to go ahead if

you would, Keiji, and contrast those two systems a little bit because they don't exactly say the same thing.

DR. FUKUDA: Sure. I think one way to look at the NVSN system is that it's close to an ideal way of trying to look at what children are getting sick with and to identify rates of hospitalizations associated with various pathogens.

By contrast, the major limitation I would say of the NVSN system is that it's restricted to a small number of sites and it's expensive. The EIP system is a program intended to look at a wide variety of issues, and so the ABC system looking at bacterial infections comes out of that system. FoodNet comes out of that system, and this is a population-based surveillance system in 11 sites in the U.S. right now.

And so what this system does is take existing data. It takes how physicians handle children or other people coming into hospitals and looks at the virus detections and so on as they're currently done, and then takes that information and makes it available and makes it available in a way

which is population based.

And so I think the strength of this system here is that it's a much larger system, and like NVSN, it represents population based data, and it reflects practice as it's actually done right now.

So it's probably comparatively less labor intensive, but I think the sensitivity of this system -- there will be an article coming out on this -- is less than the NVSN, yeah. So in a certain sense they are pretty complementary. They try to do different things, but in fact, you can see that the overall picture of the data is pretty similar. The absolute numbers are different, but I think that you both get a good sense of the rates going on, and certainly I think that these systems are going to be very helpful for looking at differences in seasons, particularly in children right now, you know, and this has been a major question. You know, how much does it vary in children and what is the impact?

CHAIRPERSON OVERTURF: Mr. Phillips.

COL PHILLIPS: Keiji, it was mentioned last week at ACIP, but I can't recall. Can you

comment on the percentage or the numbers of children six to 24 months that received immunization this year compared to last year?

DR. FUKUDA: Yes. I think that actually Melinda or Ben may remember better, but I think that when we first started out, you know, the rates in that age group were very low, I think, less than five percent, and then within a year it went up to about 45 percent somewhere; is that right, Melinda? I'm not quite sure.

DR. WHARTON: I think the most recent data for six to 23 month olds from the BRFS for this year was 57 percent.

DR. FUKUDA: Oh, 57? Okay. Sorry.

So it has really been an astounding increase in that age group.

CHAIRPERSON OVERTURF: Yes, Ted.

DR. EICKHOFF: Keiji, two things. In the very first bar graph you showed about the sentinel physician providers I missed something. A straight line had turned straight down. What was that straight line? Is that the number of sentinel physicians?

DR. FUKUDA: This is the number of patient visits. So if you take the sort of cumulative number, and I think that the downward turn just reflects that we're still going on through the season. So I think that at the end of the season that line will be going up.

So I think that the downward line is just an artifact of where we are in the season.

DR. EICKHOFF: Okay. Thank you.

The second part of the question related to the state epidemiologist reporting. Now, I know there are definitions that go with each of these categories of reporting, like regional and widespread and so forth and so on, but yet I can't escape the feeling that there may, in fact, be a great deal of observer variability in these reports.

So you have any sense of how variable these may be within a specific definition, such as regional?

DR. FUKUDA: I think there's probably a substantial amount of variability. I mean, clearly, how each state decides to report their activity

varies. I mean some states look more at their laboratory data. Other states look at perhaps what they're hearing about hospitalizations and so on, and in a sense it represents a gestalt from that state.

Nonetheless, I think it's funny, but I think that it actually pretty well represents what we see in the other parts of the system where, when we look at increases in visits to sentinel physicians, for example, in the northeast or in the southwest, and it correlates pretty good.

And what it does, you know, we really are not at a point yet with the other systems where we can break the data down to a state-by-state level and feel that they're robust enough that we can report on a state-by-state level. I think we're getting to a state where we're feeling pretty good that in a lot of the regions the data from the other systems are pretty good for those regions.

But as we get into smaller and smaller cuts at the data, you know, it becomes a little bit more -- the confidence intervals become a little bit too wide. So this really represents our way of trying

to get at what are the states themselves feeling like they're seeing and how, you know, are they responding to that and reacting?

DR. FUKUDA: There's another question. Yes.

DR. DOWDLE: First I'd like to congratulate CDC for continued expansion of the surveillance system. It's quite gratifying to see that, and I'm also really interested in your discussions, upcoming discussions in making influenza a national notifiable disease, which brings up the question: in your discussion with the states, what do you see is going to be the major challenges to get this done?

I mean, this has been discussed before, but there are many challenges to doing that. So have there been any changes? Is there different attitudes? And what do you think are the real challenges this time?

DR. FUKUDA: Walt, I think it represents a couple of things that are changing out there. One is that, in fact, it turns out that there are more

states in which laboratory confirmed influenza already is a reportable disease within the state than we really, I think, suspected.

I mean, when you look at it, it's probably around 20 states or so. So that's one difference than some years ago.

A second issue is that I think that influenza has gotten so much attention over the past couple of years that on the political agenda in a lot of states there is now a recognition that they really want to keep on track of what's going on with influenza in their states much more, and that's probably a big change over, say, five or ten years ago.

And then the third thing is that, you know, the State and Territorial Epidemiologists really pull together with CDC when there's kind of a crunch going on, and I think that there has been a big push over the past few years with the vaccine supply disruptions, the push from the Director's Office at CDC really to strengthen surveillance in a way that data is coming in a little bit more quickly. It's a

little bit more specific, and perhaps eventually can be used really to respond to emergencies a little bit more quickly.

And so based on that, this idea of moving to notifiable diseases really came out from the states. It's something, I think, that we would have hesitated to approach because of all of the practical and feasibility issues, but basically a couple of the states came to us and said, "You know, we really think it's time that influenza surveillance begin to be treated like other diseases in the U.S. and that we begin to look for confirmed cases and try to track those, and so I think moving into that direction is really the biggest hurdle is going to be to get all of the states which aren't doing that right now to agree that it should be a notifiable disease.

I think if that is done then I think all of the other issues are relatively simple to deal with, and I think for the states it's really just a feasibility issue. You know, they're dealing with bioterrorism activities and so on, and there are so many things going on that everyone is trying to

respond to, but that's the real hurdle.

CHAIRPERSON OVERTURF: Dr. Monto.

DR. MONTO: Coming from a state where we've been discussing making influenza notifiable disease and in a situation where there is concern that there would be significant under reporting or different reporting from different states using different criteria, is there discussion about standard methods that would be used in different states to get away from the situation which we have right now where the state epidemiologists basically makes a seat-of-the-pants decision about the level of influenza activity?

DR. FUKUDA: Well, Arnold, I think that if we do move to a situation where laboratory confirmed influenza becomes a reportable disease throughout the country, then the first issue is going to be laboratory confirmed what, and it will probably focus on something like hospitalizations because it's relatively restricted in numbers.

So we haven't entered into the discussions with the states about the nitty-gritty of how this

might be done because I think first there has to be discussion about whether the other states think that this is how they want to go.

But I suspect that if we get past those discussions, it will focus on how do we start off relatively narrow and then do we expand out later on?

CHAIRPERSON OVERTURF: Dr. Farley.

DR. FARLEY: Well, this is in many ways a follow-up to that question in that the issue of testing, the type of testing, rapid testing versus virologic testing, and its sensitivity/specificity issues, but also the word is that some insurance companies cover the test and some don't, and I guess if they're hospitalized things may be much different in terms of coverage for testing, but where do the policy makers fit in that equation of it we're going to a laboratory diagnosed surveillance system that's reportable, will there be recommendations on whom to test and whether it should be covered?

DR. FUKUDA: Yes, Monica, that's a big issue. If you look at everyone who is tested for influenza right now, it's clear that a majority of

them are now being tested using the rapid detection kits, and we all know that the sensitivity and the specificity of those kits is not at a level where any individual test result, particularly in the off season or when you have odd results is, you know, so solid, but you know, it's also the increased usage of that kind of testing which has made the whole discussion about moving to laboratory confirmed influenza possible.

You know, without that kind of testing we wouldn't be having this discussion with the states, and I think that some of the things that we'll have to come to grips with and which I believe will probably change over the next several years is that there are undoubtedly going to be regional differences, individual physician differences in terms of how often and how they're willing to use those tests, and that will change.

And so I think that all of those will be somewhat problematic. Nonetheless, I think that they're all addressable issues, and I think that when we look at the data coming in as a large lump of data,

it will be pretty analyzable. I mean, that's what I suspect.

CHAIRPERSON OVERTURF: Other questions?

(No response.)

CHAIRPERSON OVERTURF: If not, Dr. Cox, are you ready to present now?

Okay. Dr. Cox will present.

DR. COX: Okay. Good morning, everyone. I'm very pleased to be here presenting the virologic data once again and shifting from a domestic perspective to a global perspective.

I thought I'd spend just a few minutes at the beginning of my presentation talking about the H5N1 situation in Asia, and then we will be able to focus exclusively on the task at hand, which is vaccine strain selection for this coming year.

This slide actually shows the countries that have reported H5N1 outbreaks in poultry since December 2003. The countries shown in light purple are the two countries, Japan and South Korea, that have their outbreaks under control and the H5N1 virus as far as we know has been eliminated from their

borders.

The countries shown in purple have outbreaks in poultry, but no human cases have been report, and the three countries shown in red have outbreaks in birds and at least one case in humans. The countries in cases with humans are Cambodia, which has reported a case recently; Thailand, which has reported 17 cases of which 12 have resulted in death; Vietnam, which has had a lot of activity recently and a lot of publicity recently. There are 37 H5N1 laboratory confirmed cases with 29 deaths, for a total of officially reported cases of 55 and 42 deaths.

Now, of course, the case fatality rates are very high. We know that case ascertainment is not perfect. It's far from perfect, in fact, and so this probably represents an over estimate of the case fatality rate. Nevertheless, it's a very sobering picture.

We've noted that there's a high case fatality rate regardless of age, although the illnesses, the detected cases have tended to be in children and young adults.

The clinical symptoms are similar to the earlier cases in 1997, and lymphopenia is a prominent feature.

Diarrhea has been reported as being a prominent feature in some of the recent cases.

There was a second wave of infections that began in August of 2004, sort of tailed off a bit, and then increased again during late January and February.

And then, of course, I'm sure many of you have heard in the press and perhaps have even read the paper in the New England Journal about the Thai family cluster, where because of particular circumstances it was possible to document probable human-to-human transmission from a child to her mother and to her aunt.

Now, we have been looking very carefully at the antigenic properties of these viruses, and I probably showed you this slide before, but this slide shows that the viruses have actually drafted antigenically quite dramatically from 2003, where we had the Hong Kong/213/2003 virus, which had been used

in the -- the wild-type virus had been used in Rob Webster's lab to produce a vaccine reference strain, and we had hoped that it would be appropriate to use for pilot lots for the situation that was developing in Asia.

Unfortunately, you can see that the ferret antisera against the Hong Kong/213 virus has a very nice homologous titer. However, that antiserum covers the Vietnam/2004 and Thailand/2004 viruses very poorly.

Likewise, we were able to see distinct differences between the Hong Kong/97 (H5N1) viruses here. We see the homologous antiserum titer, and this antiserum covers the 2004 viruses very poorly.

These viruses themselves do induce a good antibody response in ferrets that have been infected intranasally, but by using these sera we can also see distinct differences between 2003 and the 1997 H5 viruses.

So it became very clear that new vaccine candidates needed to be developed for the ongoing situation. Candidates have been developed and perhaps

Pamela or someone else from NIH will give an update on the current pilot production situation for candidates that have been developed with these two particular strains if there are questions.

I'd just like to give a very brief summary of the highlights of points I'd like to get across to the committee. Obviously avian influenza viruses including all of these subtypes, but particularly the H5N1 viruses, can pose a major risk to global public health. Early detection of human to human transmission of novel influenza viruses is essential. It's difficult in Asia, but surveillance has been ramped up, and if there are questions about what the U.S. has done to help improve surveillance in Asia, I would be happy to field those questions.

The 2003 through 2005 Asian viruses are heterogeneous both in their antigenic properties and in their resistance to influenza antivirals. They are also heterogeneous with respect to pathogenicity, and the current strains are more lethal in mammals by the current measurements we have than the 1997 strains, and I'm talking about animal models here.

There is ongoing vaccine development, ongoing antiviral stockpiling, and pandemic preparedness activities at many levels within our own country, within other countries, and within WHO.

Surveillance in animals, including birds, swine, and other susceptible hosts, such as felines is critical, and a research agenda needs to focus on enhancing our understanding of the genesis of pandemic influenza viruses.

We have a unique opportunity to view how new pandemic strains may or may not develop, and there is now a very broad global recognition of a need for better communication between human and veterinary health authorities, and we are all working very diligently on improving communications.

So now I will be shifting gears and talking about the current influenza season, which is as Keiji has just shown you increasing and really getting going.

I'd like to provide a bit of an overview by way of introduction to the global situation. Now, we have compiled information from all of the four WHO

collaborating centers, which are located in London, Atlanta, Melbourne, and Tokyo.

And we have also included information from the European influenza surveillance scheme, which is a very comprehensive influenza surveillance system in Europe, and have also included the very good data from our Canadian counterparts who report on a weekly basis their analysis of influenza viruses that have been isolated in Canada.

Generally speaking, between October 2004 and January of 2005 through the current time, influenza activity has been reported in Africa, the Americas, Asia, Europe, and Oceania. In general, influenza activity has been relatively low compared to the same period last year globally as well as nationally.

The influenza season began in October in North America where viruses were first detected, and it has increased quite gradually in countries in the Northern Hemisphere, including countries in Europe and Asia.

As you can see here, Influenza H3N2

viruses have predominated worldwide and were responsible for the majority of outbreaks. Influenza B viruses from both the Yamagata and Victoria lineages have continued to circulate globally and have been responsible for a few outbreaks.

Influenza A(H1N1) viruses have been detected less frequently and have been reported to be responsible for only one outbreak so far.

I would like to note that of the Influenza B viruses, those on the Yamagata lineage, which is represented in our current vaccine, have predominated. If you add up the 303 and the 74 and look at the proportion of B Victoria viruses on a global basis, it's about 20 percent in the United States. You can see clearly here it's also roughly 20 percent, in the same ballpark at least.

We have relatively few viruses from Central-South America because they haven't had much Influenza B activity, and you can see that in Africa and Oceania B Yamagata lineage viruses really did heavily predominate.

So now we'll move on to Influenza A(H1N1)

viruses. Now, I would encourage anyone who really wants to see these numbers to move forward because I know it's very difficult to see the HI tables on the screen. You do have copies, but they're not color copies. So it's sometimes a bit harder to see.

I mentioned that we had relatively few H1 isolates, but we do have some relatively recent strains, some December strains from Florida represented here as test antigens.

We also have quite a number of Asian isolates. There was a fairly large outbreak of H1N1 in Thailand. We received quite a few of the viruses. They were isolated mainly in September and October, and we also have some viruses from Hong Kong down here at the bottom.

We do, of course, distill the information that we receive and try to present representative data to you. We couldn't possibly present all of the HI tables to you.

I gave you a bit of an orientation, well, when we looked at the H5N1 antigenic table, but I'll remind you that what we're looking for is a fourfold

or greater difference between the homologous titer with the vaccine virus, in this case a New Caledonia/20/99, which is in our current vaccine. We have a homologous titer of 640 here with the New Caledonia antiserum, and we're looking for differences, fourfold or greater differences with the current viruses.

Now, you can see very clearly from our own CDC data -- and this was confirmed by data from the other four collaborating centers -- that the New Caledonia antiserum covers the current viruses very well.

this is reflected in a frequency table. We have only in our collaborating center had a total of 14 viruses, H1N1 viruses. They were all H1N1. We detected no H1N2 viruses at CDC, and 100 percent of them were New Caledonia-like.

And if we look back at the previous period from April to September when influenza viruses were circulating in the Southern Hemisphere, we picked up only one virus that was low to the New Caledonia antiserum.

Now, I'm going to go on and remind you that we sequence the hemagglutinin genes of geographically and antigenically representative strains. So we tended to sequence the majority of H1N1 viruses that came into our laboratory simply because we had so few and we were trying to track exactly what was happening.

Our New Caledonia vaccine strain is located down here at the bottom of this evolutionary tree for the hemagglutinin genes, and it may be just a little bit difficult to see, but we've color coded the dates of isolation because we were very interested sine we have two distinct clades or sublineages of (H1) HA genes. We wanted to see which of these two clades had the most recent viruses, and it's this clade at the bottom which has the most recent viruses.

Now, Roland mentioned that we had focused much more of our efforts on obtaining egg isolates, and we have shown in all of our evolutionary trees the viruses for which we have egg isolates. So you can see for H1N1s where really there hasn't been very much change. We were prepared in terms of having egg

isolates ready should there be a surprise.

Now we're looking at the neuraminidase genes. As I mentioned, we have only detected H1N1 viruses over the past few months, no H1N2s, and you have a similar sort of pattern generally speaking with two different sublineages or subclades, but there haven't been that many amino acid changes associated with the ongoing evolution of the neuraminidase genes.

I forgot to mention for this previous slide that, of course, we are unable to distinguish antigenically the viruses in this sublineage versus this sublineage. So there are no antigenically detectable differences with post infection antisera between these two groups.

I'm going to skip the serologic responses. There are a number of tables in the CDC package. We did a lot of post vaccination human serology this year. We actually had two panels of serum from children, one panel from children zero to 23 months of age and another panel from children five to eight years of age.

And so if you have specific questions

about those tables of serologic results, I'll be happy to answer them, but Roland will be doing a summary talk in which he compiles all of the serologic data accumulated by all of the collaborators to the WHO Global Influenza Program.

So our H1N1 summary is as follows. Relatively few H1 viruses have been detected worldwide. The majority of the H1 viruses were closely related antigenically to the New Caledonia vaccine strain, and no significant variance of H1N1 viruses were detected during recent months.

No H1N2 viruses were detected, and that is true with respect both to the U.S. strains and the strains analyzed globally.

N1 neuraminidase genes of recent H1 viruses were similar to those of viruses isolated prior to October 2002. So you can see the H1 situation is fairly straightforward.

Okay. We'll move on to H3N2. H3N2 viruses always cause us a lot of headaches. They are responsible for more severe influenza seasons, generally speaking, including a higher numbers of

hospitalizations and deaths.

I'll walk you through this table which includes our reference panel up here. Here's our Wyoming vaccine strain right here with a homologous titer of 640.

Here is the Wellington virus here, Wellington/1/2004, which was recommended as a vaccine strain for the Southern Hemisphere. It has a homologous titer of 320, and then we have some relatively new variants which will be mentioned later on. We have the North Dakota/1/2004 virus.

And I would like you to note that the Wellington, North Dakota, California, and Singapore/37 viruses are all egg isolates, and therefore, I'm concentrating on data generated with viruses and antisera to these viruses that are potential vaccine strains.

Now, at the beginning of this season we were seeing that the majority of the viruses were similar to the Kentucky and New York/57 strains, and they were really quite well inhibited by antiserum to Wyoming. If you see a twofold difference, it's not

considered significant because that's within the error of the test, but as the season progressed, we began seeing more viruses with titers of 80 and even a few viruses with titers of 40 against to Wyoming serum.

Once we got the California egg isolate and product a post infection ferret antiserum to it, what we found in this test and which has been borne out in our laboratory in other tests as well as in the other collaborating centers is that the antiserum to the California egg isolate covers recent strains better. It has a lower homologous titer, and there are not reductions or there are no more than twofold reductions compared to the homologous.

The same is true to a great extent with the North Dakota strain, although the California strain did seem to cover viruses slightly better, and we found out that the North Dakota egg isolate did not grow particularly well.

So I'll show only one more table, and I'd like to mention that this particular hemagglutinin inhibition test was done using getting pig red blood cells. The H3 viruses, the current ones grow

relatively poorly, and sometimes it's necessary to use guinea pig red blood cells to detect high enough titers to do HI tests, and we do all of our screening for H3N2s using guinea pig red blood cells.

And if we have a virus with a low titer, it's too low to test with the turkey red blood cells, which were the red blood cells used for the previous HI test. Then we use guinea pig red blood cells to do the HI test.

Now, turkey cells are the standard cells used in all of the WHO collaborating centers.

What we have found, and it has been very, very interesting, indeed, that with guinea pig red blood cells, we often see that there's greater differentiation between strains, and so if you look at the Wellington homologous titer, it's 640 here, and it's dropped even lower against a couple of current strains, Victoria/500 from the Southern Hemisphere and the California/7/2004 from our recent season.

It doesn't matter whether you use guinea pig red blood cells or turkey red blood cells. The antiserum to the California strain covers recent

isolates and even those that are difficult to quantitate using turkey red blood cells very well. In contrast, you see a homologous titer of 640, and a number of titers of 80 here with recent strains. And that's true no matter which continent you're looking at.

So in summary, I'd like to try to explain this frequency table which is a little bit more complex than the frequency tables that we normally have simply because we didn't have the ferret antiserum to the California egg isolate until January 5th.

Since that time, since the time we've been using that, we've been able to characterize 30 percent of the total 261 H3N2 strains that we've looked at from global sources as California-like, but we also had prior to the introduction of the California ferret antiserum been characterizing a number of strains that we haven't had a chance to go back and test retrospectively that were low to the Fujian.

Our guess is that until you do the studies you don't know for sure. Our guess is that

these will look California-like when we eventually are able to test them retrospectively.

Last season, which isn't shown here, we had a bumper crop of H3N2 viruses, and we had well over 1,000 strains that were analyzed during the period preceding this, which was our influenza season last year, and the majority of those viruses were Fujian-like, as you will recall.

Okay. Now, you see the evolutionary tree for the H3 hemagglutinin genes. Our vaccine strain, Wyoming/3/2003, is right down here shown in red. Once again, the blue strains are our egg isolates. The Wellington strain, which was recommended for use in the Southern Hemisphere is here. You can see that we've moved up the tree from Wyoming for the Southern Hemisphere vaccine recommendation.

The one change that does not appear, the one amino acid change that does not appear in the Wellington strain that appears in the majority of the currently circulating strains is this change at amino acid 145 that you'll note. It's a K to N change, and it has in the past proved to be significant in terms

of antigenic variation.

Our California reference virus is shown right up here. It is designated as a low reactor. Some of the other egg isolates that have been sent out to other collaborating centers and to vaccine manufacturers include New York/55/2004 shown here and New York/40/2004 and Wisconsin/19/2004, and these are all quite representative of the currently circulating strains.

The Singapore/37 strain, which was shown on the previous HI table, is right here.

When we look at the pattern of evolution for the N2 neuraminidase genes, we see that the neuraminidase genes are clustering in a fairly tight group. Of course, for those of you who aren't so accustomed to looking at the evolutionary trees, it's really not -- the distance between viruses is measured like this, not like this. These are spaced out.

So the vertical distance is not the important distance, and so these are clustering fairly tightly.

Here is the Wellington strain. Here is

the North Dakota strain, and here is the California/7/2004 strain. New York 55 is right here, and of course, its neuraminidase is right on the backbone and very close to the consensus sequence for neuraminidase genes.

So in summary, Influenza H3N2 viruses have circulated in many countries, in the Americas, Asia, Europe and Oceania. In HI tests, H3N2 viruses were antigenically heterogeneous. Viruses isolated early in the season were often more closely related or most closely related to Fujian/411 and Wyoming/303 viruses, our two reference strains.

But an increasing proportion of recent isolates were antigenically distinguishable from these vaccine reference strains, and as I have shown you, were most closely related to the California/704 reference virus, both antigenically and genetically.

And sequence analysis of N2 neuraminidase genes of recent H3N2 viruses indicates that neuraminidases of recent viruses are genetically distinguishable from the Wyoming virus with these changes, but were very similar to the neuraminidases

of Wellington and California.

Okay. Well, now I'll move on to Influenza B viruses. As Roland mentioned, there are two distinct genetic and antigenic groups of influenza viruses circulating globally. As I mentioned before, the Yamagata lineage viruses which are represented here in yellow have predominated both in the U.S. and worldwide. The Victoria lineage viruses are shown here represented in green. They are still circulating. The viruses that you see here are from Asia, but we had a number of viruses on the Victoria lineage from Florida as well -- from Hawaii as well.

We can see here from this table that the Shanghai/361 reference vaccine virus antiserum covers the current Yamagata lineage viruses quite well. That's true also in this test for the Jilin/20, a little bit less true for the Jiangsu, but there's the very high homologous titer here, and you'll note that there's a recent virus from Florida. We also did have some B activity in Florida earlier, and we had an egg isolate, which we were able to put into ferrets, and that particular egg isolate covers the current strains

very well.

With the B Victoria lineage viruses, you'll remember that the previous vaccine strain was Hong Kong/330-like. Hong Kong/330 was used by some manufacturers. Hong Kong/1434 was used by others, and we're seeing that there's drift away from the previous vaccine strain. We've worked very, very hard to get a vaccine strain that would be suitable on the Victoria lineage, and what we found rather disappointingly is that as soon as we put the B Victoria lineage viruses into eggs, as soon as we isolate them in eggs, they lose the glycosylation site, and they tend to produce ferret antisera which don't uniformly cover the currently circulating B Victoria lineage viruses.

So we put a lot of effort into this, and have been relatively disappointed with the results. Nevertheless we're continuing to pursue this.

This is an updated summary of the Influenza B isolates characterized by CDC. Remember the previous table I showed as a compilation from all the WHO collaborating centers. As I mentioned, we're

seeing quite a number of the B Hong Kong low, the viruses that are fourfold or greater reduced in titer compared to the homologous Hong Kong virus.

But the Victoria lineage viruses are a minority compared to the Yamagata lineage Shanghai-like strain, and the majority of the Shanghai lineage viruses that have been isolated recently are well covered by antiserum to the current vaccine strain.

Okay. I'll be showing evolutionary trees separately for the Yamagata lineage and the Victoria lineage. This is an advantage because you can actually see the strains better on the tree, but it's a disadvantage because you can't see the rather distant relationship between the Victoria and the Yamagata lineage viruses because they're not both on the same tree.

But I think for the purposes of our discussion today, it's best to do the presentation this way.

Here we have our Shanghai/361 reference virus. You can see that there are a number of amino acid changes that have occurred, but that we don't see

a consistency in terms of viruses which are low reactors.

Again, shown in blue we have egg isolates designated. We have a large number of egg isolates, and I think I'll move on to the B Victoria lineage, HA genes.

Our previous recommended vaccine reference strain was Hong Kong/330/2001. You can see that the viruses have moved on. Here are some of the Hawaii strains, the egg isolates that have lost the glycosylation site and haven't produced good antiserum in terms of covering the currently circulating strains.

Again, I'd like to emphasize that the minority of viruses are on that lineage.

Now, if we look at the evolutionary relationships among the Influenza B neuraminidase genes, you can see that there are two distinct subgroups here, but the majority of viruses have neuraminidases in this group here, which indicate that they are reassortants between the two lineages.

So anyway, the neuraminidase genes are

being tracked, and we can see that there are some differences, but we have representative strains from both lineages.

So in summary, Influenza B viruses continue to circulate in many countries. The majority of analyzed Influenza B viruses belong to the Yamagata lineage and are closely related antigenically to the B Shanghai/361 reference vaccine strain.

Most B Victoria/287 lineage viruses that we analyzed were reassortants bearing Hong Kong-like HAs and the Szechwan or Yamagata lineage neuraminidase genes. B Victoria lineage viruses were antigenically distinguishable from the previous vaccine strain from this lineage that was used a few years ago.

And then I just put up the summary table one more time in case there are any questions about the circulation of the different groups of influenza viruses that have caused problems around the world.

Okay. I think I'll stop there and entertain questions.

CHAIRPERSON OVERTURF: Are there questions? Dr. Monto.

DR. MONTO: Given the diversity between the Yamagata and Victoria lineage occurring in Asia at the WHO meeting last week was there any concern expressed in making a global recommendation for continuing with the Yamagata lineage?

DR. COX: We discussed that at length, and I think that what you can see here is that at least for the Asian viruses that we've had, there is approximately a 50-50 split. However, Japan is just experiencing the beginning of its influenza season, and it's predominantly B, and all of the viruses that they had obtained so far were B Yamagata lineage viruses.

So you know, our most current information was that B Yamagata was continuing to predominate in Asia even though the numbers we have are relatively small here for Asia and indicated about a 50-50 split.

DR. MONTO: Do we know anything from China? Because they've diverged from the recommendation, as we all know, in the past.

DR. COX: China has, as you probably know from press reports, had to close down their Institute

of Virology due to a SARS incident, and that led to delay in analyzing and shipping influenza strains from the National Influenza Center in the Institute of Virology in Beijing to the WHO collaborating centers.

So we have not yet received a recent shipment with viruses from December and January.

CHAIRPERSON OVERTURF: Dr. Markovitz.

DR. MARKOVITZ: Yes, I wanted to ask a couple of questions. One, this is just for my information. With the two different strains of Influenza B, in the past when there has been serious illness in kids with Influenza B and deaths, is one strain more likely than the other, you know, one lineage, I should say, Victoria versus Yamagata more likely to cause serious illness?

And then the second question I had is if you could just tell us a little bit more about efforts to develop vaccines for avian flu. I know it's a long story, but if you could summarize a little bit about what different institutions are doing about that.

DR. COX: Okay. With respect to the first question about whether more serious illnesses are

caused by Victoria or B Yamagata lineage viruses, we really don't have enough data to say definitively, but based on my knowledge of the characterization of viruses from children who have died or had serious illnesses, I would say that both lineages are capable of causing serious illness in children.

I would like to offer the opportunity to Pamela McInnes to really talk more about the vaccine development issues. I think I mentioned that vaccine reference viruses had been produced in three different laboratories around the world, one in the U.K. and two in the U.S., and a couple of those reference viruses have been given to manufacturers for production of pilot lots and so on, and Pamela has much more recent information than I have. So perhaps she could make a few comments.

CHAIRPERSON OVERTURF: Dr. McInnes, do you want to do that?

DR. McINNES: Do you want me to do that now or you want to finish any questions for Nancy? Whatever your preference.

CHAIRPERSON OVERTURF: Are there any

further questions for Dr. Cox? Yes, Ben.

DR. SCHWARTZ: I just have a question about interpreting some of the HI data, and specifically with respect to the Type B. You've emphasized in your presentation that what one should look for is a fourfold difference between the various strains with a particular antisera, but you don't really emphasize at all the absolute height of the titers.

If you look at the B data and you look at the Shanghai 361 and compare it with the Florida/7, and both of them seem to be very good across the whole Yamagata lineage, but the Florida/7 titers are higher compared with the Shanghai, and I was wondering if that has any meaning whatsoever and whether that has any predictive value in terms of which may be a better vaccine strain.

DR. COX: We haven't noted that titer -- there is some ferret to ferret variation in terms of the height of titer, and sometimes when we get a very low titer with the particular ferret, we'll inoculate the same strain and we'll get a higher homologous

titer. So there is ferret-to-ferret variation.

We have not noted a correspondence of the homologous titers that we obtain with ferret serum, and a corresponding either enhancement or diminution of titers in humans using those strains for vaccines, but it's a good question, and we have -- there are some factors about the hemagglutinin which we don't understand which makes some strains inherently more immunogenic than others.

We have been discussing and thinking about ways to get a better handle on what those factors may be and how to predict which strains might be the best vaccine strains. So far we don't have a handle on that, and we've often been very, very limited in terms of the number of egg isolates that we had available. I think we've put after we faced the Fujian situation where we didn't have an egg isolate. We've put an enormous amount of effort and had partnership with industry in this effort to obtain more egg isolates. So we really may have more options in the future, and it may be more important to really have a handle on predictors for immunogenicity in humans.

CHAIRPERSON OVERTURF: Dr. Eickhoff.

DR. EICKHOFF: Nancy, a question about the H3N2 data. If I'm reading the dendrograms correctly, and I may be stumbling on them, is the drift represented by the recent A/California-like isolates in the same direction as that started by the A/Wellington strain, or does it go off in a wholly different direction?

DR. COX: You are correct. The A/California virus has simply moved on from the Wellington strain. So it's just an advance. It's just Wellington progeny with a few more changes.

DR. EICKHOFF: And I also get the impression that the shift, the degree of drift, rather, is much less dramatic in this instance, in the A/California strains than the drift of the A/Fujian strain was from its predecessor. Is that correct?

DR. COX: That is correct.

DR. EICKHOFF: Up to a point.

DR. COX: Up to a point. I mean, you really have to look at the gestalt, and I think that when Roland begins discussing the human post vaccine

serology, you'll see why I was greatly surprised by the human post vaccine serology.

It seemed to differentiate current strains even better than our ferret sera did, and that is the first time in my memory that that has been the case. So I was, shall we say, unpleasantly surprised by results for the H3 post vaccine human serologic testing that was done, and we'll get onto that later.

DR. EICKHOFF: Can I ask a further question then?

DR. COX: Certainly.

DR. EICKHOFF: And maybe this is a question that Keiji can answer also or can't answer also, as the case may be. Do you have any sense, considering that the A/California strains now at least in some parts of the country seem to predominate? Is this strain behaving any more aggressively epidemiologically and can we, therefore, anticipate that our season this year may go on further than it already has? Is that a fair inference to draw or not?

DR. COX: I think it is very difficult to say. I think we could have in areas of the country

that were not so heavily affected by influenza last year, we could have continuing H3 and B activity. It's really difficult to predict how the strains are going to behave in the population. I think we just have to wait and see. We can't predict.

CHAIRPERSON OVERTURF: Yes.

DR. KARRON: Two questions actually about the H5 presentation. One was that you mentioned heterogeneity and antiviral susceptibility, and I assume that means a susceptibility to amantadine and rimantadine, and these are all susceptible to the neuraminidase inhibitors, or is that not the case?

DR. COX: You're right. I didn't go into a lot of detail. Not all of the H5N1 viruses that we received last year were resistant to the adamantanes, but all of those that were isolated from humans were resistant to adamantanes. So there were some in birds that were sensitive to adamantanes. We have tested all of the H5N1 viruses that we've received, and in laboratory tests, the viruses are sensitive to the neuraminidase inhibitors or we use oseltamavir. We don't use zanamivir.

And animal experiments done by Rob Webster and others have indicated that in vivo in animal models the viruses are also sensitive.

DR. KARRON: And then my second question was actually about I noticed that you had said with the ferrets when you -- obviously there's tremendous drift of the H5s, but they all, in fact, make antibodies to all of the viruses. I was wondering if you had any data from the survivors of H5 human infections about the quality of their HI responses to these H5 viruses.

DR. COX: A very good question. It has been extremely difficult getting serum from survivors. Oftentimes individuals are reluctant to give blood for a variety of reasons, and then it's often difficult to get the serum sent to us. We do have some serum in very limited quantities and have requested additional amounts and we're looking at the ability of serum from survivors to inhibit in neutralization tests a variety of viruses.

So we should have a better handle on that, and of course, one of the ideas for the pilot lot

testing in humans is to look at the ability of the antibody induced by the pilot lot vaccines to inhibit a variety of the antigenic variance of H5.

CHAIRPERSON OVERTURF: Dr. Couch.

DR. COUCH: I want to pursue Arnold's comment a little bit, and I guess I really have a comment rather than a question for you, Nancy, and I was not here last year, but I'm sort of back in the same mode I was two years ago with the Influenza B strains.

And you look at these epidemiologically. Well, I think mostly people know they were dominant in Asia for a number of years before they began to show up in the rest of the world, and then they've been jockeying with each other for dominance would be the way I would describe what's gone on in the last few years.

And our approach to handling that dominance is to guess which one is going to be dominant in a coming year, and it has been amazingly successful that the Victoria derivative was guessed the right year and then went back to Shanghai. But I

think it emphasized that we're guessing is the point I wanted to make.

And we've looked at the serologic data in the past that looks very much like the same data we have this year, and that is that adults and elderly individuals have a reasonable degree of cross-reactivity to vaccine responses to either one. You get the Yamagata derivative and you have a reasonable cross-reactivity to the Victoria and vice versa.

It's children where the differences are really distinctive. If they got the Victoria vaccine, they have very little immune response that you would say would be protective against the Yamagata derivative and vice versa, and if you wanted to look at some of that data, what's going to happen with some of our guessing, some of you remember an old term that Paul Gleason brought in a few years ago of herald wave. We're looking at a herald wave, you see, of the Victoria derivative, and here we're guessing that that's not going to be true. It's going to be the Shanghai.

I think I asked Walter the last time I did

this if he could remember, but the two separate Bs have been used in the vaccine in the past. I meant to go back and check when that was done, and you see, I tried this a couple of years ago and it didn't fly. I'm going to try it again.

You see, based on what we know about these immunologically, if you took that 15 micrograms, and let's assume that at least for the time being is fairly rigid, and you split it between those two and you look at the responses in the elderly, adults and the elderly, that they would be pretty good to either one if you've split it, you know, based on what we know about the cross-reactivity of the 15 micrograms of each.

That might not give you as much response as you'd like in those children, but it would insure that you've got protection against both of these strains, which will be present, we would say, and hopefully when we only pick one we're guessing the dominance, but that would be of less concern.

Now, I know that has not been pursued, and you need immunologic data to go along with that kind

of thing, but if we continue to see these two jockeying, I think we need to think about ways to approach that other than immunologically with vaccines rather than just guessing which one is going to be dominant.

So I didn't have a question. I meant it as a comment, unless you want to add to that.

DR. COX: I think that you have hit the nail on the head. As long as we have these two quite distinct lineages of Influenza B circulating worldwide, we are making an educated forecast for which virus is likely to predominate, and we could be wrong.

I think that in an ideal world, we would have a tetravalent vaccine, but we're not in an ideal world and we know that that would reduce the number of doses of vaccine in an environment where we already are concerned about vaccine supply. We know that young children respond relatively poorly to the influence of the B component of the vaccine. We have to think about the manufacturing issues involved and the standardization issues, the whole complex of

issues that these changes bring up.

And I think we are in a dilemma, and we should talk about these things, but we should also recognize that there are many practical issues that would go along with the departure from the way we've been doing this.

Roland may wish to add something or others may wish to.

CHAIRPERSON OVERTURF: I'm going to give Dr. Couch the last say for this segment and then we'll take a break for 15 minutes, come back, and we can discuss that.

DR. COUCH: Manufacturers certainly would not like to hear adding a different antigen, but part of my point, Nancy, was that we have had a tetravalent vaccine. So we have the precedent of it being available and it having been circulated, and that tetravalent was with the B strains.

CHAIRPERSON OVERTURF: So I would propose we take a 15 minute break and be back at 10:45.

Thank you.

(Whereupon, the foregoing matter went off

the record at 10:31 a.m. and went back on the record at 10:55 a.m.)

CHAIRPERSON OVERTURF: Dr. LaRussa.

One more comment about the B issue, and then we'll turn to Dr. McInnes.

DR. LaRUSSA: So a number of us pediatricians were talking on the side during the break, and before I make this comment, I want to emphasize that I'm not proposing we do this for this coming year, but just to plant this seed for the future.

If, in fact, it could be shown that if you put the two B lineages in the same vial and you could get good immunologic responses in children, one way around doing this dance we do every year about which B lineage we're going to pick is to make a separate pediatric vaccine, which you'll already do. You'd know that you'd have a stable demand for it every year. You'd make your eight million doses. It would be there because we do very well with immunizing kids, and you could get around this whole issue because one of these years we're going to do the wrong dance and

pick the wrong strain.

So what I would propose is that we think about the kinds of serologic studies you would need to do to show that you could put two B lineages in the same vial and get a good response in kids, and then think about a separate pediatric vaccine for the six to 24 age group.

CHAIRPERSON OVERTURF: Dr. McInnes.

DR. COUCH: It's testable.

CHAIRPERSON OVERTURF: Yes, you can stay there.

DR. McINNES: Thank you very much.

This is a summary update. A year ago at the vaccine strain selection meeting, Dr. Lambert made a presentation on H5, and the initial responses of different agencies within the Department of Health and Human Services, and this is an update for you.

It is personally been one of the most gratifying experiences in government because I think the flu machine within government has always worked very, very well, but this has been really a marvelous experience of people really working extremely well

together, as well as with manufacturers and other government contractors, working very hard.

Nobody should underestimate how seriously the department is taking the threat of pandemic influenza. It is the subject of a great percentage of our lives and of our time, and I will just summarize. I'm not going to provide lots of details.

The reference virus, you heard Dr. Cox talk about the reference virus for the H5. The particular reference virus that is being used to provide the pilot lots of vaccine that I will be talking about was produced under a government contract, and it utilized reverse genetics technology to make this reference virus, and it turned out to be a real test of the select agent rule.

And so the dry run of, in fact, going through the process of generating the data and the pathogenicity data on these genetically engineered viruses did go through the select agent rules and, in fact, the data were very compelling, and it resulted in the exemption from select agent rule.

And we still though were subject to the

U.S. Department of Agriculture permitting process to move this virus. So the reason I am sharing these pieces with you is that many of the pieces that will be in play during pandemic response have, in fact, been tested in this past year and hopefully will facilitate the path for future journeys.

Pilot lot contracts were awarded to the two licensed and inactivated vaccine manufacturers in the United States, licensed in the United States, and that was Aventis Pasteur, and I'm not sure if I should be calling it Sanofi now, but when I say "Aventis," I hope I'm calling it the right name, and Chiron.

So the contracts were awarded around May of 2000, May through June 2004. The reference viruses were produced, characterized, exempted from select agent and moved to both manufacturers, and both manufacturers have been underway with pilot lot production of an H5N1 inactivated vaccine candidate.

The quantities of doses that have been procured for the pilot lot scale is less than 10,000 doses from each of the manufacturers, and they're in two different dose concentration formulations.

Aventis has completed its bulk manufacture, as well as its formulation and filing and finish and testing, and the IND. We have filed the IND for the clinical evaluation of this candidate.

Their clinical development plan has been designed and laid out and will be implemented through the NIAID vaccine and treatment evaluation unit contracts. We have proposed two different programs, one for the Aventis candidate, one for the Chiron candidate because they'll be available at different times, as well as we want to insure access to the appropriate number of individuals in each of the target population groups.

The clinical trial scenario will begin with a trial for safety and immunogenicity in healthy adults, and with those data in hand, we'll move to evaluation in the elderly and in younger children.

Coupled with this for the pilot lot scale of production, the department awarded a contract for the commercial scale production of an H5N1 vaccine and the intent of this was to test the commercial production capacity and the ability to respond, as

well as handling of these candidates in the facilities. This is a much larger scale.

This has been completed. The vaccine bulk has been made. The formulation, finishing and vialing will be dependent on the data that come out of the clinical evaluation program of the investigational pilot lots.

In addition, the department has awarded a contract to secure egg supply year around to enhance our capacity to respond to produce pandemic vaccines. Couple a deliverable under this egg securing contract is, in fact, pilot lots of investigational candidate vaccines for pandemic preparedness, and so over a period of years, several of those will be made and will be evaluated, all of which is designed to build on our knowledge of safety and immunogenicity, the human response to these novel antigens.

That's really a summary of where we are on the response to H5.

CHAIRPERSON OVERTURF: Dr. Markovitz.

DR. MARKOVITZ: Yes, thanks.

I had a couple of questions. One is how

did people get around the issue that these tend to kill eggs, chicken eggs?

And then second of all, how are the vaccines that you're talking about -- are they going to be able to deal with this heterogeneity issue that Nancy Cox was alluding to or is that going to mean that we're going to have to be, you know, similar to what we do with the other strains, sort of constantly revising them?

DR. McINNES: Sir, the issue around being able to get a meaningful yield by growth in eggs is dealt with by engineering the virus, the wild type virus so that, in fact, you're going from the tiger down to the pussycat that can, in fact, be grown in egg, moved to the manufacturers and dealt with under usual biocontainment levels. So that, in fact, happened very successfully and yield was quite good.

We would anticipate that the early clinical studies will, in fact, be generating sera in response to this particular reference virus candidate that can be the subject of investigation in terms of what sort of protection one might derive to strains

that have some change in them or some drift in them.

DR. MARKOVITZ: Can you tell me more about how it was mutated without violating proprietary matters?

DR. McINNES: There is, in fact, a publication on this, which I'd be happy to share with you.

DR. MARKOVITZ: Yes, that would be good.

CHAIRPERSON OVERTURF: Dr. Eickhoff.

DR. EICKHOFF: Pamela, I know regarding the reverse genetics technique great concerns have been expressed in the past about intellectual property rights. Have those been resolved or is that being addressed?

DR. McINNES: It has been, I think, addressed extensively, and I think there are paths to resolution for this. In the investigational framework and experimental framework it's not an issue. The issue comes around the commercial area. So, yes, this is the subject of a lot of discussion, and I think there are solutions on the table to deal with it.

CHAIRPERSON OVERTURF: Dr. Karron.

DR. KARRON: Are there differences in this Sanofi and the Chiron products or are they essentially the same product?

DR. McINNES: Our goal was to go as close as possible to their currently licensed methodology and formulations because we felt that that would assist in a licensure process in an emergency situation. So you wouldn't be dealing with trying to deliver huge amounts of vaccine under IND.

So given that they produced them in a pilot facility, it's not identical, but the hope was that the process would be as close as possible and the formulation would be as close as possible to their license formulation.

CHAIRPERSON OVERTURF: Were there any other questions or comments anybody else wanted to make? Yes, Dr. Royal.

DR. ROYAL: Thank you.

One would expect that since this is a genetically engineered virus that one could introduce a series of mutations and establish panels that one could use to screen different strains. Is that sort