FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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VACCINES AND RELATED BIOLOGICAL PRODUCTS
ADVISORY COMMITTEE

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MEETING

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WEDNESDAY,
FEBRUARY 28, 2007

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The meeting convened at 8:00 a.m. in Salons A, B, and C of the Hilton Washington D.C. North/Gaithersburg, 620 Perry Parkway, Gaithersburg, Maryland, Ruth A. Karron, M.D., Chair, presiding.

ADVISORY COMMITTEE MEMBERS PRESENT:

RUTH A. KARRON, M.D. Chair	
ROBERT COUCH, M.D.	Temporary Voting Member
NANCY COX, Ph.D.	Non-Voting Member
THEODORE EICKHOFF, M.D.	Temporary Voting Member
MONICA M. FARLEY, M.D.	Member
BRUCE GELLIN, M.D., M.P.H.	Temporary Voting Member
WAYNE HACHEY, D.O., M.P.H.	Temporary Voting Member
SETH HETHERINGTON, M.D.	Industry Representative

LISA JACKSON, M.D., M.P.H.	Member
PAMELA McINNES, D.D.S.	Temporary Voting Member
JOHN MODLIN, M.D.	Member
CINDY PROVINCE, R.N., M.S.N., M.A.	Temporary Voting Member
STEVEN SELF, Ph.D.	Member
JACK STAPLETON, M.D.	Member
MELINDA WHARTON, M.D., M.P.H.	Temporary Voting Member
BONNIE WORD, M.D.	Member

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FDA PARTICIPANTS:
CHRISTINE WALSH, R.N.
Executive Secretary
NORMAN BAYLOR, Ph.D.
Director, Office of Vaccines Research and Review
SARA GAGNETEN, Ph.D.
Scientific Reviewer, DVRPA
RAKESH PANDEY, Ph.D.
Division of Vaccines and Related Products Applications
GALINA VODEIKO, Ph.D.
Division of Viral Products
JERRY WEIR, Ph.D. Director, Division of Viral Products
ZHIPING YE, M.D., Ph.D. Division of Viral Products

SPEAKERS:
TONY COLGATE Novartis
ANGELA OWENS, M.P.H.
Air Force Institute for Operational Health
ALBERT THOMAS Sanofi Pasteur

A-G-E-N-D-A

TOPIC 4: INFLUENZA TYPE B STRAIN - DISCUSSION ON CIRCULATING LINEAGES

P-R-O-C-E-E-D-I-N-G-S

(8:12 a.m.)

DR. KARRON: If everyone would please take their seats. We're going to begin this mornings session.

Yesterday we heard mostly about pandemic influenza and today we're going to hear mostly about seasonal influenza.

Christine?

MS. WALSH: Thank you, Dr. Karron.

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 this meeting of the Advisory Committee.

Today's session will consist of presentations that are open to the public.

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

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

"This brief announcement is in addition to the conflict of interest statement read at the beginning of the meeting on February 27 and will be part of the public record for the Vaccines and Related Biological Products Advisory Committee Meeting on February 28, 2007.

This announcement addresses conflicts of interest for the discussion of Topic 3, Discussion and Recommendation on Strain Selection for the Influenza Virus for the 2007-2008 Season, and Topic 4, a Discussion on Circulating Lineages of Influenza B Virus.

In accordance with 18 U.S.C. Section 208(b)(3), waivers have been granted to: Dr. Robert Couch, Dr. Lisa Jackson, Dr. Ruth Karron, and Dr. John Modlin.

Dr. Seth Hetherington is serving

as the industry representative, acting on behalf of all related industry and is employed by Icagen, Incorporated. Industry representatives are not special government employees and do not vote.

In addition, there may be regulated industry or other outside organization speakers making presentations. These speakers may have financial interests associated with their employer and with other regulated firms. The FDA asks, in the interest of fairness, that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. These individuals were not screened by the FDA for conflict of interest.

With regard to FDA's guest speaker for Topic 3, the Agency has determined that the following information is essential:

The following information is being made public to allow the audience to objectively evaluate any presence and/or

comments.

Mr. Albert Thomas is employed as Director, Bio-Manufacturing, Sanofi Pasteur in Swithwater, PA.

This conflict of interest will be available for review at the registration table.

We would like to remind members and participants that if the discussions involve any other products or firms not already on the agenda for which an FDA-participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Committee of any financial relationships that you may have with any firms, its products and, if known, its direct competitors.

Thank you. And Dr. Karron, I turn the meeting over to you.

DR. KARRON: Thank you, Christine.

Our first speaker is Dr. Rakesh Pandey from the FDA.

DR. PANDEY: Thank you, Dr. Karron.

Good morning, everyone. I welcome you all to this mornings meeting.

I am Dr. Rakesh Pandey from the Division of Vaccines Applications at CBER's Office of Vaccines where I have been a scientific reviewer and have been involved with the review of influenza files for the last 12 years.

I'm going to introduce a topic for today's discussion on the composition of 2007-2008 season influenza vaccines.

This meeting has been an annual activity for years. And around this time, this Advisory Committee meeting is convened to get its recommendation on the composition of the influenza virus vaccine for the next season in the United States.

So why do we change influenza vaccines annually? Influenza vaccine is probably the most widely used human vaccine in the United States and millions of doses are produced and used year after year.

Influenza vaccines do not give long lasting immunity and generally do not protect well against the strains that are not included in the vaccine. So as listed on this slide, efficacy of the influenza vaccine is related to two things:

The efficacy of the influenza vaccine is considered to be related to vaccine potency. That's the amount of hemagglutinin antigen present in the inactivated vaccine, which is measured by SRID, or a single radial immunodiffusion acid. The antigen content relates to the immune-SRID, which is measured by the immune response seen in HAI assay.

Also, the efficacy is related to the match of HA and NA antigens to those of the circulating strains. The HA and NA

antigens keep on changing continuously, and that is why influenza virus is considered to be a moving target as far as the vaccines are concerned.

Influenza vaccines were licensed in 1945 for the first time in the United States. And, in fact, within two years of their use, evidence came up for reduced vaccine effectiveness because of the antigenic drift.

In order to ensure the effectiveness of influenza vaccine from season to season, we review the antigenic composition of the vaccine every year and change one or more strains as need, as and if needed.

However, in order to come to a conclusion that a change in vaccine composition is warranted, these are the four questions that we need to answer.

First, we need to know if there are new influenza vaccines out there that are antigenically different from the ones in the

vaccines. And for this purpose, the WHO, CDC, and other agencies are involved in global surveillance, which is a collaborative effort to monitor the emergence of new influenza viruses that might be showing an antigenic drift or shift.

Then, we need to know if these new viruses are actually circulating and spreading from one geographical location to another in human populations. Are such viruses confined to one geographical location only? Many times we may see that a new isolate may appear in one location and then it might just simply disappear. So we may not have to worry about those viruses.

Now, if an answer to these first two questions is yes, then we need to know if the currently used vaccines work well against the new isolates. So serological studies are conducted to compare the inhibition of these isolates against serum obtained from those vaccinated with the current vaccine. And this

is to answer if the current vaccine strain is well matched or whether it will work against the newly identified strains.

Finally, if we determine that the current vaccine strains do not match well against the new isolates, then we need to ask, is a suitable vaccine candidate available for including in the next seasons formulation.

So, if you make a recommendation to include a new strain in the vaccine and it does not grow well in eggs, it would not help much, since all the currently licensed vaccines in U.S. are made in chicken eggs.

On this slide we have listed the recommendations for 2006, 2006-2007 influenza season. Those are the vaccines that are currently being used.

Last season was one of the few in recent years when we had two strain changes, and those were the H3N2 and the B strain. And as is shown on the slides, you can see the ones in the red are the actual strains that

were used by the manufacturer of influenza vaccines in the United States.

Just a few years ago, the number of influenza vaccine manufacturers with inactivated license vaccine had gone down from four to two, leaving only Fluzone and Fluvirin on the market. This happened when King Pharmaceuticals and Wyeth went out of the influenza vaccine business.

However, since then we have made a lot of progress. We have overcome the shortage situation of 2004 and we have two new inactivated vaccines available for use.

Besides Fluzone and Fluvirin, which have been on the market for quite some time, we have now GSK's Fluarix and ID Biomedical's FluLaval licensed. GSK's Fluarix vaccine was licensed in 2005, and last year we licensed FluLival.

Besides these four inactivated vaccines, we also have MedImmune's live attenuated vaccine, FluMist, which was

licensed in 2003.

This slide shows the time line for vaccine production, and it also highlights the activities relative to influenza vaccine manufacturer, which go on for the whole year, in order for us to have vaccine for use during the September to January time frame.

For the vaccines to be available for use, one of the other production activities, as I said before, goes on for the entire year.

New isolates are made available to the manufacturers by CDC and CBER throughout the year, and the manufacturers keep working on them to make sure they are usable in case they are recommended for use in the vaccines.

Then from ordering the eggs to making the monovalent strains for use in the vaccines in the U.S., the activities go on from January and sometimes up to the late end of fall. And to that point, they will switch over to the strains for making monovalent for

use in the southern hemisphere vaccine.

So the formulation of trivalent vaccines usually starts somewhere around June, and the activities related to filling, testing, and release of the vaccine could continue until the end of the year.

And finally, any, sometime around July when the animal strain change supplements are approved, the distribution activities begin, and they continue for the next few months.

Now, in order for all of this to happen, the support activities go on for the whole year. Around this time of the year, WHO, U.S. Public Health Services, and VRBPAC gives recommendation. Then towards fall, the Southern Hemisphere recommendations come out.

And the whole process of surveillance, identification of new relevant strain, and preparation of regents continues for the entire year.

So basically, even though we

consider influenza vaccines as seasonal vaccines, they are seasonal only in the sense of use. In the sense of manufacturing, they are essentially a non-stop process with hardly a break in manufacturing.

So time taken for the trivalent vaccine lot to be available after a strain change, now since there can be a significant impact of the Committee recommendations on the manufacturing process, later in this session, the industry representative will go over this thing in more detail.

As you can see from the slide, it can take up to six to eight weeks for the manufacturers to optimize a strain for production after it has been made available to them. So any delay in identifying the strains to be used in the vaccine could delay the availability of vaccine in the fall.

Now, another great limiting step in this process is the availability of reagents needed for the manufacturers to

standardize the vaccine and the assigned potency value.

Now, although the manufacturers may start production of some of the vaccines monovalent at risk, a timely VRBPAC recommendation is critical for trivalent vaccine to be available in fall, in time.

Basically, it could take up to 18 to 20 weeks for the first trivalent lots to become available after the change in a single strain and the recommendations. If there is an additional strain change, it could delay the process by another few weeks. And if all three strains have to be changed, the situation could become really challenging.

The WHO held its meeting for the 2007-2008 Northern Hemisphere formulation from the 11 to 14 of this month, where they reviewing the surveillance information and the information on antigenic and genetic characteristics of the viruses circulating around the globe. They also reviewed the

serological data as how the circulating viruses, isolated from different parts of the world, react against the serum obtained from currently used vaccines.

Now, based n the discussions, WHO gave the recommendations for the vaccine composition for the 2007-2008 season for the Northern Hemisphere, and that's published on their website, which is listed here.

And I also have that listed on this slide, the recommendation basically reads, "It is recommended that the vaccines to be used in the 2008 Northern Hemisphere winter contain the following:

An A/Solomon Islands/3/2006 (H1N1)-like virus.

An A/Wisconsin/67/2005/(H3N2)-like virus.

And a B/Malaysia/2506/2004-like virus."

And out of these three, only the H1N1 A/Solomon Islands is a new

recommendation. The other two have been from the last years vaccine.

Finally, the agenda for the Committee would be to review the surveillance data on epidemiology and antigenic characteristics, and the serological responses to the vaccine, and the availability of candidate strains and reagents, which would be presented by the next few speakers, and to discuss which strains should be recommended for the antigenic composition of the 2007-2008 influenza virus vaccine.

So, at this point I will stop and, unless there are any questions from me, I'll turn it over to the next speaker.

DR. KARRON: Our next speaker will be Dr. Anthony Fiore from the CDC.

DR. FIORE: Hi, I'm Anthony Fiore from the CDC, Influenza Division. I'm standing in for Joe Bresee, and I am going to provide an update on the influenza surveillance for this current flu season.

This depicts the various different surveillance systems which come into CDC, are compiled, and then go back out again to you, and the public, and healthcare practitioners, and so on.

We do conduct laboratory based surveillance with strains coming into CDC from a variety of different sources to be characterized.

We have Sentinel Provider surveillance, which consists of a variety of different providers who provide isolates and clinical information on patients that come in with influenza-like illness.

Population-based hospitalization surveillance, which is conducted in a number of different areas in the U.S., which were, those of you who went to David Shay's talk yesterday saw the map of where our population-based hospitalization surveillance is conducted.

Assessments by state and

territorial epidemiologists about flu activity weekly from their states.

A pediatric mortality surveillance system, which was setup in 2003-2004 after the early and fairly severe season that we had that year.

And vital statistics and registrars who provide us with data for 122 cities mortality surveillance for pneumonia and influenza, and sorry, influenza, right.

And the next five slides are going to sort of give you a time lapse version of this years flu season. The season started off in November with a number of interesting small town, apparently school-based outbreaks in North Carolina, some influenza-B outbreaks. And over the course of the next few weeks, it kind of evolved to be a southeast-U.S. phenomenon.

And again, mostly concentrated in the southeast toward the end of last year, and then as we came into this year, spread

throughout other states.

And you can see by the color-coding, regional activity as assessed by the state and territorial epidemiologists is depicted in blue, and widespread activity in red.

And then this past week you can see where we have a widespread or regional activity in most states.

This is the Sentinel Providers surveillance system. And what you see here is the last two years tracked by the solid lines, and this current flu season by the red line with the diamonds on it. And it predicts the percentage of visits to the Sentinel Providers for influenza-like illness by week. And as you can, there's a dotted baseline there which depicts what the average is thought to be, the national baseline, and then over the course of the year the people who come in for INI is shown by the lines.

And what you can see here is this

season, which is depicted up to about week seven or so, we have a fairly typical percentage of visits for ILI. It tracks more or less the same as the last two years.

Here is information from our influenza hospitalization surveillance. This is laboratory-confirmed influenza in the new vaccine surveillance network, which is three sites around the U.S. And it tracks hospitalizations due to lab-confirmed influenza among zero to four year olds.

And this shows the last six seasons, the previous five seasons by the solid lines, and this season by the incomplete red line with the red circles on it. And what it shows you is that this season is very similar to four out of the last five seasons, that the blue line is the 2003-2004 season, which had early reports of illness among children, severe illness.

This is the Emerging Infections Program, this is, I believe, eight sites

around the country. It again was shown yesterday by David Shay on the map. Again, this is lab-confirmed influenza vaccinations. This is just shown for the last three years, sorry for the last four years counting this one. And this shows not only 0 to 4 year olds, but also 5 to 17 year olds. The younger children are shown with solid lines, the older children with the dotted lines. And you can see this season's information, again with the red lines with the circles showing the 0 to 4 year olds, and then right there on the x-axis the dashed red line showing the 5 to 17 year olds. And this is a cumulative number of hospitalizations and that's why the number go up like that.

And then this is the pneumonia and influenza mortality surveillance system, often called the 122 city surveillance, showing the pneumonia and influenza mortality as reported by death certificates and registrars around the country. What is depicted by the black

lines, the top black line is the epidemic threshold, and the bottom, the bottom black line is the seasonal baseline. And then the actual reports are tracked with the red lines. So you can see, we haven't actually spiked up over the epidemic threshold in this flu season.

Now, I mentioned that in 2003-2004 we started a pediatric death surveillance. And as of February 15 of this year, CDC has received 15 reports of influenza-associated pediatric deaths. Ten of these were among children five years of age or older. Three had underlying medical conditions. Five had no known underlying conditions. And two's previous health status are yet unknown. Nine of these children were unvaccinated, speaking strictly of the ten that were 5 years of age or older.

And then as compared to the last couple of flu seasons, in 2004-05, 44 deaths were reported. In 2005-2006, 48 deaths, and

then going back to 2003-2004, 153 deaths.

This is the Collaborating Laboratories Strain Surveillance Summary for 2006-2007. And what you see depicted here is, let's see, yes, of the 10,458 viruses typed, 84 percent of them had been Influenza-A, 16 percent, B. Of the 28 percent of those that have been sub-typed, 87 of the As were H1, and 13 percent of the As were H3. And we've seen an increasing percentage in the last couple of weeks of H3s.

Switching over to anti-viral resistence data generated so far this year and as compared to last year, you'll recall last year there was the identification of high levels of adamantine-resistants among isolates, starting in 2005. And for comparison, in the last flu season, two out of eight, or 25 percent of the H1s are adamantine-resistant. And 192 of 209 H3s tested, or 92 percent, were adamantine-resistant.

There are fewer of these adamantine-resistants, or the proportion of the adamantine-resistants is lower this year, but there is still a considerable amount of it. And global surveillance so far, three percent of the 199 H1s tested have been resistant. Forty-four percent of the H3s tested have been resistant. Among U.S. isolates, the numbers are similar, one percent of H1s and 33 percent of the H3N2s, although we don't have very many of those tested so far.

As far as resistance to neuraminidase inhibitors, oseltamivir or zanaminivir, among the isolates tested so far since 2005, and that's 437 isolates, there have been none identified as being resistant.

And just to update you on issues that will come up in front of the ACIP over the next year, and also came up at the meeting last week, of course the new vaccine strains, which we're here today to discuss. The

recommendation, the ACIP recommended, as you would expect, that adamantine not be used in treatment of influenza-A viruses.

We did make one change to the recommendations. And this had to do with harmonizing the American Academy of Pediatrics and the ACIP recommendations for young children in a specific subset. As you would recall, young children who are six months to less than nine years of age who get vaccinated for the first time are supposed to get two doses. What, the disharmony occurred had to do with children who only got inadvertently only got one dose in that first year. And what the ACIP recommendations have been changed to, and what the AAP recommendations already were was that those children who got one dose in their first year of being vaccinated in that age range, in the second year of being vaccinated should go ahead and get two doses.

Now, what was not changed was the

age groups or the risk groups that were recommended for routine vaccination. And there is going to be continuing discussion of advancing the recommendations to include other age-groups or risk groups over the next several years. But for this coming flu season, the recommendations have not changes as far as that goes.

And that's all I have to say. I can either take questions now or do you want to wait after the session, either way.

DR. KARRON: We can take questions now if there are any.

Okay. Thank you, Dr. Fiore.

Our next speaker is Dr. Nancy Cox from the CDC, who will tell us about worldwide surveillance.

DR. COX: Thanks very much. It's a pleasure to be here. And I'll try to make my presentation as comprehensible as possible. For those of you sitting in the back of the room, I know you won't be able to see the

slides, so there are plenty of seats in front if you would like to move up and have a better view.

I'm going to be talking about what we're seeing globally with respect to influenza activity and influenza viruses.

I will be talking about hemagglutination-inhibition data, with post-infection ferret sera.

I will be talking about the genetic analysis of the HA and the NA genes of the viruses.

And I will not be talking too much about the serology, the post-vaccine serology unless you have specific questions, based on the data in your packages, because I think that data will be covered by Dr. Zhiping Ye later on.

Influenza H1 activity has been relatively light, although influenza H1 viruses have predominated in the United States and a few other countries, and in a few other

countries have caused moderate outbreaks, or moderate levels of activity. But really, H1N1 hasn't caused many problems, except in the United States.

If we look globally at the number of H1N1 viruses that were isolated within WHO's global influenza surveillance network, we can see that for 2006-2007, which is shown in the blue line, we really have relatively low numbers of H1 activities isolated worldwide.

What that means, of course, is that we have a limited amount of data. If we look at the viruses that are characterized in all of the WHO collaborating centers, our own included here, we had the largest number of H1 viruses characterized during this period from September to the current time. But there were also a significant number characterized in Australia.

So, what we see is that we have, the majority of viruses are still New

Caledonia like, but there are a number of low reactors. And they were seen particularly at the WHO collaborating center in London, where they had a higher proportion of low reactors.

I apologize for the HI table, but I think it's important for us to go over carefully and to understand the kind of data that we're looking at on a weekly basis.

All of the WHO collaborating centers generate one or two HI tests per week on average, or at least we do. And we often have to retest viruses if they appear to be low and we want to make sure that they're actually low reactors.

So what we have here are the reference antigens, starting with New Caledonia, the vaccine strain, and we have a number of other reference antigens, which we have put into ferrets to develop post-reaction ferret serum.

So these across the top are the corresponding reference ferret antisera. And

what we're really looking for is a lower level of reactivity than we see with the homologous virus interacting with the homologous serum.

So here you see a number of viruses, the Kentucky, the Virginia, and the St. Petersburg, which are very well inhibited, equally well-inhibited by anti-serum to the New Caledonia vaccine strain, as New Caledonia is itself.

Starting here with the Hawaii/15/2001 strain, we see quite a marked reduction in the ability of anti-serum to the New Caledonia virus to inhibit hemagglutination of this virus.

And if we look across here, we can see that it's true not only for the New Caledonia serum, but for the Kentucky serum and the Virginia serum, as well.

So Hawaii/15/2001 was one of the first viruses that we saw which had a specific amino acid change and a corresponding difference in activity with the New Caledonia

serum.

When we put the Hawaii virus into ferrets, we got a homologous titer of 320 and viruses like it in having that same amino acid change, which I'll talk about in more detail later, are well-inhibited by anti-serum to this particular virus.

So we've, we've been able to really distinguish viruses that have a change from lysine to glutamic acid at amino acid 144. And that is antigenically important area of the globular head of the HA.

So we can really group these viruses into two groups, those that are well inhibited by the New Caledonia serum and those that are not, but that when we make antiserum to these viruses, they cover viruses with that 144 change.

So here we have a lot of test antigens that have been isolated, many of them during the last couple of months in December and January in the United States. And really

the majority of them are well-inhibited by the New Caledonia serum. However, you can see this Texas virus, which is not, is well-inhibited by serum to these viruses, including the Solomon Islands reference strain, which I'll talk about later.

Likewise, if we look at viruses from Asia, we see that there are some viruses that are still well-inhibited by the New Caledonia serum, but we see a larger proportion of viruses from Asia, which fall into this other group with the change from lysine to glutamic acid at amino acid 144, and they're well inhibited by antisera to these reference strains, including the first one, the Hawaii/5, and the Solomon Islands/2006, which is the current reference strain.

I should note here that this is Solomon Islands IVR 145, which is a high growth re-assortant, which has been produced in Australia and circulated to the other collaborating centers in time for us to

produce antiserum against this particular virus.

So, in summary, while we still have a number of viruses which are well-inhibited by the New Caledonia antiserum, we see a growing proportion of viruses, particularly in Asia, which do have the signature change and which are better inhibited by antiserum to viruses like the Solomon Islands virus.

If you look at just our own CDC data, you can see quite clearly that although the proportion of viruses that are, that have a reduced titer to New Caledonia is really a moderate proportion, and actually somewhat less than we saw during the period of April to September. We have, we see viruses predominantly from the United States during this October to February period, but if you look at where we're seeing the low-reacting viruses, it's in Asia and Central and South America. And so, specifically, the majority

of the viruses that have been sent to us from Asia during this period from October to February, as well as the period from April to September 2006, from Asia, are low-reactors.

Now, I apologize. This is going to be very difficult for you to see in the back of the room, and I realize that your handouts are not color coded. The color coding actually helps a great deal because we've color coded the viruses by month of isolation so that we could really depict where we're seeing, if we're seeing a trend toward more viruses being in one group or another.

What you can see here is that the H1N1 viruses genetically divide into two distinct groups, or clades, Clade 1 here and Clade 2 at the top. These changes did not confer antigenic changes on the viruses, however. So we were not able to distinguish viruses from these two groups until we started seeing the change 144, the lysine, oh, this is the lysine to arginine, which is a different

change, until we started seeing the lysine to glutamic acid change pop up.

And it's a little bit, well, it's really quite interesting actually, because we're seeing that this change is occurring in separate subgroups. So we see the change up here independently occurring, or so it appears to be independently occurring, and in this group here, where the Solomon Islands referenced strain and reassortant viruses.

And so no matter where the virus is on the tree, if it has that lysine to glutamic acid change at 144, it is poorly inhibited by the New Caledonia serum and well inhibited by antiserum to the Solomon Islands.

And so what, when you see a change that is occurring, apparently independently in different parts of the tree, what you tend to think is there may be selective pressure in the population to select that particular amino acid at that position.

If we look at the evolutionary

tree of the neuraminidase genes, you can see that we don't have as many strains on this tree and we haven't really sequenced quite as many neuraminidase genes. We'll be sequencing more in the future because we'll be trying to do more high throughput sequencing, but you'll see that the Solomon Islands virus here is in the Clade 2 just, neuraminidase is in the Clade 2 just as the hemagglutinin was.

So there is correlation between where in the tree the hemagglutinin is and neuraminidase. And you'll see that we do have a number of viruses -- I should back up one and say that we do, we're still seeing quite a few viruses from the U.S., recent viruses from the U.S., in this group down here, which doesn't, and most of the viruses in Clade 1 do not have that 144 change.

So here is the old vaccine strain, which I should point out is the 99-strain. The Solomon Islands reference strain in Hong Kong/2652 is another of the reference strains

that has been important in our understanding of what's going on with the H1N1 viruses.

So if we look, step back and summarize what we've seen globally, we can say that H1N1 viruses have been circulating at a low level, but sporadically in Canada, South America, and the Russian Federation.

H1N1 viruses, however, predominated in the United States. Many H1N1 viruses have remained antigenically like the New Caledonia vaccine strain, but a proportion of recent H1 viruses, particularly those from Asia, have been antigenically distinguishable from the vaccine strain. And, as I mentioned, these viruses were more closely related to early-Hawaii/15 strains and then these other reference strains, specific, and I want to note the Solomon Islands/3/2006. And the majority of those viruses do have this mutation that I spoke about.

Okay. We'll move on to the H3N2 viruses. H3N2 activity has been very moderate

in many parts of the world. We started out with some H3N2 sporadic activity in a lot of the world, and then some increasing activity in Scandinavia. And then by January, we were seeing a number of European countries with slightly greater intensity of H3N2 activity, and Canada was having quite a bit of H3N2 activity.

If we look at the number of viruses that were H3N2 viruses that were isolated with the Global Influences Surveillance Network, again looking at the blue line here, we see that there really were not many viruses isolated globally compared to previous years, where we had a lot more H3 activity than we had this past season.

And this is reflected in this table here. If you look at the H3 table, you can see that between February and September of '06, there were over 1,000 viruses isolated, between October '06 and January '07 we've only had, or had only 319 viruses characterized by

all of the four WHO collaborating centers. And that was as of the second week in February.

This is our most recent H3HI table. And again, I'll walk you through it fairly slowly and carefully. We have included only one HI Table in our package this year because we felt that it was the best summary of what's going on and includes the Ferret Sera from some of the most recent viruses. And these data were not even available from the WHO Meeting, so these are very fresh data.

So we'll look here, starting from the left with the California/07. This is an old vaccine strain. The current vaccine strain, Wisconsin/67/2005 and its corresponding high-growth reassortant, 161B, and its corresponding antiserum.

We have other viruses, including one from the U.S., Kentucky, one from South America, Santiago, a Florida, and then you'll see the last two antigens, Nepal/921 and

Canada/1212, which I'll talk about later.

The Canada/1212 was actually used as a serology antigen, as was the Santiago virus. And you'll see those data later.

Now, what we've been seeing over time is that there's an increasing number of viruses that are poorly inhibited by antiserum to the wild type Wisconsin/67 strain or the actual vaccine strain, R161B. And you'll see that these viruses, however, react quite poorly with all of the ferret antisera that we've been able to generate.

Now, this table just shows a small number of the failed antisera that we've been able to generate, either using cell isolates or egg isolates. And I'll talk more about how many egg isolates we've actually had in hand later on, because that's increased significantly and I think it's important for the Committee to know.

But what we can see here in this reference panel is we don't get a great deal

of differentiation. It's not like the situation that we saw for the H1N1 viruses where you could see that clearly there were viruses which were low on this side, and then a group of viruses that were high on this side, and the antisera that corresponded to those viruses didn't inhibit the other viruses very well.

So, we have here what is a much less clear-cut situation. We have really struggled with what these low-reactors mean. And there is a tendency right now to think that these, many of these low reactors are actually low avid viruses in the hemagglutination-inhibition test. And the way that you can eyeball this and determine whether they are low avid or not is to look at what the difference is in the titer between the virus and the reference strain that you're looking at, and it if a four-fold difference, just multiply everything by four; if it's a 16-fold difference, multiply all these values

by 16, and see whether you get a pattern that's similar to that for the reference strain.

And what we've determined, and I'll show you a graphic representation, is that many of these appear to be low-avid viruses. Now, we don't really understand as much as we would like to about avidity. And we think that, well we know that the receptor binding properties of H3 viruses have been evolving over time, and that some changes occurred a few years ago that we believe have affected our ability to discriminate viruses using the hemagglutination inhibition test.

Nevertheless, whether we're looking at viruses from the U.S., Canada, Europe, or Asia, we do see viruses that are well inhibited by the Wisconsin antiserum. And if we look at these two most recent antisera, we see that while they cover some of the low reactors somewhat better than the Wisconsin antisera, or both that the antisera

do, they really, you still are seeing a lot of viruses which have a 4-fold or greater reduced titer against these strains.

The Nepal/921 is an egg-isolate. And that was put into ferrets. And the Canada/1212, which is related genetically is a cell-based virus put into ferrets. And whether you have an egg isolate or a cell based isolate, you still see these low reactors.

So if we don't take avidity into account and we just strictly look at the number of viruses that are, that have a 4-fold or greater reduced titer to the antiserum to the vaccine strain, we see that we have about 59 percent of viruses which are low reactors. And we do have relatively small numbers compared to what we've had in the past, but these viruses are geographically spread, so we're seeing low reactors around the world, but they are behaving similarly in perhaps being low avid.

We have been trying very hard to improve ways to look at the HI data, the ferret data, and these methods will be extended to look at the human serologic data. Derek Smith from the University of Cambridge, has developed a field which he has called antigenic cartography. He's pioneered this using data from the WHO Global Influenza Surveillance Network. And basically what it does is mathematically calculate different distances, antigenic differences between viruses and then display this information graphically.

Well, if you're accustomed to looking at HI tables and you look at them everyday, your brain is actually doing a lot of it. It's amazing what, how much your brain can actually do on its own, but it's nice to have a visual display, especially when you're getting up in front of a group like this.

So Derek has, here is some of the old vaccine strains, the Sydney, the Wyoming,

the New York, here is our current vaccine strain here in blue, and some virus strains that were used previously. And we're starting to see some outliers. You want to see some viruses really clustering around your vaccine strain. And if you look over time, which I haven't done here because we don't have enough time to review old data, but you would see that for the time that the vaccine, this vaccine was used, that there were, the majority of viruses were really clustering very closely around this. And each one of these squares represent a two-fold difference in antibody title.

And then if you look at our CDC data generated from viruses that were isolated in December, you can see a scatter somewhat away from the list of Wisconsin/67 virus. And then if you look at January again, you see the scatter.

Derek has written a program which will account for avidity, and so he's

incorporated into his program an avidity correction, and so I'll just go through those same data. And what you see is that the viruses are actually, when the avidity corrections are done, the viruses are actually pulled closer to the Wisconsin/67 vaccine strain, although there are some viruses which are fairly far away, getting to be 4-fold, or 8-fold, or greater. But certainly the differences are less for the July data.

For the December data, we are still seeing viruses out here. This is the Canada virus, Canada virus here, and Nepal virus here. So these viruses are really not being pulled toward the Canada and Nepal.

And then for the few January viruses that we've had in hand to analyze, we're still seeing this scatter over here, but a few more viruses that are clustering around Canada and Nepal.

If we look at the genetic data, we've actually sequenced a fairly large number

of HA genes. Even in the last couple of weeks, we've been able to sequence well over 50 HA genes from recent viruses. And we were very interested because we were starting to see two primary groups emerging. One here, which is represented by the Brisbane/9/2006 virus, which was isolated in June during the Southern Hemisphere season, and another which is represented up here by Nepal/921, which I pointed out on the HI table, and the Canada/1212 virus, which was isolated in December.

I should mention that a lot of the data on here has, the data have been provided, the sequence data have been provided by some of the national labs. The Canada lab provided us with sequence data. And we actually get data exchanged among the four collaborating centers and as many of the National Influenza Centers as possible. So we really have a lot more data than I'm showing you on here, but I'm just really trying to demonstrate what

we're seeing.

Again, the most recent viruses are shown in purple. The December viruses in pink, November in orange. So you're looking for the more intense red colors here to see where the trends are. And what we're seeing is that the most recent viruses, and it is about 50/50, slightly more in this group than this group, but about 50/50 distribution of recent HA's into this group here, which has characteristic arginine to glycine change at 142, and then some additional changes. You can see that there are subgroups here with additional changes. We do have a lot of viruses, and they are from Asia, from the U.S., and Europe in this group as well.

Likewise, if we look at the NA genes, here is our Wisconsin vaccine strain. Here are the two groups that I was referring to before, the Brisbane Group and the Nepal Group. And you can see that the viruses, again, they're color-coded so that the most

recent viruses are shown in purple and pink, and the NA's are segregating along with the HA's.

So, in summary, Influenza A H3N2 viruses have been difficult to analyze. However, activity caused by H3N2 viruses was low, generally speaking, around the world. However, there were outbreaks during the period September to the current time in Madagascar, Canada and a number of European countries.

Many of the viruses globally were antigenically closely related to Wisconsin and Hiroshima. The Hiroshima virus is the vaccine virus used in Japan. But an increasing proportion of viruses was antigenically distinguishable from the vaccine virus, viruses.

And increased heterogeneity was observed in the HA sequences from recent viruses and no emergent antigenic variant group was identified. And that is, I think,

the key to focus on. If you'll remember, we really didn't see the same king of dichotomy in the ferret antisera that we saw with the H1N1s.

Okay. We'll move on to Influenza B Viruses. Influenza B has also circulated at low levels. There really hasn't been much activity, except for sporadic activity in a few school outbreaks and so on. But if we look overall, the Influenza B viruses have circulated at relatively low levels, which is shown very clearly here in the number of Influenza B viruses isolated in the WHO's Global Influenza Surveillance Network. And you see almost a baseline the number of Influenza B viruses.

So the total number of viruses that we've had to look at is even smaller. And we have them divided into two distinct lineages. And of course, this afternoon's discussion will concentrate on the fact that we have these two distinct lineages of

Influenza B viruses.

So these are the four WHO Collaborating Centers, and sorry that this didn't get, that it must've got transposed. But you can see that in Australia they had 95 percent of viruses being Victoria-lineage. In the U.S., we had more B viruses than any other Collaborating Center to examine. And 76 percent of the viruses that we examined were Victoria-lineage viruses, thus matching the vaccine lineage.

But we're seeing some low reactors, nothing really different than what we've seen before, as I'll show you in the next table. Here, we have color-coded in this yellow mustard color the viruses that are on the B/Yamagata lineage. And to the right we have the viruses that are on the B Victoria lineage, including the Malaysia vaccine strain, which has been used in all countries by all manufacturers.

These are the most recent viruses

we have. We have some from December, just I think only one from January. We'll expect to get some more later on. But we have viruses from the U.S. and from Asia, and we see that if we look at the homologous titer here of 1280, we do see a number of viruses that are reduced in titer. But that has been something that we have been seeing for a long time.

And what we know about the B Victoria viruses is that once they are isolated in eggs, they lose an important glycosolation site, which is right up at the tip of the hemagglutinin. And once they lose that glycosolation site and are put into ferrets, they induce antibody that is not as broadly cross reactive as the cell counterpart. And we have put many viruses into eggs and have found that even if you retain a glycosolation for one or two passages, if you pass it sequentially you eventually lose that glycosolation site. So this has been problematic for egg-based

manufacturers.

So, if we look at what we are seeing at CDC, we're certainly seeing the majority of viruses in the Victoria lineage. That is, in the same lineage as the vaccine strain. A smaller number, which we're calling Florida-like, which would be a potential vaccine strain if we were to move to the Yamagata lineage, but of course, globally and within the strains that we've had from the USA, we've certainly seen a predominance of the Victoria like viruses.

If we look at the HA genes, now we're looking at the Yamagata lineage. And this is just for full information, not really as pertinent to our discussion today, but just to let you know that if we were to have, to move to the Yamagata lineage, we have some very good vaccine candidate strains, which produce antisera that do a very good job at inhibiting viruses on that lineage. So this is the old vaccine strain, so we do have

contemporary egg run viruses that could be used, should that become necessary in the next few years.

For the Victoria lineage, you see that we really have much slower genetic change than we have seen for the H3N2 viruses. And this is typically what we see. The HA of the Influenza B virus does evolve more slowly.

So here we have the vaccine strain, Malaysia/2506/2004, and then the viruses that are more contemporary that we've been seeing. And you'll see some of the viruses that are egg isolates. As I've mentioned, they've all lost the glycosolation site. And we have a number of them. They are noted by the hatch mark, so you can see that we really do have quite a lot of egg isolate.

The neuraminidase genes are also not changing all that much. Here is the B Malaysia vaccine strain. Here are a number of the viruses, and again, you can see that we do have a number of egg isolates shown here.

So, in summary, Influenza B viruses have circulated in many countries; however, outbreaks or large outbreaks, apart from institutional outbreaks, have not been reported since September 2006 and January 2007.

Both lineages have continued to circulate, but the Victoria lineage viruses have predominated. And if you look at the WHO data overall, it was about 82 percent of viruses were of the B Victoria lineage.

The Yamagata lineage viruses were closely related to those strains that I mentioned that were egg isolates and could be used. And most B Victoria lineage viruses were antigenic closely related to B Malaysia, taking into account that we have an egg isolate that's gone into ferrets and we're looking at mostly cell-based, cell isolated viruses.

Now, this is just to show you that we've been working very hard to increase the

number of egg-grown viruses. And this is shown by fiscal year. And our fiscal year and our influenza seasons sort of start at the same time officially on October 1. So we have really increased the number of egg isolates that would be available to manufacturers, should that particular egg isolate look like it's an appropriate vaccine strain.

So, for the last fiscal year, which ended September 30, 2006, we had 255 egg isolates distributed fairly well across the different types and subtypes. Now, I should mention that obtaining H3N2 isolates has been exceedingly difficult. And if we put 100 clinical specimens into eggs or into kidney cells and then pass on to eggs, we're likely to get out five if we're lucky. So it really does require a lot of work for the H3N2 subgroup of viruses.

I think I'll stop there and take questions. If anyone has questions about the human serology data that you see in the

package, I can answer those questions now because I have the slides available.

DR. COUCH: Just one quick question, Nancy, for clarification to see if my assumptions are correct. When you say a low reactor, you spent a good amount of time on the H3 antigens with the ferret sera, a low reactor would be low reactor with say the Wisconsin antisera. But with your other ferret sera, no reactions that gave it a different identity? Is that --

DR. COX: That's correct.

DR. COUCH: -- what low reactor means?

DR. COX: So, okay, so when I say low reactor in my table, I'm really talking about the number of viruses that have a 4-fold or greater reduced titer to the antiserum to the vaccine strain. But when I was looking at the H3s, we were looking very specifically because we're seeing this pattern of low reactors across the board. So, in many cases,

your low reactor is a low reactor across the board and you don't see better inhibition using any of the other ferret antiserum, or only moderately better inhibition.

DR. COUCH: I guess being specific, that would count for some of them, but when you say low reactors that reacted only with ferret sera, or is a battery of ferret sera?

DR. COX: We always use a battery of ferret.

DR. COUCH: Only the Wisconsin -- a battery?

DR. COX: We always use --

DR. COUCH: So it's a low reactor across the board?

DR. COX: We always use a battery, but in order to really be specific when we're talking of the WHO Meetings, we really are looking at the number of viruses or the proportion of viruses that are low reactors to ferret antiserum to the vaccine strain. So

that's what is in those tables. But when we're looking more broadly, we're looking for patterns of reactivity. And so many, so for the H3s, the majority of the low reactors are low reactors across the board to the battery of antisera. And we never test viruses on their own. We always test with a whole battery of ferret sera.

I don't know if that answered your question.

Ruth?

DR. KARRON: Yes, two questions. One is so can you contrast these H3N2 viruses where you say there is no emergent antigenic variant group, and I assume that's based on the ferret antisera data, with say the situation we were in several years ago with H3N2 Fujian. There we saw an emergent new variant, is that correct?

DR. COX: We saw there an emergent new variant, which we could clearly see using ferret antisera. And we could see, we could

see the two-way, 4-fold or greater difference. So antiserum to the Fujian strain didn't inhibit the old viruses as well, and antibody to the previous vaccine didn't inhibit the Fujian strain. So we had the two-way, 4-fold difference, which was very clear. And that also corresponded to changes that we saw in the genetic data.

DR. KARRON: Thank you. And then just a question either for you or for Dr. Fiore. Would you happen to know the school-based outbreaks of B in North Carolina, whether those were Yamagata or Victoria lineage. Is that something you would know?

DR. COX: The North Carolina, and Tony correct me if I'm incorrect, but the majority of those viruses were, they were Yamagata. And that was an early outbreak before the season really got rolling. And so we were feeling rather uncomfortable with the fact that they looked, that they were Yamagata lineage viruses and we had Victoria. But then

it didn't hold true for the rest of the season.

DR. KARRON: Thank you. I think we'll go on now to Angela Owens from DoD who is going to talk to us about vaccine effectiveness and responses.

MS. OWENS: Hi. I will also fill in for Luke Daum as well, as we provide the sequence analysis overview.

Let me go back, sorry. We are actually part of an overall Department of Defense Global Influenza Surveillance Program which is a WHO collaborating laboratory and it has two parts.

One part is Sentinel site surveillance that is managed at the Air Force Institute for Operational health, and another part is a population based surveillance that takes base at eight training camps and is managed at the Naval Health Research Center in San Diego.

For our Sentinel sites we have,

thank you, 43 medical treatment facilities that are located throughout the service. We also have 22 sites associated with four separate DoD Overseas Research Facilities. We provide naval wash kits, collection material, education material, shipping supplies, so they can send us specimens on a weekly basis. We contact them every week. We expect six to ten specimens every week from patients with a fever greater than or equal to 100.5 and/or a cough or sore throat. We also request an influenza surveillance questionnaire to be completed that describes vaccination history, travel history, any additional symptoms other than cough and sore throat.

We have so far collected about 1,200 specimens this season. Twenty-six percent have been influenza positive by culture and the majority have been Influenza A. We also test for adenovirus, enterovirus, RSV, pair influenza, and HSV, which is a background virus.

About 93 percent of our isolates have been sub-typed at this time. The majority have been Influenza A, H1, and the majority of B have been from the B Victoria lineage.

This is Luke's portion, so let me describe this. For Influenza B, the hemagglutinin genes of over 40 DoD Influenza B viruses were analyzed from the influenza strains obtained from summer of 2006 to present. Of these isolates, five strains were Yamagata like, with the remaining isolates being B Victoria like.

B Yamagata like viruses are antigenically and genetically distinct from the current vaccine strain, which is the B Malaysia vaccine strain. These five strains were collected from Peru, Maryland, and Illinois.

The remaining B viruses were B Victoria and shared 99 to 99.6 percent sequence identity to the current B Malaysia

vaccine strain.

Depicted in this slide is a phylogenetic analysis of influenza strains represented by 38 Influenza B Victoria like strains and 5 B Yamagata like strains. As you can see, the B Malaysia indicated within the red box is find within the cluster of B Victoria like filled strains collected during the current season.

For Influenza A H3N2, the phylogenetic analysis of Influenza A strains collected during the 2006 through 07 season have been the minority this year, taking a backseat to the H1 subtype. At present, we've collected and sequenced about 70 strains, including a summary outbreak of H3N2 isolates in Nepal depicted as a distinct branch, which is at the top.

Shaded in the circle is Clade of Influenza A H3N2 Viruses that are forming a distinct branch in the current tree of H3 viruses. These viruses show a genetic

variances in several nucleotides, inter-defined by the R142G mutation, which forms the distinct branch point, I apologize, let me go back. I think every time I touch this -- I apologize. I've been touching the bottom. About 50 percent of our isolates, including the July outbreak in Nepal are contained within this branch, phylogeny. Indicated in the red box is a current A Wisconsin strain and the older A California vaccine strain. And as you can see from the phylogeny, the A Wisconsin strain shows genetic variance from viruses belonging to this Clade.

And this is the A H1N1 phylogeny of the strains collected during the 2006 through 07 season. They've been the predominant circulating strain, and two distinct Clades have formed with Clade II viruses showing somewhat reduced titers according to the H1 analysis. While the two Clades are currently noted in this phylogeny, isolates obtained in the U.S. are Clade I,

which are the current A New Caledonia vaccine strain. Clade II isolates were obtained from South America, which are Peru, Nepal, and one isolate from Saipan. Clade II viruses are defined by several key amino acid changes, some of which are located within the antibody combining isolates.

Again, we are a WHO collaborating lab. All of our information is uploaded to CDC's national surveillance system, and they also receive our isolates of interest.

For vaccine effectiveness, this is a descriptive preliminary review. We looked at patients seeking care from U.S. Military Treatment Facilities from October 1 to 12 February. This includes active duty and DoD beneficiaries.

Our outcome was lab confirmed influenza results by viral culture and isolation. We defined fully vaccinated patients as patients who received the vaccine greater than 14 days prior to the clinic visit

date. Any of those patients receiving the vaccine prior to August were defined as unvaccinated unless they received another vaccine later.

Our vaccination data were gathered form the Military Immunization Database, and our influenza surveillance questionnaires. Those are completed at the time of the clinic visit.

A total of 796 specimens were included. 170 of these were influenza. 65 of the 170 hadn't identified vaccination status in the breakdown of FluMist versus the injection. 23 of these patients has a possible vaccine breakthrough, meaning they had the vaccine greater than 14 days prior to the clinic visit in which they obtained the isolate. All age groups were represented.

And the isolates obtained were Influenza A, H3, from California, Texas, and South Korea. And the South Korea information is also described in the sequence data that

was mentioned before. H1 was identified in Alabama, Oklahoma, South Carolina, Texas, and Antarctica. And our Influenza B, one B was not sub-typed at this time. It was actually recently collected. And that was both identified from Alabama.

The Naval Health Research Center also provided a vaccine effectiveness review at the eight training camps, which six of them had influenza identified. All of the trainees are vaccinated upon arrival, so their vaccination to identify a fully covered vaccinated person is within the 14 days. They are not fully covered.

And they had 48 isolates. 38 of them of them were unvaccinated. And if you'd like more information regarding this review, please contact NHRC. And I have their information so afterwards I can get with you.

We did not, Geis, of course, is our funding and guidance agency. CHPPM and AMSA provided us with the vaccine information,

and Pop. Health, CDC, and of course all of our Sentinel sites. We do expect a full review of vaccine effectiveness at the end of the season. This is a descriptive review. There is no random sample applied yet.

Here is our contact information. And I do apologize that Luke was not here.

Do you have any questions?

Yes?

DR. FARLEY: I was a little surprised at how often you did not know their vaccine status in the first part. Is that because they really weren't all enlisted military? It was families and other people? Because otherwise I would think your record keeping would be very tight.

MS. OWENS: Yes, for Sentinel site surveillance, our population, it's gathered from family clinics, pediatric clinics, hospitals, and ER's. The majority of our population is DoD beneficiaries, and unfortunately for the Navy and the Army it's

hard to gather that vaccination status from DoD beneficiaries. That's where we come in play with the influenza surveillance questionnaires. That's why we actually look from the surveillance site, we request that they all fill out that. And unfortunately, a lot of these came from both Sentinel sites and non-Sentinel sites. We had about 22 non-Sentinel sites that submitted specimens this season.

But hopefully at the end of the season also we'll get more information.

DR. KARRON: Any other questions? Thank you very much.

MS. OWENS: Thanks.

DR. KARRON: Next on the agenda is Dr. Ye who will talk about vaccine responses and availability of strains and reagents.

DR. YE: Thank you.

I think the whole purpose of doing the human serological study is to see whether the HI antibody response to the vaccine strain

will confirm that the antibody response to the isolated, newly isolated, viruses reach as Nancy mentioned in her talk.

It seems the serum sample from human was pre-selected to choose the antibody, positive antibody response. So the whole purpose of this study is not to compare the antibody response from different vaccine string, but rather to see, to use this serum to study, to compare the antigenic difference of the newly isolated circulated viruses.

Serum sample actually comes from different centers worldwide. As shown on this slide, the serum sample comes from, there are five serum samples that come from different centers. One is from Australia. The serum sample represent the human serum which immunized, was the vaccine that contained New Caledonia for H1N1 and New York/55/2004 for H3N2, particularly for the Austria serum samples.

Then the B strain is Malaysia and

that is the same for the rest of the serum sample.

And the other serum samples from Europe, from Japan, and from U.S., the serum sample comes from the human serum, from the human population that immunized the vaccine strain containing New Caledonia for H1N1, and the Wisconsin like strain for H3N2. The actual vaccine strain contains Wisconsin itself or Hiroshima for H3N2 for the European, and also for the Japan. The European contained two serum samples, two serums, one is for Wisconsin itself, another one is for Hiroshima. But what I presented in this study is the same sample for Wisconsin itself. And also to have the same sample from a pediatric.

Okay. The antigen used for human serological study has been carefully chosen. And one is, of course, is the vaccine strain itself. Here is New Caledonia/20/99 for H1N1. And the representative or current vaccine, current strain used for serological study,

choosing according to antigenic and genetic characteristics of the strain, but also the geographic characteristics of those viruses.

Here you can see that I have one strain from New England, from Hiroshima, and from Fukushima, and from Asia, also from European. And here I marked a group of the antigen with the asterisk over here as it represents the signature of antigenic differences in amino acid 144, substitution of amino acid from lysine to glutamic acid as mentioned in Nancy's talk. So we will see what the main response of those groups of viruses to the vaccine strain.

And here, this slide shows HI antibody response to H1N1. And this slide I choose a representative serum panels in one of the centers who did the serological study. By the way, there are four or five centers conducting the human serum study, and this is only one I choose as positive representative for H1N1. Here I chose from U.K study.

On the left column shows the serum panel, where the serum panel comes from. And here it shows the serum panel from adults and from European, which immunized for Wisconsin. They solved for H3N2, but here we're talking about H1N1. And then the panel coming from Australia. Since Australia human serum sample comes from human population immunize H1N1, so that's valid for this study. And here it shows the viral strain or antigens that has been used in human serology study. And here is what vaccine strain is solved and here is the representative circulating viruses.

And here I show the tradition of things that shows the percentage of post-immunization, HI or eco to 40, 1 to 40. And it also shows the percentage over 40, for the race.

But here I liked to focus on the GMT reduction. Unlike the serum panel studies in using ferret study, human serum we don't have the antibody of the serum against the

individual as related to viruses. So what we focus on is to see the GMT reduction.

And I'd like to spend a few minutes to explain how we summarized the overall study from different centers.

Here you can see the post-vaccination GMT titer to the vaccine strain. Absolute number is not meaningful, but the comparison of the GMT vaccine strain to the isolated virus is what you want to focus on. Here you can see that the GMT titer to the vaccine strain is 1 to 90, 1:90, where the GMT from the newly isolated virus is a 36. What we want to see is whether this reduction is a 50 percent reduction. Here you can see that's over a 50 percent reduction. That's one layer of information I'd like to you focus on.

The second one is the different panels. This only shows the one panel of this particular strain of 50 percent of reduction. And in the next serum panel, it's the same thing. It's the GMT titer to vaccine strain

and it compares with the newly isolated virus. And here, again, it's a 50 percent reduction. Now, we can see that there are two panels and two out of two panels have a 50 percent reduction. And remember that because of that, the way you translated to the summary data I will present later on.

And here is another two panels which I show, which are shown in this slide. So here is a panel from U.S. and Japan. Again, you see that this GMT to the vaccine strain itself is 273, where to this particular strain, England is 40. So, it's a, one time, one panel, a 50 percent reduction. By the same token, the same thing happened to the Japan group. The GMT is a 59, where the GMT to this particular strain is a 22. The reason I said even in the beginning of my talk, we're not to see response to the particular vaccine strain, rather we see the difference. Since the serum sample from Japan was not preselected to choose the high positive

response of the post-serum sample, so they are, the GMT is relatively low compared to the other centers.

So now, have this one in your mind that I put the five different centers together to see the overall picture because individual lapse of data, you know, may not be well represented of overall data. And here is a summary of the GMT, 50 percent of GMT reduction by composed the serological study from different centers.

As I mentioned in a few slides back, four of four panels for this particular strain have a 50 percent reduction. So that indicates that there is a strain which is different from the vaccine strain. The same thing for A/Fukushima. Here is like 12, in 12 serum panel, some of them have a reduction. So now you can see, I can give you the sense of overall, of the strain and composed from different centers, different centers of studies.

And here I have to point out that the Solomon Islands/3/2006 in 19 serum panels, only two have the 50 percent of the reduction in this serological study. But however, overall, the representative circulating virus, the antigen that are used in serological study, shows that in 55 panels, 30 of them had 50 percent GMT reduction. That indicates those viruses antigenically is different from the vaccine strain. And the last column shows the average 50 percent of reduction. And also, that gives you the sense of the antigenic difference by using human serum.

And I apologize that the handout that you have was typed and corrected over here, this 51 percent. So that's an indicator that the 50 percent of GMT reduction isn't quite significant in this study. And it also shows that H1N1 newly isolated circulating viruses is antigenically different from vaccine strain by using human serum study.

And now we go on for the H3N2.

And as I mentioned, the vaccine strain is Wisconsin-like. So the actual strain for the different vaccine components either is Wisconsin itself or Hiroshima. And again, this representative occurrence strain, which we choose according to the antigenic and the geographic differences. Here I like to emphasize again that the Canada and the Lyon strain which is asterisks, indicates there is a Canada or Nepal genetic group, as mentioned in Nancy's talk. So we want to see how this strain behaves in the human serology studies.

And again here I choose the one of the serum panels from the CDC to give you the sense of what's the antigenic difference by using human serum studies. I am not going to explain it again. Here, like folks on the GMT reduction of the newly isolated viruses, here in this column you can see that the GMT to the vaccine strains is a 101, where the GMT to the Brisbane is a 65. It's not quite a 50 percent reduction; however, the rest of the

circulation viruses that we used for antigen in the human serum serology study included Canada antigen at more than 50 percent of reduction in a GMT. And something again, it's true to the other different panels, such as from U.K. and also from Japan, and from Japan and also from a U.S. serum panel.

And if we put the serum study from different centers together, now here we show the summary of the viruses. We use a 50 percent of GMT reduction in adults. And again here, we show the Brisbane in the 16 serum sample, serum panels, 7 of them had 50 percent of GMT reduction.

And another one is Sendai. And in 8 serum panels, 2 of them have the GMT, 50 percent of GMT reduction. However, the rest of the virus includes the Canada and the Nepal variance here. We can see that every one of them had a 50 percent GMT reduction.

And if we put the whole thing together, as shown in here in 73 serum panels,

55 of them had 50 percent of GMT reduction, as indicate that this virus really antigenically is different from, from the vaccine strain.

And again, as a true for the average, the average percent of a GMT reduction, 65 percent of reduction in the summary. So, that is for H3N2.

Now, we go on for the B-strain. Again, the B-strain, everyone uses the B/Malaysia, which is Victoria-like HA lineage. And the representative current strain was a two group. One was Victoria itself, and another one was the group that represent the viruses from the, represent the Yamagata lineage.

And here, again, I choose the serum panel from the CDC. And here you can see that the vaccine strain, here there are two vaccine strains, but I don't think anybody used Ohio for their vaccine strain, for licensing the vaccine strain. And here, as you can see that the Malaysia has a 69 GMT and

Ohio is 126. And the rest of the strain you can see that the newly isolated viruses from Victoria like, you can see that there's been no reduction. Include the Yamagata strain, they are not 50 percent reduction. Probably that's due to adults that has been pre-immunized, immunized the previous year with Yamagata vaccines. So this is true for the rest of the serum panel including from Japan and U.S.

And here is a summary of the GMT reduction in adults. So here you can see that in 22 serum panels only four of them have 50 percent of GMT reduction. Seventeen is the average percentage of GMT reduction. So that indicates that the circulating viruses that we used for serological study are antigenically close to the vaccine strain.

And although the strain from Yamagata had lower GMT reduction, but compare with Victoria and the reduction is more than those with Victoria like strain.

So in summary of the serological study, with the sera collected after immunization with current vaccines show that:

With H1N1, the recent viruses was not well inhibited compared to the current vaccine strain.

And the same thing with the H3N2, the current viruses was not well inhibited compared to the current vaccine strain.

Where the B, for B, the recent B/Victoria lineage viruses generally well inhibited compared to the current vaccine strain.

And I'll stop here if you have any questions.

DR. COUCH: Again, just a question to be sure I understand and have the data straight. On your summary tables of GMT reductions and you say four out of four panels, that's four out of four sources of sera tested at that particular laboratory?

DR. YE: Yes.

DR. COUCH: And that's their results. So we're looking at maybe CDC or CBER data where you're looking also at the data from Japan, Australia, and Britain.

DR. YE: Right.

DR. COUCH: With that summary table?

DR. YE: I think do, as we discussed yesterday, the HISA, the variations from center-to-center from lab-to-lab, so in order to se the whole picture we have to use the serum from different centers. Here we have to use it from five different centers to get the whole picture.

DR. COUCH: But your serum went to those laboratories and they tested it. Is that correct?

DR. YE: Can you repeat your question please?

DR. COUCH: The FDA sera, the CBER sera, you have a panel of 24 sera. Those sera went to Australia, for example.

DR. YE: Right, okay.

DR. COUCH: And they tested. It went to Japan and they tested the same sera. All this is a change of sera.

DR. YE: I should've explained it in my talk. Yes, we exchanged the serum sample from center to center. Every single one of the center had the same serum panels from all the centers. So all the centers used the same serum samples. But the study may vary, such as using different red blood cells or the way they diluted for the same samples.

DR. KARRON: John?

DR. MODLIN: You didn't show us the data from the pediatric samples. I'm sure you've looked at that, but probably the numbers are small. But I wonder if you could just summarize the age range of which the kids with sera came from and maybe just give us a summary of what they showed.

DR. YE: I know you going to ask this question. Actually I have a back slide

for that but I took it out.

DR. MODLIN: I'm getting to be that predictable.

DR. YE: I think although this same, okay, for this pediatric serum, since the majority of them are naive, relatively, so you will see the better picture. But in this particular study --

DR. MODLIN: Oh no, I'm sorry.

DR. YE: So to answer your question that the serological study from pediatric study more represent, for H3 for H1, is similar to adults. Where the B, you can see some difference between Yamagata and Victoria. Did I answer your question?

DR. MODLIN: Yes, in general. That's fine.

DR. KARRON: Actually, I have an H1N1 question. The A/England/555/2006, I didn't see that in the ferret sera panel or in the evolutionary diagram. But is that virus like Solomon Islands?

DR. YE: I'd like Nancy to answer this question. It should be there.

DR. COX: In your slides it should've been designated if it had that change. Let me look at that. I've got all the data here.

Could you mark it on your slide so that he could go back and look at your slides and see?

So the England did not have that change?

DR. YE: Right. England has no change in, I think it should be 144.

DR. KARRON: I guess I was just trying to understand was the England virus and H1N1 virus that is neither like the New Caledonia nor like the Solomon Islands. I guess that was just my question.

DR. COX: That wasn't a virus that we used in our serology, sorry. What was the strain designation again?

DR. KARRON: 55/2006.

DR. COUCH: What question are we trying to answer?

DR. COX: I'll get back to you. I'll find it and get back to you.

DR. KARRON: Thank you.

Other questions for Dr. Ye?

At this point, I think Dr. Vodeiko --

DR. YE: Yes.

DR. KARRON: -- is going to speak?

DR. YE: Yes, talk to Dr. Vodeiko from the FDA, our next talk.

DR. VODEIKO: Thank you again for this chance to present the next part of information. My name is Galina Vodeiko. And from the end of 2005, I am in charge of potency and reagent preparation in CBER with big help from Christian Anderson.

Let me introduce you information about availability from CBER on vital strains and for vaccine for reagents for potency.

I think I go to four.

We start from Influenza A, H1N1 viruses. The currently available strain is New Caledonia/20/99 and it's reassortant IVR-116, prepared in Australia. Many of you know the designation for many reassortant prepared in Australia started with IVR, and prepared in New York Medical School, it's usually X with a number.

With three kinds of candidates for new vaccine strain, one of them is A/Solomon/3/2006, and is available in high yield reassortant, IVR-145. The second strain is A/St. Petersburg/8/2006, and is available as a high yield reassortant, designated as X-163. And the third strain is A/Fukishima/141/2006, a high yield reassortant preparation is ongoing in Melbourne. And it expects to be available in late-February, so now.

Influenza A H3N2 currently available vaccine strains, we have two of them. A/Wisconsin/65/2005-like. One is a

high yield reassortant prepared in New York Medical School, designated as X161B for A/Wisconsin/67/2005. And another, A/Hiroshima/52/2005 is Australian high-yield reassortant IVR-142.

We have one candidate for strain changes, it's A/Nepal/921/2006, and the preparation of high-yield reassortants is ongoing in New York Medical School and expected to be available in early-March.

For Influenza B, we have available current vaccine strains, B/Malaysia/2506/2004 and B/Ohio/1/2005. There is no superior candidate strains available by now.

Availability of potency reagents from CBER, H1N1, A/New Caledonia/20/99 strain, we have available reagent antigen and reagent serum. For H3N2, A/Wisconsin/67/2005, reagent antigen and reagent serum. The same reagents are available from other centers, in U.K. and Australia.

If new strain will be chosen, we

expect reagents, potency reagents available by the May of this season.

For viruses B, in CBER we have reagents for both lineages. For Victoria lineage it's a current vaccine strain, B/Malaysia/2506/2004, reagent antigen and reagent antiserum. And for Yamagata lineage, we have seen from the previous year, reagents for vaccine for the previous year, B/Jiangsu/10/2006. The same reagents are available from other chosen centers.

If new strain will be chosen, as it is out of Advisory Committee work, the reagents are going to be available in May of this season.

That's it of what I wanted to say. Any questions?

(No response.)

No questions.

DR. KARRON: Thank you very much.

At this point, we'll take a break. And I think we're a bit ahead of schedule. So

instead of reconvening at 10:35, we'll reconvene at 10:30, when we'll hear comments from the manufacturers.

(Whereupon, the above-entitled matter went off the record at 10:07 a.m. and went back on the record at 10:36 a.m.)

DR. KARRON: We're now going to hear from Mr. Albert Thomas, who will give us comments from the manufacturers.

MR. THOMAS: Good morning. My name is Albert Thomas. I am with Sanofi Pasteur.

I would first like to thank the Committee for the opportunity to present the comments from manufacturers at today's strain selection meeting, and would like to begin by discussing several of the critical factors that are involved with influenza vaccine supply, and how the strain selection process can impact each of those factors.

The first critical factor is the growth potential of each monovalent strain

seed virus. There are many factors that can impact the total number of doses of influenza vaccine that can be produced, such as the overall capacity that is available to each manufacturer, as well as the average yield of all three monovalent strains, but most typically the number of doses of vaccine that can be produced is limited by poorest growing or least yielding monovalent string.

For example, a manufacturer may be successful in producing 40 million doses of the H1N1 monovalent strain, 40 million doses of the B strain, but if only 20 million doses of the H3N2 strain can be produced, there will only be 20 million doses of trivalent vaccine that are available.

To evaluate the potential impact of a low-yielding strain on vaccine supply, we only need to look to 2006, to last year. Due to the initial low-yield from the A Wisconsin/67/2005 strain, as part of the initial production, if it were not for the

greatly improved yield of the improved reassortant, the X161B, the supply of trivalent influenza vaccine last year would've been significantly reduced. Even though a record number of doses of influenza vaccine were ultimately available last year, the late availability of the much better yielding A Wisconsin X161B reassortant did have a timing on the impact of vaccine supply.

The most critical overall factor is time. The timing for influenza vaccine manufacturing is limited at the beginning by the timing of the strain selection meeting, and is then limited at the end to distribute and administer the vaccine prior to the onset of the influenza season. Thus, the total time to develop production seeds, manufacture the monovalent components, formulate the trivalent vaccine, fill, package, release, and ultimately distribute is quite limited.

Also, please keep in mind that production seeds typically require at least

four weeks from time of receipt for development and release prior to use in large scale manufacturing.

The potency of, the availability of potency test reagents is another factor that must be taken into account. The potency or hemagglutinin titer of each monovalent component lot must first be determined prior to formulation of the trivalent vaccine. And as we've heard, that's done via single radial immunodiffusion, which requires a strain specific reference antigen and antiserum. These two potency reagents must be manufactured and standardized for each new strain prior to initiation of trivalent formulation. The time to prepare and standardize the reference for reagents typically requires 8 to 12 weeks.

The final critical factor is the timing of the annual Biological License Supplement Approval. Since formulation of the trivalent vaccine typically changes from year