and September 2000, we analyzed 255 H1N1 viruses. About 10 percent, actually 12 percent were Johannesburg-like, while the remaining viruses were related to the New Caledonia lineage.

And of those that are in the New Caledonia lineage, the majority are really closely related, antigenically, to the vaccine strain. That is true, that generally story is true, for the most recent period, even though we have fewer viruses that we have analyzed.

We have 8 percent now, of viruses, which are Johannesburg-like. The majority are New Caledonia-like, and are closely related to the vaccine strain.

Now we are going to move onto the influenza AH3N2 strains. As Keiji has mentioned, we really did have predominantly H3N2 viruses in the United States last year, as well as in many other countries throughout the world.

During the season in the southern hemisphere we had a significant amount of H3N2 activity in some areas, but clearly the seasons were mixed in a number of countries.

The viruses that were circulating in the southern hemisphere were A/Panama/2007/99-like, that

is like the recommended vaccine. And although we have had little H3N2 activity globally during the period from October to January 2001, the viruses that we have analyzed are also A/Panama-like.

Now, it is really fairly interesting to see how the antigenic patterns of viruses sort of change over time. This particular test was done in November. And it has a number of viruses from the southern hemisphere.

These Brazilian viruses were isolated during our summer. These viruses from China, they are all from south China, from Guangzhow and also from Hong Kong, were isolated during the spring and summer, and into the early fall months.

What we can see is that with the ferret antisera that are produced to our reference antigens, which include the old A/Sidney/97 vaccine strain, Moscow/10, which is the recommended strain, Panama, which is in the vaccine, and then a couple of 2000 strains,. we can see that the strains that we were looking at, during the summer, actually are well inhibited by antisera to all, against all of these reference antigens.

Now we are looking at viruses that were isolated during October and November of this season.

And we see the same thing. We see that these viruses are, indeed, very well inhibited by antisera to all of these reference strains.

There have been a few exceptions among the viruses that we've tested. And one of those exceptions is shown here, in this table, with antigen 13, A/Fugian/140/2000, which is also a serology antigen.

And we saw that there was a four-fold reduction in titer with both the Panama antiserum, and also with the Moscow antiserum.

So if we summarize the antigenic information that we have you will notice that during the southern hemisphere season there were quite a few H3N2 viruses isolated and sent in for analysis.

The majority of those were either Sidney-like, or Panama-like. And in some tests it is really difficult to tell them apart. And there were only a few viruses, including the Fugian virus that I pointed out before, that were low to Panama.

We only have a total of 13 viruses that we've looked at, from the isolated, during the period October to December 2000. Of those ten are from the U. S., and one is from Canada. And all of those viruses are clearly A/Panama-like.

Now, we are going to move on to the influenza B activity picture. Last year in the northern hemisphere we had relatively little influenza B activity.

There was, however, some -- there were some outbreaks of influenza B in Asia, and certain Asian countries. During the season, in the southern hemisphere, there was really relatively little influenza B activity, although a few isolates were obtained.

And during the current influenza season in the northern hemisphere, Canada is having local outbreaks caused by influenza B, and Hong Kong, and a few other areas in Asia are reporting occasional outbreaks. And there have also been a few outbreaks noted in Europe. But, basically, the influenza B activity has been relatively low.

Now, I need to mention, before I start out, for those of you who remember presentations in other years, that there are two very distinct lineages of influenza B viruses that have been circulating globally since about 1988, actually.

The circulation of the B/Victoria-like viruses has really been much, much more limited. And the circulation has been primarily in China, although

Japan did have some significant activity caused by B/Victoria viruses a few years ago.

On these overheads I won't have any viruses, any antigens that represent the B/Victoria lineage. All the antigens here are representative of the -- what we use to call the Yamagada lineage, and we now call it the Yamanashi lineage, I guess.

So what you can see here is a table which has, as reference antigens, B/Beijing/184, which is the recommended strain, Yamanashi, which is the strain that is actually in the vaccine; Johannesburg/599 which is a strain which has been used for production of vaccine in the southern hemisphere.

And then the B/Sichuan/379/99, which is a prototype reference strain for the new variants that we are seeing. This is a typo, I apologize, it should say 40, not 49, I don't know how we missed that one.

This is the picture that we were seeing through the summer and into the early fall in many of the tests that we did. That is to say that the viruses were well inhibited by antiserum to the Beijing/184, recommended strain, and pretty well inhibited with antiserum to the B/Yamagada vaccine strain itself, although we were seeing a few viruses that had a four-fold reduction in titer.

Those viruses that were four-fold reduced in titer to the Yamanashi strain were pretty well inhibited by antiserum to the B/Johannesburg and B/Sichuan variant strains. They are very similar to each other, they are considered to be B/Sichuan-like.

In this particular table we are moving on in time to viruses that were isolated during November and December. We have a number of strains from North America here, and then we have a strain from Japan, and one from India, and a couple from Hong Kong.

What we are seeing is that there are increasing numbers of viruses that have a four-fold reduction in titer with the Beijing/184 antiserum, as well as with the B/Yamagada vaccine strain.

These viruses are still pretty well inhibited, are very well inhibited by antiserum to the Johannesburg and Sichuan antisera.

This is another example of the reduction in titers that we are seeing for current strains. We have a number of strains, again, from North America, and a number from South China.

Once again we are seeing better reductions in titer, sorry, better inhibition with the antiserum to Johannesburg and Sichuan. And we have antiserum to Victoria/504, which has also been used for production

of vaccine in the southern hemisphere.

We have included an antigen from Japan, here in our reference battery, because this particular strain is being considered for production of vaccine in Japan.

So I think I have one final table with the most current data that we have. There are actually a couple of viruses from January, here. So these are the most current data that we have on influenza B viruses.

And as you can see we do have many viruses that are reduced in titer with the Beijing/184, and the Yamagada/166 antisera.

As I said before, the Sichuan antisera to this Sichuan-like strains, which are listed up here, they are all really fairly similar to Sichuan, do cover the current strains much better.

So if I can summarize the antigenic properties of the influenza B viruses that have been isolated, first of all, during the southern hemisphere influenza vaccine season.

You can see that the majority of strains were B/Beijing/B/Yamagada-like. But that about 20 percent of strains were low to Beijing and Yamagada.

That percentage has increased, the

percentage of low strains has increased fairly substantially in recent months, so that at the current time we would say that about 72 percent of the strains that we are looking at, are reduced in titer to the Beijing/184 and Yamanashi reference strains.

I think that that concludes my presentation. I do have overheads made for the serologies, but I think that it is better to consider all the serologic data together.

CHAIR DAUM: Thank you very much for a very clear, concise presentation, Dr. Cox.

Are there one or two questions for Dr. Cox before we move on to our next presentation?

(No response.)

CHAIR DAUM: Okay, thank you very much, Dr. Cox. We will move on to Dr. Klimov to complete the influenza branch trilogy.

DR. KLIMOV: I would follow the same format Nancy presented to you, and all the pictures and tables I'm going to show you, you also can find in our package, in case you don't see some details.

Again, I would follow the order Nancy used, H1s, H3s, and Bs. And I'm going to show several phylogenetic trees, and for those who are not very familiar with the tress, I'm going to notice that --

CHAIR DAUM: This is page 14 of the CDC handout, to orient committee members.

DR. KLIMOV: Yes, thank you very much.

And I need to notice that the horizontal distance is essential for understanding the relationships between different strains. They are placed in a vertical order just for convenience.

Actually the vertical distances are not important, at all, to estimate the difference between different strains. For example, the difference between this strain and that strain is like, you know, from here up to here, and from here up to here. So it is only horizontal distance.

But, essentially, it doesn't matter much because we will be talking about genetic groups. So as to the H1N1 hemagglutinin genes evolution in recent times, in recent couple of years, you can see that the viruses which are here, are genetically quite moved now from the Beijing/262/95, which was previous vaccine strain.

And still pretty much a similar to the vaccine strain which is just now New Caledonia/20/99. The vast majority of viruses are close to the New Caledonia genetically.

At the bottom you can see another genetic

antigenic group of the viruses which Nancy mentioned. This is viruses similar to A/Johannesburg/82/96. And, as you remember, we have approximately nine or ten percent of viruses from this genetic antigenic group.

Next slide, please. I did mention we did see some so-called low reactors, but they do not grow in the phylogenetic tree in some particular groups. So they are randomly distributed among the tree, in general.

This is the table which shows the amino acid differences between some of those strains which could be potentially vaccine candidates, because they are grown in eggs.

And so-called consensus sequence. And usually this parameter we use as an additional parameter to see whether new strains are evolutionary moved from the vaccine strain.

From the previous year's experience we know that the closer the sequence of the HA to the consensus sequence, the better in terms of inducing immune response, which would work with the majority of viruses.

So from this table you can see that A/New Caledonia/20/99, the vaccine strain is sort of the best match to the consensus sequence.

Next slide, please. The neuraminidase genes is a gene coding for another surface antigen of the influenza virus. And during recent years we started to monitor evolution of this gene, as well.

You can see from this slide that, again, the majority of viruses, the majority of neuraminidase genes of recent viruses are still pretty close to the vaccine strain A/New Caledonia.

You can see, also, that these do have viruses from the Johannesburg, or we call this sometimes Bayern/95 group. They form another group of the viruses. So genetically we also have two groups of the neuraminidase genes.

And the next table shows the amino acid differences between the consensus of the neuraminidase protein sequence, and several egg grown strains. We can see that New Caledonia is not the best match to the consensus of the neuraminidase protein, but still not very far from the consensus, which is good sign in terms of vaccine.

So as a conclusion we can say that genetically, as well as antigenically, great majority of current strains are similar to the New Caledonia vaccine strain.

H3 part, Nancy mentioned that we had very

few, actually, H3 strains this year. And most of them are actually, all of them are still pretty close, genetically, to the A/Panama/2007/99 strain.

In spite of existing of sort of couple of genetic groups, which are not diverged very much genetically, we do not see any difference, antigenic difference between those two groups.

And also very, very few low reactors are randomly spread among the branches of this tree.

Next slide shows amino acid differences between some egg grown viruses, and hemagglutinin protein consensus sequence. So you can see that Panama/2007/99 is still the best match to the consensus sequence among viruses grown in eggs.

The neuraminidase genes of most recent viruses belong to a group which we call a Moscow/10/99, which is genetically different from the A/Panama neuraminidase genetic group.

It is obvious that some -- we still have some viruses belonging to the Panama neuraminidase genetic group, but the majority belong to so-called Moscow/10/99 genetic group.

As I mentioned before, and as Nancy mentioned, it doesn't influence, at least so far, on the antigenic properties of the current viruses.

Next slide shows the table about the amino acid differences between the neuraminidase protein consensus and the Panama has 10 amino acid differences from the consensus. And in this sense is not the best match to the neuraminidase protein consensus.

As a conclusion we can say that, essentially, all current H3N2 strains are antigenically and by the HA genetically close to the A/Panama vaccine strain, also the neuraminidase gene belongs to another genetic group.

AS to the evolution of influenza B viruses, Nancy mentioned that there are two genetic antigenic lineages of influenza B viruses, B/Victoria-like viruses, and previously we called them B/Yamagoto, or B/Beijing/184-like, or B/Yamanashi-like viruses.

So this tree includes exclusively viruses from the B/Beijing/184 or B/Yamanashi group, because we did not see B/Victoria, we didn't receive B/Victoria-like viruses in last almost year.

You can see that this is Yamanashi current vaccine strain. And you can see that the majority of viruses genetically are moved from the Yamanashi vaccine strain, and form a group along with the B/Sichaun/79?99 reference strain, which is the strain

recommended for southern hemisphere, as you know.

So, by the way, we mentioned that in red you can see the viruses which are grown in eggs, and asterisks indicate the viruses which are used in the serology tests.

The Beijing/184, or Yamanashi genetic group is also actually includes some another genetic sublineage, which we call B/Harbin/795 sublineage. And -- I'm sorry, that is about -- yes, this group is B/Harbin/794 genetic lineage.

We continue to see very few strains belonging genetically to this genetic group, but do not see any significant antigenic differences between those two groups.

And the percentage of these groups, and the percentage of B/Harbin-like genetically, B/Harbin-like viruses is actually pretty low, it was about 7 percent during the summertime, and now it is about 90 percent total.

As I mentioned, we do not see B/Victoria-like viruses at all.

The next slide shows the amino acid difference table, which indicates that B/Yamanashi/166/98 is moved apart from the consensus sequence for the HA protein. And, for example,

Sichuan/379 reference strain represents better match to the consensus sequence of the hemagglutinin protein.

As to the neuraminidase gene, again, we see that in general most viruses are not very far from the B/Yamanashi vaccine strain, but still they are forming a new sublineage similar to Sichuan/379 genetic group.

In the terms of amino acid differences from the neuraminidase protein consensus, again, Yamanashi is moved quite far from the consensus, while Sichuan is one of the best matches in the sense of the neuraminidase protein sequence.

I will probably stop it here.

CHAIR DAUM: Thank you, very kindly. Questions from the committee for Dr. Klimov. Dr. Ferrieri first, then Dr. Estes.

DR. FERRIERI: Very brief question. How very different is the HA1 sequence in B, from the AHA1, for example, are they like 75 percent different?

DR. KLIMOV: You mean H3 and H1?

DR. FERRIERI: No, AH1 and BH1.

DR. KLIMOV: They have approximately not more than 30 percent of homology, as far as I remember, something like variable homology.

DR. FERRIERI: Thank you.

CHAIR DAUM: Dr. Estes, please.

DR. ESTES: With the introduction of the neuraminidase inhibitors do you have any evidence that that has influenced either neuraminidase or HA in terms of evolution of these viruses?

DR. KLIMOV: Not so far. And I know that there is a group of, information group of people, actually, who is trying to monitor what the percentage of the strains which may be resistant to the neuraminidase inhibitors after the licensing of these drugs in several countries.

Not much attention paid yet to the possible influence of the possible drug resistance onto the antigenic properties. But so far we don't see any dramatic changes.

CHAIR DAUM: Thank you very much, Dr. Klimov.

What I would like to try and do, with the committee's pleasure, is to get through the next three presentations, and following that we will break for lunch, and then resume our session in the afternoon.

The next speaker whose name I hope I'm not going to butcher is Linda C. Canas. Is that how you say it? Good, I did it. Who is the chief of

diagnostic virology at Brooks Air Force Base in the Department of Defense.

MS. CANAS: Good morning. The Department of Defense has a historic and even continuing interest in the surveillance of respiratory viruses. It is absolutely essential that we know what is going on.

CHAIR DAUM: We need -- can you speak right into the mike, or can we get some more gain from it?

MS. CANAS: It is essential that we know what is going on from a public health standpoint in the military facilities. The Air Force has long engaged in influenza surveillance, and recently it has become a tri-service program that has operated under the direction of the global emerging infection system here in Washington.

This program is tri-service, and it operates on two different levels. The Navy in San Diego, under the Naval Health Research Center operates a population-based surveillance system.

They have, at the recruit centers, all of the recruit centers from all services collect a certain number of samples, each week, according to case definition, based on the population of that particular center.

And these are analyzed to determine what is going on in that population. At the Air Force Center at Brooks Air Force Base, we have surveillance sites that are set up, and we are basically just trolling for bugs. Whatever we can find we are going to report and keep track of.

Our interest is influenza, and that is what we are interested in, that is what our case definition is aimed for. But we actually will report anything we find.

And this is the process that I'm going to talk about today. The data is from all three services. What the Army collects from the medical treatment facilities, what the Navy collects from the recruit centers, and what our program collects.

But the process is what we do in San Antonio. The epidimiologists and the laboratory personnel decide on sentinel sites each year, and how the program will be run, and information is then sent to the Surgeon General of the Air Force.

And because there is such emphasis on influenza prevention of illness, and we know that the vaccine is the single best way of preventing illness, it is a requirement that all active duty individuals be vaccinated annually.

So the message that goes out, that directs this influenza program, will also name the sentinel sites that have been decided on, and we make sure they all have supplies and directions on how they are going to collect this.

The public health office is in charge, and they collect samples and send them to Brooks Air Force base, where they are worked up according to standard laboratory practices.

And we do try to treat these as clinical samples, and get the results back as quickly as possible. And they do go into a computer where they are sent back as patient results.

And in addition we send the results to the disease surveillance branch where they keep analysis, and make reports that public health office is notified in a timely manner what is going on at their base, so they can react with any interventions, and they get some feedback from the program so they can react to it.

In addition we get to make lots of reports and presentations. We do make -- take selected isolates and share those with CDC, because they have a much more detailed analysis, and they can see what is going on in our program compared with the rest of

the programs, and decisions can be made at meetings like this one.

This is a map of our current sites listed in the handout, they are actually named by location. But I wanted you to see that we do have a global presence. Most of it, of course, are from our military sites where we have people stationed, and we are seeing people in the treatment facilities.

But we've been able, under this tri-service arena, to be able to hook into the Army and Navy research centers in more remote locations of the world where they also already have ongoing research projects, and have now instituted influenza surveillance.

This has been very productive in Napal and Thailand, several sites in South America. And it is a very -- the program is flexible, and we try to maximize our resources compared with everyone else, to see where surveillance is needed.

If it is already well surveyed, and we don't need it for our own public health issues, then we move on to other areas.

We have recently been able to confirm that Honduras will be a collection site, they are going to be submitting samples. This is especially exciting

because we lost Howard Air Force base when we moved out of Panama.

And as you've heard many times today, the A/Panama/2007 is the vaccine strain, and that did come from this program.

South America, too, has been very productive. We were able to identify, early, the variant H1N1, which is now New Caledonia, was actually the second time in the Americas that this strain had been recognized. So these remote sites are important.

We have the possibility, probability, of bringing on Uganda. Everything has been set up, we have the shipping organized. There are still some political considerations there that will have to be considered and worked out.

When we look at the number of samples that we received from all sites, compared to last year, it is a little bit deceiving. It looks like our season, like everyone else's, has been much lower than last year.

One of the confounding factors here is that last year the Air Force experienced an extremely overwhelming incidence of adino virus disease, respiratory adino virus. And while that continues it is not quite as overwhelming as before.

So in fact our number of samples that we are receiving for, other than adino virus, is almost higher than last year. And there is a couple of reasons for this.

Namely, while we do have a dependent and retired population that we are conducting surveillance on, and they fit, in many cases, the fidicional risk groups, our main population of concern are the relatively young, healthy individuals.

This is not one that you all are considering, but we have to keep these people healthy. Their readiness mission is what is important. And the commanders have been very concerned, this past year, that they have been able to rely on the past in the vaccine, and this year they weren't going to have the vaccine.

And never knowing exactly for sure what the mission will be, and where these people will be sent, and what they will have to do on a daily basis. There was a great deal of concern about the vaccine. So there was a very heightened awareness of surveillance. and we've received many specimens, a lower productivity, but many specimens this season.

In North America, and I think our results are somewhat different from many others. We've had

nearly equal numbers of As and Bs, 45 percent of all the flus in North America have been B. Let's see, I'm not sure that is exactly right.

41 percent have been A, and 56 have been B in our North America. And these are at the same places. I've daily reported out As and Bs from the same locations. It hasn't been a spotty thing. We've seen it in California, we've seen it in Texas, we see it from the very beginning, in Alaska.

And that continues, this co-circulation. We also have a lot of peri influenza and interal viruses that are going around. So from workload standpoint in our laboratory, we are basically working these samples up for anything it could be, instead of ruling out what we've been seeing.

Our numbers in the Pacific have so far been considerably less, but that is changing. In the last couple of weeks we are starting to see a lot more activity in this area.

We saw our first isolate of the season in September in Okinawa, and that was a flu B. Those numbers have continued, in very low numbers, in Okinawa and in Hawaii. We've seen a predominance of B.

We've had virtually nothing from Japan,

but Korea is suddenly starting to see influenza A. We started getting isolates within the last two weeks, and I've had requests for more supplies because they are seeing more illness.

Our numbers from Europe are quite low, very low numbers. I'm not sure we can make a lot of prediction. From that we've had 3 As and one B, from those.

South America, I present, this information is maybe not timely for this committee. But, again, I think it shows our more equal numbers of A and B that we are seeing from this area of the world.

And, of course, when we talk about getting samples from South America, for these remote sites, they don't come very often. So they are truly surveillant samples. And the miracle is that we are getting five and six month old samples that we are able to get isolation. And that has been exciting.

We've also seen a good bit of adino viruses in South America, especially Argentina.

Nepal and Thailand has been especially exciting. Last Tuesday, one week ago today, we received in our lab 59 samples. And the pressure was on to get some information for this committee to look at.

These samples ranged from collection dates clear back to March, but some of them were up to January, and a good many in November. So there was some timely issue here.

We did put them in culture but our molecular biologist randomly chose 16 samples and went in with just PCR directly out of the tube that we got in the lab. And he was able to isolate two As and a B from those 16 samples.

When I left on Friday, when I left the lab on Friday, we had confirmed those three types. And in all, in our first culture results, we have 18 isolates. The majority of them are A, that is 30 percent recovery, which we are really quite excited about, and we still have the rest of this week before we would finish reporting out the viruses.

If we look at the subtypes, like everyone else, we have a strong H1 season, much stronger B than we've seen in many years. And, in my experience, the co-circulation in these As and Bs, especially at the same location, is unprecedented.

The B started out early, and first, mainly in the Pacific and Alaska. We had quite a bit of B in Alaska, to begin with. That continues, even though the As have come up.

The Bse in our HAI subtyping, using rabbit antisera, have been lower titers than we've seen in the past. A great many of them are four-fold less than the reference strain that we are using in our laboratory.

The Pacific Rim still has low levels of B, but they've actually been matching fairly well. H1s have matched very closely with the reference strain, and we do have a predominance of that, especially in North America.

In the Pacific the H1 is much -- we do have more of the H1s, but we have H3, also. And H3 is what we are seeing in the Pacific. These new ones that we are just seeing in Korea, that we've just identified last week by PCR, those were H3.

Now, whether that will continue I don't have any idea at this point. But it is interesting that that group does seem to be coming up as H3.

And, again, to emphasize the same thing that has been reported elsewhere, we've just flipped this year. H1s we've seen very little of in the last several years, but it is the predominating strain.

I would say that from a laboratory standpoint they are much easier to work with, so it doesn't bother me any.

This chart didn't print out in your handout. It was the nucleotide homology, looking at the hemagglutinin gene, and we did show very close homology, pretty much what Dr. Klimov reported earlier.

I think that our results have shown that the current strains are covered quite nicely, the hemagglutinin strain.

Mostly we have seen the H1 and the B, like other groups. Perhaps our numbers are a little closer. One reason for that could be because of the increased interest in surveillance. Perhaps people who weren't quite as ill, and may be in the private sector, would not have sought medical attention, or actually getting cultured in our program, which would show more equal numbers.

The Nepal isolates have just come in, they are currently being analyzed. Several of our isolates were collected in November, so they do have some timely aspect to what we are looking at here. It does appear that if we can make a prediction from two of these isolates, both of those As were H1, nothing that was used, the H3N2 primers didn't pick up anything.

So we suspect that these are going to come down as H1s, like we've been seeing everywhere else.

Would there be any questions?

CHAIR DAUM: Thank you very much. That was -- you win the special VRBP prize for technical effects, as well as a very lucid presentation.

Dr. Huang?

DR. HUANG: I remain concerned about our surveillance, and I have a comment and a question, not only to you, but also to the CDC presenters this morning.

The comment is that our surveillance on the African continent is still really poor, if it exists at all. And I remain concerned that we don't have that, really, set up as well as we ought to.

And I know that we do have a Navy lab in Egypt, and I didn't see if that was part of your distribution there, or not, if they are active in this surveillance.

The other is that in the past we have seen data from cruise ships in Alaska that we obtained swabs in Alaska, or around Australia, that we obtained swabs of in the summer months of August, September.

And I'm wondering, I just don't see that any more, and I'm wondering if there is some reason that we haven't gone ahead to do that.

MS. CANAS: We actually do collect all

year round. Our surveillance is annual, we have that data all year. I just presented from September right here, but it pretty much agreed.

Africa is particularly problematic. We are trying to get in, we have every expectation to get in to Africa with our surveillance. But, as I said, there are political considerations.

Dr. Kelly is here if you would like him to address that.

CHAIR DAUM: Could you identify yourself, Dr. Kelly?

DR. KELLY: I'm Pat Kelly, I'm the director of the DOD infectious program.

Separate from the program that Linda operates, our lab in Cairo does do influenza surveillance and sends specimens directly to Dr. Cox of CDC. They currently are doing surveillance in Egypt and in Syria, and this year we will be bringing on line Yerubi.

It is a great logistic challenge to do surveillance in some of these overseas area. For example in Yerubi they had everything politically lined up, but there was no local source of liquid nitrogen the store the specimens in.

To get specimens out of Nepal we actually

have to ship dry ice in from Bangkok. So there are some unusual logistic constraints. We also are going to be starting, as Linda mentioned, this year new surveillance in Uganda.

One interesting challenge that we have faced in some of these countries is ethical debates over whether it is appropriate to do flu surveillance.

Uganda initially, their ethics -- they turned it down, because they said that we don't use flu vaccine in this country, and thus you should go somewhere where flu vaccine is used. This is not a surveillance program that is going to benefit us.

We ultimately negotiated with them and are providing them benefits that they find valuable. But it is much more complicated in some of these places.

CHAIR DAUM: Thank you very much. Dr. Ferrieri and Dr. Diaz.

DR. FERRIERI: I am very glad that you mentioned, Ms. Canas, the other surveillance and the high prevalence you saw with peri influenza. It is my impression in the twin cities we've had peri flu 3 that came in in November through December and parts of January, causing rather relatively severe illness in adults as well.

And so the impression of many people is

that everything is flu, and it gives a bad rap in the general public to the efficacy of influenza viruses vaccine.

And so I can't emphasize too much the co-transmission of more than influenza virus during this season. We now are into RSV with trickle peri flu, and adino virus is certainly out there as well.

CHAIR DAUM: Dr. Diaz, please? Thank you, Dr. Ferrieri.

DR. DIAZ: I think actually what you said goes back to my comment about those 93 percent of non-flu isolates, because it is important for people to understand when there are other viruses circulating, what they are, so that they can better understand influenza vaccine and how well it is protective.

But my comments that I wanted to make was in regards to your comment about the cruise ships. And perhaps somebody from CDC can correct me if I'm wrong.

But I think that cruise ship data came not from necessarily surveillance that was being done on cruise ships at the time, but rather was prompted by outbreaks of influenza-like illness on those cruise ships at the time, and then an investigation.

CHAIR DAUM: Are there more questions for

Ms. Canas?

(No response.)

CHAIR DAUM: We have a clarifying comment coming in regarding cruise ships.

DR. FUKUDA: Just to clarify. In Alaska there were large regional outbreaks involving cruise ships and land travelers identified in 1998, summer. Also in the summer of 1999.

Interestingly this past year we haven't seen the same phenomena occur up there. There have been a number of other outbreaks reported on cruise ships in different areas. And so that general phenomena occurs.

So I think that when we presented those earlier Alaska outbreaks, one of the outstanding questions has been whether this is sort of a change in pattern in that area, or not. And I still think we don't know the answer to that, yet.

CHAIR DAUM: Thank you very kindly.

DR. GRIFFIN: Are the cruise ships like canaries, then?

(Laughter.)

DR. FUKUDA: Well, someone has termed them large virtual populations. And in a sense they are this very big populations of people from all over the

world. And a fire may ignite, or may not ignite in that population.

CHAIR DAUM: Dr. Griffin, if it is brief.

DR. KIM: Yes. I just wondered if somebody else could clarify. So we saw what the surveillance, and heard about the surveillance that the Armed Forces does in Africa as far as influenza is concerned.

But I'm just curious about what the WHO is doing. Clearly South Africa, we get a lot of samples from there, but -- and maybe from Egypt and the Mediterranean region, but how about the middle?

DR. COX: I will try to address that. Basically it has been well recognized for some time that Africa really doesn't generate a lot of information for vaccine strain selection, with the exception of South Africa, and now Egypt that has come on line.

It is, as Pat Kelly pointed out, extremely difficult to convince people to do surveillance in these countries, if they don't see that there is a direct benefit.

And I think that what we saw in South America is illustrative of what we are likely to see in Africa. When the countries get to a point where

flu vaccine is on their radar screen there will be a very much increased interest in doing flu surveillance.

So, basically, what we have to do in the interim is figure out where we can best put resources to expand knowledge about what is going on. There are a number of efforts underway to try to see if there are ways to increase the amount of funding that might be available to try to enhance surveillance in some areas of the world that are less well served at the present time.

CHAIR DAUM: Thank you, Dr. Cox. I would like to move on now to hear from Mr. Hampson, the director of the WHO Collaborating Center for Influenza in Melbourne. Welcome.

MR. HAMPSON: Thank you Mr. Chair, it is always a pleasure to speak at this meeting, and maybe a little bit daunting, because I have to present, very briefly, some surveillance information, antigenic analysis, genetic analysis, and some serology.

So if you would like I'm going to be Keiji Fukuda, Nancy Cox, Roland Levandowski, and I can't remember who the others -- Sasha Klimov all rolled into one.

It is also a little daunting to see that

the U. S. Military probably has more surveillance sites than we do.

This is just to show you the area of our collection of samples at our center, which is one of the four WHO collaborating centers for influenza.

And I am going to give you just a little bit of epidemiology from the three main collecting areas that we have. Australia, of course, from which you will see that looking at sentinel surveillance, this is influenza-like illness measured over a number of years in general practice, and virus isolations measured in laboratory studies.

That, in fact, we did not have a very severe season during the year 2000, it was a substantial reduction of the previous years in both the total influenza-like illness, and in particular in the number of clinical isolates that we received last year.

That was even more marked in New Zealand, where you see this yellow line showing the level of influenza-like illness in comparison with other recent years, and in particular in 1996, when there was a very severe outbreak, a very, very flat year of influenza in New Zealand.

And this has been characterized through

much of our surveillance area, showing that in New Zealand it was a mixture of influenza A and influenza B, with influenza A predominating.

And in Thailand our other major collecting area, apart from an early outbreak, early during the year 2000, which was mainly H1, so there had been a shift already there to H1 influenza from predominantly H3 early in the year.

Very little influenza in terms of isolates seen during the remainder of the year. So I suspect that you are having a year, in North America, which is going to be very similar to what we've seen through a lot of the Pacific area.

Just showing you where our viruses are collected from, principally from Australia, New Zealand, Thailand. But we do have a spread of collection sites where we could receive some viruses from Singapore, South Africa, up into the Pacific region, New Caledonia, Malaysia, and occasional samples from Vietnam.

We have recently received a shipment within the last two weeks from both Singapore and Vietnam. And, interestingly, in comparison with the results that Dr. Canas just presented, all of those viruses appear to be H3 viruses.

This is the distribution of subtypes and types that we've seen during this last 12 month period. In Australia H3 continued to predominate, although we did have a significant amount of influenza A H1, the second most prominent type was type B.

We missed the type B last year, we normally have a two year outbreak of influenza type B, we had had a very severe outbreak in 1997, we essentially missed our second year of the outbreak in 1999, and it seems to have come back this year.

New Zealand H1 predominated but was similar in levels to the H3 with a minority of influenza B. Throughout Asia, though, we have seen a predominance of H1, and approximately equal levels of H3 and B, and through the Pacific something similar, but with influenza B less prominent, there.

Now, I'm showing you very, very restricted and representative tables of antigenic analysis of our H1 viruses. I'm showing you that the great majority of strains that we have seen are very well neutralized by New Caledonia antiserum.

They are less well neutralized by the previous reference strain, antiserum Beijing/262, which was a previous vaccine strain, particularly when you look at the homologous titer of the sera, the

Beijing being higher than the New Caledonia, with the New Caledonia producing very good protection.

We are also putting, in some of our essays, a normal human serum pool, a post-vaccination pool, to have a look and see whether there is any sign of variants coming up which would be escaping vaccination. And the pool is showing very good protective level against these recent isolates, and gives us comfort that the vaccine is working.

A second set of H1 assays just showing that there are still some residual strains of this Bayern or Johannesburg type, which was mentioned previously by Dr. Cox, including this recent Texas strain, which we put into this assay.

We have occasional unusual strains like this England strain, which is showing very low reactivity across both types of viruses, we don't understand this at the moment, but reassuringly neutralized by the human serum pool.

But, again, we have a very good protection by the New Caledonia 20 strain, as shown by Dr. Cox, and by this variant from Japan.

If we have a look at the overall analysis of the strains that we've seen this year, there have been very, very few Bayern strains, in fact all of

these Bayern strains that we've seen came from a single outbreak in South Australia, and we have seen them nowhere else in our surveillance area.

The greater majority of the virus isolates that we did analyze came from this January to August period with fewer in the September to January 2001 period.

I apologize for this dendrogram, I did have it hyperlinked, but the technology didn't function properly and so you are going to have to see it in a slightly blurred fashion.

But simply what I'm showing here, here is the reference vaccine strain, New Caledonia 20. Here is the previous vaccine reference strain Beijing/262, and the viruses are falling quite close, genetically, to the New Caledonia strain.

There is a tendency for them to have moved and to have broken into two separate claves, and the majority of recent viruses we are finding now in this upper clave. But the difference is not great, and certainly while there is a genetic difference, there is not an antigenic difference.

As shown by Sasha also, the viruses, the recent viruses are staying very close to New Caledonia, genetically, in terms of the neuraminidase

sequence. I apologize, this 88 up here should be a 2000 virus, not an 88 virus.

So all the recent viruses are, again, close to the New Caledonia virus, with the exception of these very different viruses, such as the South Australia viruses, which remain in this Bayern or Johannesburg clave, which is quite different.

H3 influenza virus analysis has been very similar to recent years. We've seen a move, a drift away from Sidney to this Moscow type of virus, or viruses represented as Moscow-like, the Panama vaccine strain, and these other three strains, which are antigenically very, very similar.

We get possibly more than some of the other reference labs strains which are low, we call low reacting strains. They react poorly right across the range of antisera that we have.

When we sequence these viruses they don't show any outstanding features. When we make antisera against them, they make antisera which are characteristic of these other recent strains.

So we refer to them as low avid viruses, and we haven't found a reason for this low avidity, as yet.

They don't appear to be significant,

though in terms of vaccine protectiveness, although they do, again, react very poorly with our pooled human serum. So this is something that is ongoing further investigation in our lab at the moment.

If we have a look at the representative strains that we've had over these two periods, January through August, prior to the WHO meeting in September, we saw a preponderance of Moscow-type of viruses, still some Sidney-type of viruses, and low reacting strains in both these groups.

We've now moved, quite definitely, away from Sidney-type viruses to Moscow-like viruses, but with a fairly high percentage that I've just showed you of these low reacting strains.

When we have a look at the genetic analysis, the dendrograms, we found that these are broken into two major trees, as represented by the Panama vaccine strain, and viruses which are closer to the Moscow referenced strain.

So there is a genetic difference between these two viruses, although the Panama antigenically represents the Moscow virus. A number of the other strains that I showed you previously were also falling into this group, and we find that most of the recent isolates that we have seen from late in the year, and

we did have isolates coming through into October and November in Australia/Asia are falling into this Panama group.

On the other hand, with the neuraminidase antigen, and again similar to what Sasha showed you, the virus are clustering close to the Moscow with the neuraminidase than they are to Panama. So, clearly, an ideal vaccine strain if we would take into account both antigens would be a virus that fell into this group, in terms of its neuraminidase, but into the Panama group in terms of its hemagglutinin.

And when we have a look at the influenza B, I apologize if these colors did not come out very strongly. We do see a more dramatic difference, I think, than some of the other labs, in terms of the differences between our Yamanashi serum, and the sera against these recent strains, the reference strain Sichuan, and the vaccine strain B/Johannesburg, which are producing excellent protection against very recent virus isolates.

The Yamanashi is producing poor protection against a large number of our recent isolates, and in effect much poorer even than the reference strain, which are represented in the vaccine, the Beijing/184 strain.

And we see that in the second set of HI assays here. Yamanashi showing exceptionally poor titers in some cases, against some of the recent strains, less than one in twenty. Whereas the Sichuan, the Johannesburg, and the alternative vaccine strain which has been used in some countries in the southern hemisphere, the B/Victoria/504.

I will just mention, at this point, that these two vaccine strains were selected after trolling through many, many egg isolates of virus. They were the best growing strains that we could find, and undoubtedly you will hear a little bit more in the future.

But the general feedback has been that these viruses do not grow awfully well.

Again, dividing our analysis up over the two time periods prior to the WHO southern hemisphere meeting, we were labeling most of our viruses as B/Beijing viruses at that stage, because that was the reference strain. We have only recently switched into the Sichuan type of viruses, and quite possibly a high percentage of these strains that we call B/Beijing-like were, in fact, closer to B/Sichuan, and certainly on dendrograms they appear that way.

And since the September meeting clearly a

major move to Sichuan-like viruses in the isolates that we have analyzed since that time.

And, again, having looked at the dendrogram, we see that these fall into a number of subclaves. Here is the Sichuan-like virus, quite distant now from the Yamanashi virus, and from the Harben virus, and Beijing/184 virus, which was the reference strain.

So there has been quite a significant genetic move in these viruses. They are falling into, maybe, three or four separate claves. We've seen all of these this year, and I think the major virus grouping, in fact, is around this Sichuan group, or possibly with some recent isolates moving up into this slightly further separation.

And the neuraminidase very, very similar. Not as great a move as in the hemagglutinin but clearly a move in these recent virus isolates into the Sichuan grouping, and away from the Yamanashi, and quite distant from the previous reference strain, Beijing/184.

Now, I put some tables of serology into the handouts that I provided, and they are always rather difficult to look at. And I've tried to summarize, graphically here, a little bit of the

information in that.

And I've selected simply the older adults, and simply two groups of sera, the U. S. sera, and the Australian sera. And I've show two parameters, especially the geometric mean titer which I've expressed in terms of a percentage of the homologous vaccine percentage, and that is the New Caledonia.

And what we see, quite clearly here, is that the New Caledonia has been producing good antibodies to all except one recent strain that we've tested in this, this Texas/87 virus.

We've also looked at the total number of people who have presumptive protective titer, that is a titer in one in forty, or above, in this elderly group. And, again, we see with recent strains, and including this Texas virus, a high percentage of people with protective titers.

The Australian sera is showing very similar results to the U. S. sera in this group.

Looking at the H3s, and just pointing out that the U. S. recipients here received a vaccine containing the A/Panama virus, or A/Panama virus and a Moscow-like virus, so this is the one hundred percent starting point.

I've referred back to Sidney in here,

because the Australian recipients actually received a Sidney containing vaccine in view of the difficulties we had getting the Moscow-like virus into the vaccine for last year.

Again, over recent times, and these are results taken up to the point where we made our decision on vaccine formulation in September, very good protection both in terms of GMT, relative to the vaccine virus, and to the level of protective antibody, certainly a high level, up around 80 percent of people achieving protective titers.

And that was similar, regardless of whether the vaccine contained the A/Sidney virus, or the A/Moscow virus. To our surprise, although we were forced to put in A/Sidney-type of virus into the vaccine we did achieve very good titers against the Panama virus, and against recent isolates.

There are a couple of recent strains. I think the Hong Kong/19223 virus was mentioned earlier on. And we have a strain which is being distributed for serology, the Leon virus, which is showing some lowering. And we probably need to investigate these further at the moment.

But against the great majority of strains the vaccine has been shown very high protective

levels. Against influenza B, at the time that we did our initial studies, when we had a look at the initial studies, these were the strains that we tested for vaccinees receiving the Yamanashi vaccine, up until September, you can see quite a dramatic lowering in terms of geometric mean titer.

The lowering was not as dramatic, or the lowering was not really greatly significant in terms of total, numbers of people achieving a titer of one in forty.

But I would point out that we used ether-split antigens in doing the serology. And we really can't be completely sure, I don't think, that that is not influencing the outcome of this test, to some extent.

What is interesting is the two most recent tests that we've done in the serology, two new viruses we've put in, in fact one of them vaccine strain, and the other recent Leicester isolate, we've seen a reversal of the trend that we had seen earlier.

So with the Yamanashi containing vaccine there is an indication that it may be protective against these viruses. We also are having a look at the influence of passage level of these viruses, because as we passage them on, it seems they might be

more readily neutralized by antibodies.

I think I'll stop there. Any questions?

CHAIR DAUM: Thank you very much for illuminating view of the other side of the world. Do we have committee questions, input, comments?

(No response.)

CHAIR DAUM: That means your presentation was crystal clear. Thank you very kindly.

For our last speaker before we will call on Dr. Joanna Ellis of the respiratory virus unit, public health laboratory service in London.

DR. ELLIS: Thank you. I would like to thank the committee for giving me this opportunity to present the data from the UK.

In the United Kingdom we use a number of indices to measure influenza activity. But the data we put the most reliance on comes from the Royal College of General Practitioners.

This organization coordinates about 100 sentinel physician practices throughout England and Wales, and collects all the data. These practices represent about 800,000 of the population.

The consultation rate is then calculated and is expressed as the rate per 100,000. The levels that we use to describe, the baseline level is 50 and

below. Between 50 and 200 is described as normal seasonal activity. If the consultation rate rises to 200 to 400, and that is higher than normal, and it has to be above 400 of 100,000 of the population to be described as epidemic.

As you can see, for this season, the level of consultations has hardly risen up to the baseline level. This is shown more clearly here, where we can see the consultation rates against weeks.

We have a slight peak of activity here, week two. This is last season's activity. And when we compare the death rates, or causes notified to the office of National Statistics, we can see we have a very slight increase in the death rate, but much less than previous years, which correlates with the lower level of activity.

A small subset of those 100 sentinel physicians also sent in samples for virological analysis. These are patients who are presenting with influenza, or influenza-like illness.

The physicians then take a combined nose and throat swab, and send those by post to the National Influenza Lab in Collingdale.

We test them by culture, and this year we've also been running a PCR test. This is a multi-

plex test which is able to determine whether we have influenza H1N1, H3N2, influenza B, or RSV in those samples from the community.

And these are results that we have to date. Here is out OCGP consultation rate. These grey ones are the total number of samples we received each week. The green is the RSV positives by PCR.

And, as you can see, these were detected first in the season, week 43. And the yellow are the flu H1N1, which we detected later, and then some flu Bs much later on.

But the point to take home from this is the RSV and flu circulating at the same time, they are still circulating now, in the community. When we look at the As distribution of those that were PCR positive, we can see that RSV was found, perhaps as you would expect, in the under five age group, and again in some of these older age groups, whereas flu was not found in this younger age group, it was found more in the middle age group, but not in the elderly.

We not only receive samples from the community, we also get samples from hospitals, that is public health laboratories, and national health laboratories, which have already been typed as influenza, and come in for further analysis.

So when we look at this, here again is our consultation rates. And these are the community samples, these are posted by isolation this time, not by PCR. And we also have our hospital isolates here.

When we look at the types we, as others have already described, predominantly have influenza A H1N1, which came first in the season, at week 43, and then peaked here, about week one. We do have it coming down here, and it is still coming down this week, from data that we have.

And then the later emergence of the flu B, which co-circulating now with the flu A. When we look at the As distribution of the isolates, first of all, looking at the community, we can see that we have a peak of isolation in the 15 to 44 age group, which is what we normally see in the community samples.

For the hospital samples we have mainly in the under five age group, and usually not many in the over 65s this year.

For the regional distribution of the isolates we have about 20 practices that sent in serological samples, scattered throughout England and Wales.

The isolates themselves have come from all over, quite a few from Scotland this year. Of the

about 7 or 800 samples that we've actually received, we've got mainly H1N1, and a few flu Bs, as well. But we haven't detected any H3N2 this season.

Looking at the antigenic characteristics of the strains, first of all the H1N1s, here is the New Caledonia vaccine strain, and corresponding antiserum.

Most of our isolates have reacted well to New Caledonia, like these two here, and show a New Caledonia-like. We have had a few isolates which have been like the older vaccine strain, A/Bayern/95, this one here, and one here.

In fact we've had three isolates. They've all been in children under two and a half years old, and they've all come from one area in Wales, in Swansea, so we think it is just a sporadic outbreak there.

Looking at the phylogeny of the H1N1 viruses, this is the older A/Bayern strain, and this is where our small outbreak fits on the tree. This is the New Caledonia vaccine strain, and the majority of our isolates are fitted here, closely related to New Caledonia.

When we look at the influenza B strains this season, here is the B/Beijing, the B/Yamanashi,

and the B/Sichuan/99 reference strain. Most of our isolates are showing a reduced reactivity with Beijing, fairly good reactivity with Yamanashi, but show much better reactivity with the B/Sichuan reference strain.

Some of the isolates which we are now receiving, the last one here is from December, are now showing a reduced reactivity with the Yamanashi.

This is the phylogeny for the influenza B viruses, the Beijing lineage here, this is the older Victoria lineage, which has been talked about this morning. Here is the B/Yamanashi vaccine strain, and all our strains fit here, on the Yamanashi lineage, but are much more closely related to the B/Sichuan/99 strain.

So, in conclusion, we can say this year we've had a low level of influenza activity, which has barely got to baseline levels. And we have predominantly had the H1N1 strains circulating. The majority of these A/New Caledonia-like antigenically and genetically, although we have had a small cluster of the Bayern-like viruses.

We have seen a later onset of flu B circulation, which have co-circulated with the H1N1s. The majority of B/Yamanashi-like show much better

reactivity with the B/Sichuan, and they are closely related genetically, as well, to the B/Sichuan.

Thank you.

CHAIR DAUM: Thank you very much. Do we have questions, or comments for Dr. Ellis? Dr. Katz?

DR. KATZ: Dr. Ellis, many of us are unfamiliar with what the recommendations and utilization of influenza virus vaccines are in the United Kingdom. Can you comment on that?

DR. ELLIS: Yes, I can. They are recommended for the high risk groups, but this year it has also been decided that all those who are age 65, also recommended to have influenza vaccine, whereas last season it was all those age 75 and over, who were recommended.

And they've also set a target of 60 percent uptake in this first year, and that has already been reached.

CHAIR DAUM: Do you have any kind of overall distribution relative to the population, like we have in this country? I mean, I think the order of magnitude is 70 million doses, is that right? 70 million out of 250 million, almost --

DR. ELLIS: No, the number of doses this year was increased, and it was increased to 10.8

million doses. So nothing like the amount that you have, but it has been increased to match that increased coverage in the over 65 age group.

CHAIR DAUM: Other questions, comments? Thank you very much, Dr. Ellis.

I think at this point we will take a break for lunch. I have been asked to announce, by Nancy, that there is an area for about 20 people reserved in the restaurant here in the Holiday Inn, on the first floor for committee and/or presentors to spend the lunch period, should they wish to do so.

We will take lunch for an hour. It is exactly noon, we will reassemble at one o'clock. Thank you.

(Whereupon, at 12:00 p.m., the above-entitled matter was recessed for lunch.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:05 p.m.)

CHAIR DAUM: Welcome, everybody, back from lunch.

The first -- there are three more presentations by way of background. And then we have Dr. Cox will lay out the options for strain selection, and then we will have committee discussion.

So we will begin, of course, with the three presentations, and ask Dr. Levandowski to come and present some of the serologic data for us.

DR. LEVANDOWSKI: Thank you very much. I will get started here.

I was just joking that after lunch is probably not the best time to be talking about serologic data, because I have to tell you, that having looked at this stuff for the last several days, even my eyes are sort of crossing, and I'm not sure that I'm going to be able to keep it all straight. I hope I can do a reasonable job for you.

I have, also, sort of a -- we've been having power point presentations, and some overheads, and I actually have a combined presentation where high tech meets low tech. So some of this is going to be on power point, and that is probably going to be the

easiest part to see.

Some of it I had some hiccups in my computer, and I couldn't get my tables transferred, so you are going to have to bear with me with my overheads, please.

What I'm going to try to do is really to summarize a lot of serological information that is relevant for the current strain selection process. And the serologic data that I'm going to present has been put together pretty much by way of committee, and that committee is really the ongoing collaborative efforts at a number of centers that are being sponsored by, and facilitated by, the World Health Organization and, in particular, its Influenza Centers.

This should show the serum panels that have been used for serologic studies. And these serum panels have been coming from adults and elderly people, in Australia, Europe, the United States, and now recently Japan.

So we are having a little bit of expansion of the geographic distribution of the sera that we have to look at.

This particular graphic shows where the people who have contributed the materials for use, and

what we are all looking at.

One thing I would point out to you is that as Alan Hampson mentioned earlier this morning, the vaccine that was in use in Australia during the time that these serologies were done, included as the H3N2 strain the A/Sidney/597.

And, therefore, I'm actually not going to summarize the data from those parts of the clinical trial, but all of the other information from that should be of use.

The laboratories that are participating in performing these serologic studies include the World Health Organization Influenza Center in Melbourne, Australia; the National Institute for Biological Standardization and Control in London; the Centers for Disease Control in Atlanta, and the Center for Biologic Evaluation and Research in Bethesda.

Between these four labs these sets of sera have been tested against a large range of antigens that are recent, over the last year. And the overall number for the serum panels is approximately 200 serum preparers.

The testing hasn't been completed in all the laboratories at this time. But what I'm going to present to you is data that is current to yesterday,

in fact.

So if I can get the first, or second, or third overhead, I will just have to flip through them to find the right one. That looks good.

This is a listing of the H1N1 antigens that were used for serologic testing. And what I should hasten to point out is that not every one of these antigens was used in every laboratory.

So there is a whole variety of new antigens that were examined at least by one laboratory. However, there is a core of these antigens that was tested in each of the laboratories, and we can use that as some comparison.

There are known technical differences between the laboratories, and you will see on these slides it will be obvious that for the same serum panels there are some differences in the absolute magnitude of the antibody titers.

But, generally, those things tend to be proportional. And, really, what we are trying to do here with examining these serologic responses is to have some comparison between the current vaccine strains and the newer antigens that are appearing.

So that is really what we want to focus on, that difference within a laboratory between the

vaccine strain and the new strains.

These serologic studies that will be included actually were done in several separate campaigns that coincided with other recommendations that were made during this last year.

And here I think it shows, as was also pointed out, there have been two lineages of H1N1 influenza A virus that have continued to circulate, although the strains that are related to the Beijing/262/95 strain are the predominant ones at the moment. There are still some A/Bayern/795, or as Nancy Cox mentioned, the Johannesburg/82/96, those are the same lineage of H1N1 influenza A.

This overhead shows results that were obtained from two of the participating labs, using a panel of sera from adults in the United States. And this table and the others that are like it will include data on the geometric mean titers pre and post immunization.

The percent of the titers that were greater than, or equal to 32 or 40, as the kind of cutoff numbers that we look at, as Wendy Keitel had mentioned earlier in her excellent presentation, and also percent four-fold rises.

I'm really going to concentrate more on

the geometric mean titers as a way of indicating differences between the vaccine strain and the newer antigens.

In this particular table the data at the top are from the CDC, and the data at the bottom are from the CBER lab. And the vaccine strain for these studies was the A/New Caledonia/20/99 strain.

In this particular instance the IVR/116 strain was used as the antigen for the testing. What I can say is that in this case the vaccine used was immunogenic, and it produced homologous antibody responses.

And all of the strains that are in this particular panel, with the exception of the A/England/192/2000 strain, and the Brazil, I'm sorry, the Chile/4795/2000 strain are -- all the rest of those strains are New Caledonia-like.

In both cases the A/New Caledonia vaccine produced antibodies that crossreacted well with the Bayern-like strain. And this is typical for what we have been seeing previously, as we've discussed this in the past.

And although the New Caledonia-like strains were mostly pretty well inhibited by the sera produced in response to the vaccine antigen in testing

done at the CDC you can see that there is some reduction in the results for the A/Fujian/156/2000 strain.

In none of these instances was there as much as a 50 percent reduction in titer. And I will mention, a little bit later, as I go through some summary tables, why we think that -- or why I'm mentioning the 50 percent reduction.

This overhead shows results -- I should mention that I'm not going to go through every one of the serologic panels individually, I'm just going to give some examples that will highlight some differences, or some similarities.

This particular overhead shows the results obtained from two of the laboratories using sera that were from the elderly in Japan. The data at the top are from NIBSC, and at the bottom they are from WHO in Melbourne.

The vaccine strain, again, was the A/New Caledonia strain. And in this instance the wild type strain was used as the antigen. Again, except for the England/192/2000 strains, the strains here were A/New Caledonia-like.

And what I would say again is that for the most part the vaccine produced antibody responses that

were pretty good against most of the -- or all of the antigens that were included.

Moving on to the H3N2 viruses, this slide shows the viruses that were used for serologic testing. And, again there is a whole range of them. All of these strains are somewhat related, they are more modern versions of the Sidney/597 and its progeny lines in evolution.

They are typical, I guess they are reasonably representative of the strains that were circulating during 2000, and although there is one strain that is listed as being from 1999.

This overhead shows -- should show a panel of sera from adults in Europe. And the data at the top are from the Center for Biologics, and the data at the bottom are from WHO in Melbourne.

The current vaccine strain, in both instances, was the Panama/2007/99 strain, and in one lab the reassortant used in the vaccine was the -- it was the antigen for the serology, and in the other lab it was the wild type strain.

What you can see in this particular instance is that in some instance, some of these, for some of these strains, as Alan Hampson had already pointed out earlier this morning, there are some

reductions in the antibody responses of the newer strains as compared to the vaccine strain.

That is not universally true. Many of the strains seem to be covered quite well by the antibodies produced to the current vaccine, but there are some notable differences.

And in this particular instance there is more than a 50 percent reduction in the geometric mean titers for the Hong Kong/123/2000 strain and the Leon/1242/2000 strain, as compared to the vaccine antigen.

This overhead shows the results obtained using a panel of sera from elderly in the United States. Data at the top are from the CDC, and the data at the bottom are from Center for Biologics.

A/Panama is, again, the vaccine strain, and both labs used the Resvir 17 strain as the antigen. What I would say here is that, again, for the most part there are pretty -- there are reasonably good cross-reacting antibodies that were seen, but there are, again, some notable exceptions.

In this case the A/Fujian/140/2000 strain shows more than a 50 percent reduction in the titer. And similar to what we saw in the previous slide, there seems to be some reduction, although it is not

as much as 50 percent, there is some reduction seen against the Hong Kong/1923/2000 strain.

So moving on, then, to influenza B viruses. You will notice that this list is somewhat longer than the previous two. And it reflects, to some extent, the growing concerns about influenza B viruses, and changes that are occurring.

For the serologies that were showing, just at the moment, we do not have any strains that are in the B/Victoria/287 lineage. And that reflects the fact that they have become so few and far between.

But there are strains here that represent, really, a very wide geographic distribution, and were included in the serologies the Sichuan/379/99-like strains, and the vaccine strains that are in use, and then some newer strains from around the world that would fall into the Sichuan/379/99 category.

So this one, this overhead shows results for a panel of sera from elderly in Europe. And the data are from WHO Melbourne at the top, and from CDC at the bottom.

And the vaccine strain was B/Yamanashi/166/98 for both serum panels. Here there are a number of viruses that are included, as I mentioned, looking at Johannesburg/599 and

Sichuan/379/99.

And in the case of these serologies reduced titers were found, actually, for nearly all of the antigens that were tested by the laboratories. Reductions of 50 percent or greater were found for many of the recent viruses, including this B/Christ Church/2/2000 strain, the B/Zagreb/3578/99 strain, the B/Alaska/16/2000 strain, the B/Guangdong/120/2000 strain, and the B/Hong Kong/557/2000 strains.

And although, as Alan Hampson mentioned, there may be some other strains that are appearing, what you see from this is that for some of the tests that have been done, there seems to be sort of a general trend for reduced antibody titers against the influenza B strains, even though some of these differences are relatively modest.

This overhead shows a panel of sera from elderly in Australia. And the results are from WHO Melbourne at the top, and from the Center for Biologics at the bottom. B/Yamanashi/166/98 was the vaccine strain, again.

And, again, these results demonstrate reductions in titer against all of the antigens that were tested. A reduction of 50 percent or greater was shown only for the B/Christ Church/2/2000 strain in

this particular run.

But in all of the instances, again, there is a modest reduction against these viruses, including the B/Johannesburg/5/99, the Sichuan/379/99, and the B/Victoria/504/2000 strain.

So to try to summarize this, and let me see if I can do this with high tech, again. Does that look better? This one is better? We will go with this one, then.

So to try to summarize this, there are some tables I'm going to present to try to pull together the data. This does not include all of the strains that were shown. But this will include strains for which multiple laboratories have some data.

And so in attempting to summarize this, these tables show the frequency with which we found new test antigens that gave a 50 percent or greater reduction compared to the current vaccine strain.

And the reason I'm emphasizing 50 percent, because that represents a two-fold reduction, which in geometric mean titer terms is really quite marked.

The data included in the table are for antigens that, as I said, were tested in more than one laboratory. And that is important, too, because that

reflects, generally, the interest in these strains, and their possible use as vaccine candidates.

It should be noted that not all of the testing that we would want to do for these things has been completed at this point. And actually I would like to start with a different slide, I would like to start with the H1.

So here we are showing the first -- the upper antigen shown here, the Wuhan/292 -- no, actually it is not going to work because some of it is cut off. We will go back to the overhead. Sorry.

So if we can get the other slide that shows the H1s? Thank you.

So the upper antigens here are New Caledonia-like, and the bottom two are Bayern/7, or Johannesburg/82/96-like, in the other lineage. And what you see, by and large, for these strains concentrating, really, on the totals over here, for all the laboratories, is that for the most part there doesn't appear to be too many instances in which there was as much as a 50 percent reduction from the serum panels that were examined.

And to take that one step further, to try to look at overall what the differences in magnitude were, again, there is a lot of variability. But in

most instances, at least for these strains that we are looking at here, including some of the newer A/New Caledonia-like strains, there is really not too much of a difference in overall titer.

There may be some exceptions to that, in this particular instance, one of the laboratories found that there was more than a 50 percent reduction in all of the tests. But, overall, sort of using the balance of the data to try and see the consistency here, it actually seems to fit in pretty well with what we see for the rest of the information.

So in general what I would say is that it doesn't seem to show a lot of reduction, the current vaccines seem to be pretty reasonable at producing antibodies against all of the H1N1 influenza viruses that are out there.

There are some exceptions that we can see some reductions. But, overall, it seems to be pretty good.

And if I took this one step further to try to reduce it, I would say that probably about ten percent of the tests, overall, for all of the serologic tests that were done, both shown here, and not shown here, showed some reduction for the H1N1. So it was really relatively minor there.

So if we can go to the H3N2. Again, the same kind of table, trying to look at differences. These strains are all related to, are in the same evolutionary pathway from Panama/2007, and here again, I would like to call your attention mainly to the totals here.

And what you see is that for most of the strains that are included here, and there is a range of strains from different locations, really there is not too much in the way of reductions, and overall it is really relatively minor.

So that for the most part I would say it looks like these strains are well covered by the current vaccines.

There are some exceptions, again. The Fujian/140/2000 strain, and also the Hong Kong/1923/2000 strain, in different laboratories there were some reductions seen.

But even factoring that in with all the overall data, again, it seems to be reasonably consistent with what is seen for the other strains. And here, again, I would say that there are some reductions, but it is really pretty modest.

And looking at all of the strains that we had of serologic testing on, again, it was in the

range of about 10 percent of the tests that were done, showed a reduction of 50 percent or greater.

And then, finally, for influenza B, again there weren't any strains that were in the other lineage, so these are all strains that are in the same lineage, same HA lineage as B/Yamanashi/166/98.

But, now, calling your attention to the totals, whereas before we saw lots of zeros for 50 percent reductions, here we see lots of numbers. And although it is not one hundred percent in homogenous in every test, still there is a somewhat different pattern being seen for influenza B, as compared to the other two strains.

And the magnitude of those differences also seem to be pretty consistent. It is a little bit higher than for the H1N1, or for the H3N2, but it is not dramatic. It certainly is nothing like what we would see if we did have B/Victoria/2/87-like strains on here, in which case we would see percent reductions on average of about 75 or 80 percent.

So this is somewhat modest. But still there is a fairly consistent pattern of seeing some reductions in some of the tests, in some of the laboratories.

And if I took all the tests that we did,

to pediatric serum panels for some period of time. It is very difficult to obtain that, although it would be very, I think would agree, it would be very important information.

And one thing that we don't see from serologies in adults that we see in serologies from children, is the effect of not having been previously infected or immunized, so you have a very clean baseline to work from, and very obvious differences when they are present.

And with these particular serum panels I didn't emphasize that at all. But the panels from Europe this year included mostly sera that had very low titers against the vaccine strains to begin with, that the people who were being immunized either hadn't been immunized previously, or had very low titers.

And so there was a very clean, from those particular serum panels, like in the pediatric sera, you would expect a very clean kind of difference.

But we agree that would be very important to have information on pediatric patients.

CHAIR DAUM: Dr. Kohl, then Dr. Snider.

DR. KOHL: I'm sorry to be a little bit of a pain, but we ask that question every year, and we get the same answer every year. And I'm not sure what

the problem is.

But influenza has a considerable health expense in children. There is more and more data showing that it is a very significant problem. There are large groups of at-risk children that are recommended to be immunized. And yet every year we don't have information about the vaccine in children.

Perhaps Dr. Myers, as part of the vaccine information, whatever that group is called these days, or you, but there are NIH-funded child immunization centers around the country, and I don't understand why some of these can't be plugged in to get us some relevant data.

DR. LEVANDOWSKI: Well, I think you are right that it is possible to do it. And FDA previously had its own contract for immunization of children, but it wasn't an issue of funding that resulted in termination of that contract.

So from whatever source we could get those sera I think we would be very, very interested to have them. And there have been discussions about trying to collaborate in that way.

DR. KOHL: Is there anything the committee can do to help push that forward?

DR. LEVANDOWSKI: I think you've already

done it by raising the issue.

CHAIR DAUM: Dr. Snider?

DR. SNIDER: Yes, Roland. With regard to the information about serological responses to the influenza B vaccine strain, and the -- with the other B strains that have emerged, I guess I really haven't heard us, in the past, have any discussion around at what level of reduction we might be concerned.

Is there any clinical data from years past when vaccine strains have not covered well, that would give us any guidance at what level we should be concerned? And that is for you, Nancy, or anybody that might have any information.

DR. LEVANDOWSKI: Right. I guess I have to kind of grope a little bit to try to find some way to respond to that. I think we haven't really used the serologic information to tell us that people aren't entirely being protected.

I think we've been using the serologic data here to try to say that we are seeing, or we are not seeing differences in the strains that are out there in nature.

We are using human serology as a way to back up what is being seen with animal serologic data. And what I could say is that in past years this

committee, when we have not -- even when there has been a difference in the animal serologic data, if we've not seen a very dramatic, or any change from human serologic data, particularly if there wasn't strong evidence that influenza viruses were spreading widely, we have not had -- the committee has not used that information to recommend a change in the strain.

And I think the answer partly goes back, again, to -- I guess try to predict forward for a new antigen versus what we know from strains that we've already worked with is somewhat difficult.

And just because we have had the experience where, with antigenic changes, the old vaccine does not seem to have performed very well. I guess we don't really know exactly what to anticipate. I guess we don't know what to anticipate from any vaccine that we produce until we use it.

DR. SNIDER: Thank you. Just behind that question, I just wanted to express what I see here. I think the influenza experts really have been helpful over the years in really telling us that this is as much an art as a science in terms of how you make these kinds of decisions.

And I think we all recognize that. But at the same time it would be nice to be thinking about if

there are ways to make our decisions more quantitatively oriented, if there are ways to build models, or to use data in more quantitative ways that would be predictive.

I realize that with influenza we are talking about an extremely difficult situation, because we are talking about different, three different strains of viruses, and different subtypes, and so forth.

But it is just a plea for those who might be in a position, around the table, or in the audience, or elsewhere, to try to be thinking about how we might model this, and be more quantitative in our approach.

CHAIR DAUM: I would like to follow up on that a little bit, and try to feel the elephant from a different part. And that is when these kinds of data are shown, I, a totally non-influenza expert have tried to keep my eye on this number of 40 that has been touted as a protective level.

And I wonder if that is a valid way to think, your opinion is whether that is a valid way to consider these reductions as leaving you above or below 40.

And, secondly, to maybe in a minute or a

minute and a half or so, tell us where the number comes from, I mean, is it an etched in stone number, or is it just a feeling of the art?

DR. LEVANDOWSKI: Well, I wish some other people could help me out here. But my understanding of that is that 1 to 32, or 1 to 40 came about from clinical studies that were looking at protection in the clinical trials that they were done in.

There was a correlation between a titer of greater than 1 to 32, or 1 to 40. And it wasn't perfect by any means. I think in my own mind I think of it as a 50 percent end point titer of a sort, that you can expect a reasonable number of people will be protected if you hit that titer. It doesn't mean that everybody is.

And certainly I think that the argument would be that the higher the antibody titer, and going back to the argument about how high can you get, I think probably there is a maximum for each individual that can't be overcome.

Well, how high is enough? Well, as much as an individual can achieve. And the 1 to 40 I think was useful for trying to make some sense out of use of vaccines, and whether there was protection.

I emphasize the geometric mean titer for

this presentation because, again, I think what we are trying to do here, because there are technical differences between laboratories, because there are technical differences for each antigen that we look at, that seems to me the most direct comparison between the vaccine strain and the newer antigens to get a sort of a feel for how different are they.

And it really, again, is somewhat parallel to what is being done looking at the differences with the animal serologies, trying to get that same kind of information from human serologic results.

I don't think we are trying to say that there is or there is not protection for anybody, based on what we are getting on these serologies. I don't think we are trying to make that leap with this data.

I think we are trying to use it as a way to sort out whether there are some differences in the antigens. And I think the answer to whether this means that there is efficacy for the vaccine, I think that belongs in clinical trials, which you also have told us we should be doing.

CHAIR DAUM: Dr. Cox, did you want to make a comment, then Dr. Kilbourne.

DR. COX: What Roland said is true, that the studies that were done to look at the correlation

between a high titer and protection indicated that at a titer of 40 or 32 you have protection from about 50 percent of people. If you have titers of 80 then you have a greater proportion of people protected.

And the higher the antibody titer the more likely it is that you will be protected from infection. So these values aren't absolute.

The other caution I would like to place on the table, when we are looking at serologic results for influenza B viruses is that we are using ether treated antigens.

And by using ether treated antigens we really tend to obscure differences. The titers are higher, but the differences between strains are smaller. And the reason we use the ether treated antigen for influenza B viruses is that if we don't use ether treated antigens we have such low titers that we can't see differences, anyway.

So it is a kind of compromise that we have to make. But when you look at the data you have to realize that some of the differences that do exist between antigens may be obscured by the methodology.

CHAIR DAUM: Thank you. Dr. Kilbourne, then Ms. Fisher.

DR. KILBOURNE: I think there is a great

deal of validity to that 1 to 40, or 1 to 32 figure, because it is derived from, really, a very large number of studies in the military, sponsored by the late Influenza Commission, in which fairly comparable and uniform populations of young recruits have been studied.

So at least within that kind of population it has some validity. And I think it is just a useful check point. Having said that I have to remind us all that every one of us sitting in this room has had different experience with influenza virus antigens, depending on the age of infection, depending on what array of viruses we've been presented with, either in vaccine or infectious form, depending on our HLA type, undoubtedly.

So that, again, this matter of generalizing, we are talking about heterogenous population of virus particles in human beings.

So I think that it is remarkable that we are able to come up with some kind of a figure such as that. Remember that is a figure for hemagglutinin antigen alone, we haven't even talked about the neuraminidase and very seldom do. That is also a contributory factor.

CHAIR DAUM: Thank you, Dr. Kilbourne.

Ms. Fisher?

MS. FISHER: Well, I would like to agree with Dr. Snider that we do need more information, the committee needs more information on the future upon which to base decisions to change a strain.

But beyond that, because there has been so much attention paid to vaccining children with flu vaccine, it seems that there needs to be some systematic way of looking at different populations, and how, genetic populations, and how they respond to the flu vaccine, to make sure we are doing the best we can in terms of appropriately using the vaccine in appropriate populations.

CHAIR DAUM: Thank you very much.

DR. KILBOURNE: Could I add just one other thing?

CHAIR DAUM: Yes, certainly.

DR. KILBOURNE: I think that we could do what you suggest as an idea. Studies could be mounted that would answer a lot of these questions much more precisely.

But I think it would take enormous amount of money, and resources, and BTUs, to really bring this about. What you would have to do, for example, is to take last year's vaccine and compare it directly

with its antecedent, or its successor, and really look at the relative response in this kind of population.

That takes hundreds and hundreds of people, and probably hundreds of investigators, as well. And it is not entirely art versus science, it is just simply a matter of resources, really.

And anything that this committee can do to harp on that will be very gratefully accepted.

CHAIR DAUM: Dr. Kohl?

DR. KOHL: This is directed to anybody, but I had Dr. Fukuda in mind. I guess every year we question vaccine efficacy, and every year we talk about cases of virus isolated, or virus isolated from cases, and wonder what the percentage of those people have been immunized, what the viruses are, and if possible, what their antibody response was at the time of the viral isolation.

Is there any chance we will get any of that data, or does any of that data exist from last year, for instance, to tell us how efficacious the vaccine was?

And if there is a magic level 1 to 40. And Dr. Kilbourne mentioned most of these data are from young healthy military recruits who, of course, aren't the population we are interested in primarily.

Does it take a different titer of antibody to protect older individuals, kids, etcetera?

DR. FUKUDA: You know, I think that for -- we have talked about this for the last couple of years, and I think that it has been pretty clear, for a while, that it would be really useful to have annual vaccine efficacy studies done.

And as you know the reality has been that sporadically there are vaccine effectiveness studies done, typically in outbreak situations. And then more recently, over the last three years or so, the National Immunization program at CDC has been doing vaccine effectiveness studies using data from HMOs, but without actually being able to ascertain the vaccine status accurately.

And these are clearly not efficacy studies. And I think it basically has come down to what Ed has pointed out. I mean, these things can be done, it is just freeing up the resources to do them has been enormously difficult.

I mean, I think that any number of us here would love to see those studies done. And it really does just come down to resources. And so, will the resources be there? I mean, clearly there is a lot of interest in the, you know, potential for live

attenuated influenza vaccine, and so on.

There have been efficacy studies done in support of those sorts of things, but that is clearly different than the kind of annual year round studies, I think, all of you would like to see done, and certainly we would like to see done.

So that is the situation, I think.

CHAIR DAUM: Dr. Ferrieri, please.

DR. FERRIERI: Very briefly. I would support those types of studies recognizing the financial limitations, because it might put to rest some of the anecdotal impressions that we've had on occasional years that the vaccine hasn't been, "as good as other years". And last year was a year in point.

And although there has been denial at many, many levels that there were breakthroughs, there are scientific people who claim that in their cities they had antigen test results in patients who had been vaccinated with influenza virus vaccine, who did have positive tests.

And there are all sorts of little pockets of unrest about this. But we need to have answers to that, so that we don't just speculate, were there breakthroughs or not.

CHAIR DAUM: Dr. Cox, did you want to say something?

DR. COX: I will try to make a brief comment about that. I think that we, those of us who have been involved with influenza activities for a number of years, do recognize that every year we received influenza viruses that were isolated from people who are vaccinated.

In some years we receive more viruses than other years, and we are not quite sure if that reflects a decrease in vaccine effectiveness, or whether there just is more flu going around, and so there are more people who have breakthroughs.

I think that there is a wealth of literature, and a very long history, of studies which have shown influenza vaccine to be safe and effective in young adults, in elderly, and so on.

But where we really don't have as much information is in children. And I think that we have to try to have our resources focused on those studies that might be most useful in directing activities for the future, and also link into data that already exists, because it is probably impossible for us to mount vaccine efficacy studies every year in all the different groups that we would really like to see them

in.

CHAIR DAUM: Dr. Ferrieri?

DR. FERRIERI: Briefly. At the ACAC meetings in the fall there was data presented that is no big surprise, but supporting the hospital admission rates of young children admitted with influenza, and the influenza complications.

So it would be wonderful to have more data, because vaccination could have an enormous impact on health as well as health economics in young children.

CHAIR DAUM: I think it is -- I would like to congratulate the people who presented data today from all the agencies, and from international agencies as well, because I've been on this committee several years now, and I have never heard the influenza study of the year laid out as nicely as I thought it was today.

But at the same time I think this committee is trying to say something. What I think we are trying to say, and the consensus that I hear around the table is that this is a health care intervention which we, as a society, have committed to, to the tune of 70 million doses a year.

And that we are wondering, each year,

whether the vaccine is working; we are wondering whether our children, who clearly have a bigger burden of disease than perhaps was realized before, are being protected by this.

And I don't -- there aren't too many health care interventions that are quite this massive. And I think that it is time to ask our governmental health care agencies to initiate the process to commit the resources to this task, so that it gets done.

I think the committee says the same things every year about what is missing. And although I really mean it when I congratulate everybody that the presentations today were just really fine, we need these additional resources, we need this additional information.

And I would hope that when we plan our vaccine, or help you plan it next year, that someone has made a commitment to start moving this process forward.

And with that we come to a very practical part of the study, and that is Dr. Ye Zhiping, I hope I'm not butchering his name, from the FDA, will tell us that no matter what vaccine we think we would like to design, we need a sense of practicality here.

And we will now hear about the

availability of strains and reagents, before moving on to comments from the manufacturer representative.

MR. YE: In a short presentation I will represent the status, as of today, of the potency reagents and candidate vaccine strains.

In terms of potency reagents the current vaccine is available for the vaccine is for H1N1 is New Caledonia/28/99. For H3N2 is a Panama/20007/99, and for B is B/Yamanashi/166/98.

In terms of candidate for the new strains choosing the reagent will be available in May, at the earliest.

And in terms of the vaccine candidate, the current vaccine for New Caledonia, H1N1, this strain give you a moderate virus yield. And the reassortant possessing protection antigen from New Caledonia, this reassortant giving you a high yield.

And since the strain of New Caledonia is a predominant strain currently we don't have new antigenically divergent strain now.

And in terms H3N2, still the Panama/2007 is the current vaccine. And, again this one giving you moderate virus yield, and the reassortant give you a high yield.

And although there are another three

reassortant, the three reassortant does not offer any advantage over this reassortant. And the candidate for the new strain of the new vaccine is A/Ulan Ude/1/2000.

And this strain give you moderate virus yield, and the reassortant give you a high yield.

The final one is the B strain, the current vaccine for B strain, is the B/Yamanashi/166/98, and this strain give you a moderate virus strain. And there are possible 3 candidate for B strain, getting the data from the protection serum generated from this virus against the new isolate strain.

And one is B/Johannesburg/5/99. Unfortunately this strain give you a low yield. And the B/Victoria/504/2000, and this one give you moderate yield.

Another one is B/Alaska/16/2000, and this one give you a low yield. Again is for B strain we don't have a reassortant right now. That is it, thank you.

CHAIR DAUM: Thank you, Dr. Ye. We have an opportunity for questions for Dr. Ye. Dr. Estes, start us off.

DR. ESTES: You listed, on the B strains the current strain that gives a moderate yield, and

then a candidate strain, the Johannesburg, that gave a moderate yield.

Are those moderate yields really considered sort of similar?

MR. YE: Yes, for B it is compared to A the B is usually four times lower than B, B four times lower than A. So that strain is pretty close, around 200 by inhibition, hemagglutinin HA titer.

DR. LEVANDOWSKI: Can I make a comment, also?

CHAIR DAUM: Please.

DR. LEVANDOWSKI: Actually the B/Johannesburg strain is a very low yielding strain, if that is what your question was? The B/Johannesburg/5/99, we had discussed that at last year's meeting in March.

The B/Victoria/504/2000 is somewhat better yielding. We are calling it moderate, but it is really early days for that strain, and I don't think that we have certainty, although we may hear some information from the manufacturers about this.

And Zhiping did not really emphasize, but there have been, probably, 15 or so of those strains that have been sent off to manufacturers to take a look at, to get some information on growth

characteristics.

And I would say the good news is they are very homogenous, but the bad news is they are all pretty much low yielding.

CHAIR DAUM: So if that last slide flashed back up? On the B strains, the yield at the bottom of the slide, so is Victoria truly better than the other two, or are you saying that is really open to question?

DR. LEVANDOWSKI: Well, I think we don't know the full answer to that. But I think from what we do know it is a better strain than B/Johannesburg/5/99, or any of the others. It seems to be the one that we hear from manufacturers is the best of the bunch.

But that is not to say that it is as good as it could be, or as good as might be desired.

CHAIR DAUM: Dr. Ferrieri, I couldn't tell whether you wanted to make a comment, or not?

DR. FERRIERI: No, I just wanted to emphasize the low yield of the B/Johannesburg, the impression given perhaps was that it was also moderate.

CHAIR DAUM: Dr. Kohl, then I think Dr. Myers, and Dr. Griffin.

DR. KOHL: The WHO has recommended for the southern hemisphere the Sichuan/379. Are these all in the Sichuan/379 group? I'm looking at the dendrogram, and I'm not -- the Vic looks like it is not quite in the group, or is that --

DR. LEVANDOWSKI: We might defer to Nancy, but my understanding is that we should consider the B/Victoria/504/2000 strain as a Sichuan/379/99-like strain. And there are many others, too, that are in that category.

DR. COX: That is correct. And we actually put quite a bit of effort into making egg isolates of B/Sichuan/3/79-like viruses, and have recently distributed some of these strains to the manufacturers.

So there are some additional strains that have gone out, but there are just no data yet on whether they are going to be any better than the existing ones.

So we are trying to work through a whole series of strains that are B/Sichuan-like.

CHAIR DAUM: Dr. Myers, then Dr. Griffin.

DR. MYERS: I was just going to ask about the neuraminidase because if there is as much drift in the neuraminidase as there is in the hemagglutinin in

the B strains, whether we should be considering that.

CHAIR DAUM: Does anyone want to comment?

DR. LEVANDOWSKI: Well, maybe -- okay, I will jump in.

CHAIR DAUM: Thank you.

DR. LEVANDOWSKI: The vaccines are really standardized, as I mentioned, for hemagglutinin and not for neuraminidase. We would like for both the hemagglutinin and neuraminidase to match, if possible, or to be as good a match as possible.

As Dr. Kilbourne mentioned there may be some, and I did too, there may be some protection from the neuraminidase and this committee has told us, in the past, that they thought it would be best for both the hemagglutinin and/or neuraminidase to match up.

What I would ask, as a question for Nancy Cox again, or for anybody else from one of the WHO flu centers, is how much difference is there, antigenically, in the neuraminidases for these Sichuan/379/99-like strains, is there a substantial difference?

DR. COX: We don't know, we don't have neuraminidase inhibition tests for influenza B viruses. Most labs have not been doing neuraminidase inhibition tests for almost eight to ten years now.

We are actually putting quite a bit of effort into renewing efforts to do neuraminidase inhibition testing on H3N2 viruses. But it is a difficult process to get the reassortants that you know, the proper reassortants to do the right kind of testing.

CHAIR DAUM: Thank you, Dr. Cox. Dr. Griffin?

DR. GRIFFIN: My question follows along the same line, but I was thinking of the H3N2, because there the neuraminidase definitely looks like it has drifted away.

I noticed that the Ulan Ude strain does have neuraminidase that is much closer to the drifted variety, or the current selection to the neuraminidase of the current strains.

And I guess not being an influenza virologist I wondered what the possibility was, just reassorting that neuraminidase into the current vaccine,. H3N2 selection?

MR. YE: Usually this neuraminidase antibody is not protective antibody compared to HA.

DR. GRIFFIN: I wasn't talking about changing the HA, I was going to leave the HA, and I was just going to add in the neuraminidase that was

more closely related to the current strains. But maybe that viruses would not grow, but I don't know.

DR. FERRIERI: The point is that it wouldn't matter because it wouldn't contribute much in the overall protection, is my understanding of the issue.

DR. KILBOURNE: I think that is a misunderstanding, it has been misrepresented by the last two speakers. It is a very important contributor to influenza virus immunity. And it simply has been ignored through the years because it is a test of measuring its antigenicity are somewhat difficult technically.

But I think it is high time we pay attention to this. They are doing this in Europe, a manufacturer over there. There is not even a requirement, currently, that there be neuraminidase in the vaccine.

I think in view of our vastly mature animal studies, this is an intolerable position.

DR. GRIFFIN: Not being able to measure it is not the same as not being important, it seems to me.

DR. FERRIERI: Well, and given the newer agents out on the market that may have some impact on

the disease suggests, again, its role.

And so, I'm sorry, I didn't mean to diminish its importance, but I came away with the impression, from the previous discussants, that the HA antigen induced antibodies that may have been more protective.

Do you have evidence that if you inactivated the gene for HA that you could still achieve the same virulence of any of these influenza vaccines?

DR. KILBOURNE: HA is undoubtedly the dominant, more important antigen. There is no question about that. But why ignore the other surface glycoprotein, which is also contributing to antibody formation and immunity.

And a further point about that, while I have the floor, briefly, is that if there is going to be a divergence of evolution of the HA and NA, as has been shown, then we have to be cognizant of this.

We might actually have to fabricate reassortants that are high yield, which are antigenic hybrids. Snatching, as you suggest, the HA from one and the NA from another, that adds to the complexity of the whole formula, though, which nobody is anxious to do.

But I think it has to be clearly stated and abundantly made in the literature that it is a very important antigen, and will protect by itself. But it's infection from permissive immunization, which does not prevent infection, but it may prevent disease when given in adequate quantity, all by itself.

CHAIR DAUM: Dr. Huang?

DR. HUANG: I would like to focus us back on influenza B strains and the candidate strains that we have in front of us.

I guess a very simplistic question, and I'm not sure why I don't understand this, is that if we already have the Sichuan/379/99 used as a reference viruses, why that isn't already one of the candidate strains?

DR. COX: Simply because it doesn't grow satisfactorily for vaccine production. It was the prototype reference strain that was first identified as being a variant.

And so it has been used in HI tests, and in serologic tests for both the southern hemisphere recommendation and for our own considerations here. But it just doesn't grow well.

CHAIR DAUM: Dr. Levandowski wants to make a comment, and then Dr. Ferrieri.

DR. LEVANDOWSKI: It would be analogous to our previous vaccine, that our recommendation was actually for a B/Beijing/184/93-like strain, but we've been using something else since that recommendation was made.

So the reference strain may not be the actual strain, and that has been true right along for vaccines.

CHAIR DAUM: Dr. Ferrieri?

DR. FERRIERI: I would like to go back to the serology studies with influenza B. I must say I don't feel I've memorized all the data that you presented.

But in focusing on the very at-risk population of the elderly, it would appear that the titers, post-vaccination, are rather comparable against B/Yamanashi, Victoria, and others.

And the percent of four-fold rise, although not real impressive might be, again, supported by the fact that they had rather high pre-vaccination titers in the elderly, 60-some, 58, and so on.

And so I fail to see, I would like you to refresh my memory, which has obviously been very transient, about the inadequacy, if any, of the

serology responses, serologic responses to B/Yamanashi.

I don't see a sufficient evidence for examining a seriously candidate strains, although I appreciate the antigenic studies.

CHAIR DAUM: Does someone want to tackle that one? Roland.

DR. LEVANDOWSKI: I tried to give the impression that there is evidence for antigenic drift as shown through the human serologic results.

And what I said, I think, was that what we see is, for the most part, what would be considered moderate, a moderate difference between the current vaccine strain and the Sichuan/379/99-like strains, in all the strains that have been examined overall, in fact.

There are some serum panels that were tested where there was a more dramatic decrease seen. But, overall, as I tried to do, to put it into some larger context, I guess we would have to state that what we see is really a rather modest effect in terms of reduction of antibody responses against those newer strains.

But it is consistent with antigenic drift going on within influenza B strains. And it is a more