DR. LEVANDOWSKI: Okay. Dr. Kuniaki Nerome is from the Laboratory of Respiratory Viruses at NIH in Tokyo. And, as you heard, they've had quite a different experience there this year, with H1N1 viruses, from most of the rest of the world. And we'd very much like to hear that information.

DR. NEROME: If possible, I would like to express to Dr. Levandowski from FDA and Dr. Nancy Cox from CDC thanks for their invitation to attend this important meeting and present influenza activity in Japan.

May I have my first slide, please.

In Japan, co-circulation of the H3N2 and B viruses were repeated this sick season. This is the first half was Hong Kong and second half was the B viruses. The end saw a small peak caused by the B virus Victoria-like strain. So, in Japan, two types of B viruses coincided in the second half of the season.

Next slide, please.

This is the total number of virus isolated last season in Japan. 9,373 viruses isolated in Japan in last season. They are divided into three antigenic groups. The first one with H1 subtype. There are 1.13 percent. The second type H3N2 viruses,

corresponding to 57.2 percent. The third type are the B viruses. The diversity divided into, evolutionary, the Yamagata-like lineage. So, only in Japan, two types of unrelated viruses co-circulated last season. In this season, this was a quite different.

Next slide, please.

And you are looking at this visual of a B virus strain. This indicate as two viruses in different parts of the west part of Japan, the center of a part of Japan in Hokkaido. And this red indicates co-circulating H3N2 and H1N1 viruses, but only two prefectures isolated the H1N1 viruses.

Next slide, please.

And this is the original H1N1 and H3N2. And co-circulating, H3N2, H1, and B viruses. You can see here, Japan experienced co-circulation of the H3N2 and H1N1 viruses.

Next slide, please.

This is a number of virus in isolation reported at weekly intervals. You can see here strains started in isolation with H3N2 viruses here in mid-October, like this. You see here a sharp increase in the number of virus isolation H3N2 viruses. In parallel, H1N1 were also isolated in many parts of Japan country here. You can see here a co-circulation

with H1N1 and H3N2 viruses. Co-circulating only in Japan.

Next slide, please.

This is a table explaining of the H1N1 viruses. You can see a HI index showing titer of 640. On the basis of this HI pattern, please look down here. Most of the viruses, you have the high titer 160. This is the Hiroshima strain. And the Nagoya strain also you have the high titer to 160. In several strains here you can see a 40, 20, and 80. And a Beijing antiserum inhibited very weakly these second virus here. You can see here there's two type of antigenic variants co-circulating in Japan.

Next slide, please.

I can summarize here, because the letters are very small, very hard to see the small letters. This is variant. They have the high titer to Beijing strain. And it is saying that this may be belonging to a Beijing-like variant. And the second is Sendai-H. Sendai-H is in Chiba strain. You have the high titer to Beijing and Chiba belonging to a distinct antigen group.

Next slide.

There we have sequencing of 10 strains here. On the basis of the antigen sequencing,

Beijing/262 strain like this. This is New Caledonia strain. One amino acid difference between the Beijing like this. Only one amino acid. And this is the Bayern/07/95 strain. There are 12 to 13 amino acid differences between them. These amino acid differences only molecules belonging to antigenic site A and B.

This is changing of H1N1 viruses because here a changing of viruses has evolved since 1998 two crossed like this. This recent Japanese variant belongs to indicated by New Caledonia-like strain. For example, this first variant belongs to Japanese New Caledonia-like strain. And this indicates a Beijing-reactive strain. The remaining strains are similar evolutionarily to the B/Beijing-like strain.

This is H3N2 viruses you can see here. The majority of the H3N2 viruses are reactive to Chiba-reactive strain.

And only one strain

I'll summarize here. Japanese have seen two viruses, separating into two distinct other groups. The first one reacted to the -like strain like this. Chiba and inhibited it weakly, this strain. And the second group you can see here, Osaka and Hiroshima Yamagata, reacting to high titer

reactive strain here.

And now this is a second group of the antigen variant, Fukushima and Sendai/H and Yoshima/H. and Chiba were inhibited very weakly against strain like this. And this to Sendai/H reacted with high titer to -like strain.

We also completed a analysis of this Sydney-like strain and another variant, Moscow like this. The six differences you can see here. And this is constructed from HA genes here. Our indicator, Moscow-like strain, branched across it here. The second one, strain. They are distantly related to each other. The majority of this strain belonged to this branch, indicating it is a Moscow-like strain.

This is the only one B viruses isolated in Japan. This is a Shangdong and Beijing were not reactive to this. But this is one of the varieties reactive with a high titer to Beijing like this. It is interesting that --

This is also comparing and Yamagata and Yamanashi and Shangdong-like strains. Between Shangdong-like strains, two obvious differences can be seen here between Yamanashi and Yamagata strains.

This is also then the You see Beijing here. You see Yamanashi. You see Shangdong-like

strain here. They are quite different from each other. Shangdong-like branch indicator, belongs to a different evolutionary lineage.

In conclusion, our total number isolated around 278 strains were isolated in Japan. H1 is 731, corresponding to 57.3 percent. H3 is 546 isolated and B only one.

In conclusion, as a result of what we followed up with virological surveillance, a total 1,278 viruses were isolated in Japan in this season.

Second, of the total isolated, 731 corresponded to 57.3 percent was identified and they were separated into two distinct antigenic groups. The first variant was similar to the A/Beijing/262. And the second variant was indistinguishable from A/New Caledonia/29/90 strain. This result suggests to us to change H1N1 vaccine strain from A/Beijing/262 to current epidemic strains such as A/New Caledonia strain.

Third, the rest of 546 corresponding to 42.7 percent were H3N2 viruses and 93.5 percent of them were A/Sydney/5/97-like variant. I am wondering if Sydney/5/97 viruses will still cause outbreak as a major epidemic strain in the forthcoming winter months. Having considered, we may cancel

A/Sydney/15/97 as a vaccine strain and consider the use of current epidemic strain in 2000-2001 season.

Fourth, regarding the vaccine strain of Influenza B viruses, we need, Japanwide, more information because we isolated only one strain in the season.

Finally, H5N1 and H9N2 viruses still co-circulate in poultry and wild birds in Southern China. Additionally, co-circulation of H9N2, classic swine H1N1, and human H3N2 viruses in swine population in Southern China suggest to us that influenza in the world in the 21st century may encounter the crucial issue.

Thank you very much.

CHAIRMAN GREENBERG: Thank you very much, Dr. Nerome. Roland, do you have any questions? Are there any questions of the panelists for Dr. Nerome. If not, we'll take a break. And I'm going to try to catch up a little bit here, so I would like for all of you to be back at -- it's now 10:34 by my watch. 10:50 I'd like you to be back and Roland will start.

(Recess.)

CHAIRMAN GREENBERG: Okay. I'd like to continue with Dr. Levandowski talking to us about vaccine responses.

DR. LEVANDOWSKI: Okay. Thank you, Dr. Greenburg.

Some of the material I'm going to cover has been mentioned in passing in some of the other presentations. I'd like to point out that we haven't really gotten all of the information that we would like to have and, as was pointed by Nancy Cox, there are some serologic studies that I don't have reflected in the material that's been handed out only because that information is so new. We tried to do the best we can to have as much up-to-date data as possible.

CHAIRMAN GREENBERG: Hold on. People with cell phones are in big trouble.

(Laughter.)

Especially if they're FDA staff.

(Laughter.)

DR. LEVANDOWSKI: Okay. So I'll continue. I'm going to talk about the 1999 vaccine studies. For the convenience of the committee and anybody who has one, the handouts include all the overheads that are going to be used to present the serologic responses. What I'm going to try to do is to summarize the information that's contained in materials that have come from a number of different sources and have been provided for committee review.

I should point out that the serologic data do reflect this ongoing very major international collaborative effort. And it's greatly facilitated and largely possible because of the commitment by the World Health Organization and its influenza centers to collecting information.

If we can go to the first overhead, it should be page two in the handout. This overhead shows the serum panels that are used for the serologic studies, which include three separate sets of serum panels from adults and elderly in Australia, Europe, and the United States. The vaccines used for immunization are shown on the table, I hope.

And I call your attention to the vaccine that was used in Australia, which includes as the B component B/Harbin/07/94. Data for the Influenza B viruses for the Australian sera are being presented since they provide quite a lot of information that is very similar to the data from vaccines containing the B/Yamanashi/166/98 strain.

The laboratories participating in performing the serologic testing include the WHO Influenza Center in Melbourne, Australia; the National Institute for Biological Standardization and Control in London; the Centers for Disease Control and

Prevention in Atlanta; and the Center for Biologics Evaluation and Research in Bethesda. The labs share these sets of sera, as shown, and it accounts for approximately 175 serum pairs.

Next overhead, please. This is on page three; it should be.

This slide shows the H1N1 antigens that were used for serologic testing for the material that are presented. Not every one of these antigens was used by all the laboratories, but they were used in different places to try to explore a variety of new antigens. A core of the antigens is, however, tested in each of the laboratories and that's used as a comparison between the laboratories since there are known technical differences between each of our labs in terms of serologic testing.

The serologic studies have been performed in two separate campaigns coinciding with the World Health Organization recommendations for the Southern Hemisphere in September of 1999 and the current evaluation of influenza viruses. The antigens shown include representative strains for both of the H1N1 lineages that are circulating and it includes strains related to the A/Beijing/262 strain, which is the current vaccine strain and the A/Bayern/07/95-like

strains.

Next overhead, which is page four.

This overhead shows results obtained in September 1999 from two of the participating laboratories using a panel of sera from elderly in Europe. The table includes data on geometric mean titers; the percent greater than or equal to 32 or 40 for the titers; and the percent fourfold rises. The data that are shown here are from the Center for Biologics at the top and from WHO Melbourne at the bottom. And the vaccine strain was A/Beijing/262/95.

The vaccine used was immogenic and it produced homologous antibody responses. In this particular instance, the A/New Caledonia and the A/Nanchang are A/Beijing/262-like strains and the A/Johannesburg is a Bayern/07/95-like strain. In both cases, the A/Beijing/262 vaccine produced antibodies that cross-reacted well with the Johannesburg strain. However, the other Beijing/262-like strains were not well-inhibited by the sera produced in response to the vaccine antigen. In both of these instances, there was a reduction in the geometric mean titer of more than 50 percent.

Next overhead, which is page five.

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Next overhead, which is page five.

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obtained in January of this year from two of the laboratories using a panel of sera from adults in Europe. These data are from NIBSC at the top and from CDC at the bottom. The vaccine strain, again, was A/Beijing/262/95. A/New Caledonia; A/Madrid; A/Wisconsin; A/Nanchang; and A/Peru are all A/Beijing/262-like strains. And A/Johannesburg -- and I hope I'm right on all these because I'm a little confused myself -- A/Hong Kong; and A/Argentina are Bayern/07/95-like strains.

Again, the vaccine elicited good responses to the vaccine antigen and to the A/Bayern-like strains, but the response to the new A/Beijing/262-like strains was reduced by more than 50 percent in most of the instances.

Next overhead, which is page six.

Moving on, this slide shows the Influenza B viruses that were used for serological testing. The antigens shown include representative strains for both of the B lineages that are circulating and includes strains that are related to B/Harbin/07/94 or B/Yamanashi/166/98, the vaccine strains. And to the B/Victoria/287-like strains. For the most part, these serologies have been done with ether-treated Influenza B antigens, but there are some exceptions but I'm not

going to go into that on these slides.

Next overhead on page 7.

This overhead shows the results that were obtained in September '99 using a panel of sera from adults in Australia. The data are from CBER at the top and from the World Health Organization, Melbourne, at the bottom. The data demonstrate that the current vaccine strain produces antibodies at somewhat reduced titers for some of the newer B/Yamanashi-like strains. For the B/South Australia strain, for example, there is more than a 50 percent reduction in titer shown as compared to the vaccine or vaccine-like strain.

In addition, as has been previously seen for several years, the antibody titers are extremely low against the newer B/Victoria-like strains, such as B/Shangdong/07/97 and B/Sichuan/40/99.

Next overhead which is page eight.

This overhead shows results that were obtained in January of this year using a panel of sera from adults in the United States. The data are from CDC at the top and from the WHO Melbourne at the bottom. These data demonstrate that the current vaccine produces antibodies that cross-react reasonably well with other new B/Yamanashi-like strains such as B/Tennessee/4/99 and

B/Shanghai/180/99. However, antibody titers are reduced by more than 50 percent against the B/Shenzhen/654/99 strain, which, again, is in the same lineage as the current vaccine stain, B/Yamanashi/166. And I think you can see that in both of these serum panels, that there's a fairly marked reduction for that particular strain.

Next overhead, which is page nine.

This overhead shows results that were obtained, again, in January of this year using a panel of sera from the elderly in the United States and the data are from the CDC at the top and from the Center for Biologics at the bottom. The data, again, demonstrate the current vaccine strain produces antibodies that cross-react reasonably well with many of the newer influenza viruses that are in the B/Yamanashi lineage. But, in the CDC data, again, you can see that the titers for the B/Shenzhen/654 virus are markedly reduced as compared to the vaccine strain.

We're going to skip over page 10. Go to page 11.

This overhead shows the H3N2 influence viruses used for serologic testing. And, actually, this doesn't even show all the viruses that have been

used, but I included most of them here. The antigens chosen, again, are currently circulating strains that are representative of these A/Sydney/5/97-like strains that are the current vaccine strain and also strains that appear to be less well inhibited by ferret antisera raised against the A/Sydney strain.

I think we'll skip over to page 13. And this overhead shows results that were obtained in January of this year using a panel of sera from elderly in the United States. The data are from the Center for Biologics at the top and from WHO Melbourne at the bottom. And what they show is that the responses to the newer H3N2 strains were, for the most part, similar to the vaccine strain. However, a notable exception to this is, for the A/Philippines -- and I guess I've got a typo there. I think this is supposed to be "'99" -- that the A/Philippines/26/99 strain shows a very marked reduction which is more than twofold in the test that was done at WHO in Melbourne.

Next overhead, which is page 14.

This overhead shows results, again, that were obtained in January of this year using a panel of sera from adults in Europe and the data are from CDC at the top and from NIBSC at the bottom. These data

demonstrate reductions in titer against some of the newer viruses, including the A/Moscow/10/99 strain; the A/Shanghai/42/99 virus; and the A/Panama strain. The data from NIBSC also indicate that there are good antibody titers against the A/Shenzhen/510/99 strain.

Okay, skip ahead to page 16 and I'll try to put this into a summary form. The following tables show the frequency with which we found new test antigens given a 50 percent or greater reduction compared to the current vaccine strain. 50 percent is used here as an arbitrary breakpoint since it does represent a twofold reduction, which in geometric mean titer terms is fairly substantial.

The data included in this table are for antigens that were tested in more than one lab where possible, but antigens that were tested in a single lab are included where they are of particular interest. I've not included everything that's been done here. It should be noted that not all of the testing has been completed, so there are, obviously, some holes in some of these tables we're going to see. In this particular table, the antigen at the top is one of the Bayern/07-like strains and all the others are Beijing/262-like strains.

I'd just like to call your attention to

the last columns here, for the moment, although you can look at the individual data as well. But the data for the Johannesburg strain indicates that that strain was quite well-inhibited by antisera in all of the tests that were done from sera that were collected using current vaccine strains. Somewhat paradoxically, if you look at all the A/Beijing/262 lineage viruses, including the A/New Caledonia; the A/Nanchang; A/Peru; A/Wisconsin; and A/Madrid, on average there were reductions that were greater than 50 percent overall, as shown at the end, here. And, in some instances, they were quite substantial, in some of the serum panels that were tested.

Next overhead, please, which is page 17 in the handout.

This slide shows summary data for the Influenza B viruses. The top two strains here are B/Victoria-like strains. The bottom six strains are like the vaccine strain B/Yamanashi. Some of these B/Yamanashi-like viruses appear to be less well-inhibited by sera from persons who have been immunized with the current vaccines. However, many of the strains do not appear to be well-inhibited at all, which suggests that some antigenic drift may be going on.

And I just call your attention to some of theses strains that have been tested in multiple laboratories. In particular, the B/Shenzhen/654/99, which Nancy Cox mentioned as being a new variant virus. As expected, the B/Victoria lineage viruses were not well-inhibited by the current vaccines and there's more uniformity in finding, really, the most marked reduction in antibody titers for those strains as compared to the vaccine strain. That's not news; that's what we've been seeing over the last several years.

Next overhead on page 18 will show summary data for the H3N2 viruses. All of these strains are related to the Sydney vaccine strain, but the table includes some of the strains that are less well-inhibited by ferret sera A/Sydney. The most marked reductions in this table are for the Shanghai/42/99 strain and for the A/Philippines strain. In both of those instances, there's a substantial, greater than 50 percent, reduction in titer. But you can see that there's sort of variability amongst these strains from really not much reduction in the tests that have been done so far to really quite marked reduction.

Okay, so slides off. So, in summary, the vaccines that were used for the clinical studies were

immunogenic in the populations tested. And for all of the three vaccine component strains, there is some evidence of antigenic drift, which is probably most notable or most obvious for the H1N1 virus strains, which represent drift variance, I guess, or drift of a sort from the current vaccine strain. As we've known for several years, the B/Victoria lineage persists and the current vaccines are probably of limited protection against those strains.

And that's all I've got to say. I'll stop there. I hope we're getting back on time. And if there are any questions, I'll be happy to try to answer them.

CHAIRMAN GREENBERG: Panel members, do you have any questions for Roland? Okay, if there are no questions, we will move on to availability of strains and reagents by Mr. Offringa.

MR. OFFRINGA: If I could have the first overhead.

I'm just going to give a brief overview of the vaccine strains, current candidate strains, and potency reagent availability. I'll start with the H1N1 strains. The current vaccine strain is A/Beijing/262/95. The reassortant used for vaccine production is X-127, which has a high-yield growth

character.

There is one H1N1 candidate strain which is A/New Caledonia/20/99. This is also in the Beijing/262 lineage. There are two reassortants available for New Caledonia: IVR-116 and X-139. The IVR-116 has a moderate-to-high yield growth character and the X-139 has a moderate yield growth character. The IVR-116 reassort is currently being used to produce vaccine for the Southern Hemisphere.

I'll continue with the B strains. The current B vaccine strain is B/Yamanashi/166/98, which is in the Yamagata lineage. Influenza B reassortants are not available, so the wild-type strain is used for vaccine production and this wild-type strain has a moderate yield and growth character. There's currently one candidate strain distributed to manufacturers, which is B/Johannesburg/5/99, also in the Yamagata lineage. Unfortunately, all manufacturers have experienced a very low yield with this strain.

And I'll continue with the H3N2 strains. The current vaccine strain is A/Sydney/5/97. There are two reassortants being used for vaccine production: IVR-108 and RESVIR-13. Both of these reassortants have a moderate-to-high yield growth

character.

We also, again, have one candidate strain distributed to manufacturers, the A/Panama/2007/99, which is a Sydney-like strain. There are several reassortants distributed to manufacturers: the NIB-41 and NIB-42. Both of these strains exhibit a moderate yield growth character. And then we have recently isolated two Panama reassortants in our laboratory: RESVIR-16 and RESVIR-17. We are going to distribute these to manufacturers next week and hope to get some information on their growth character shortly.

I'll move on to availability of potency reagents. For all current vaccine strains, the Yamanashi/166/98; A/Beijing/262/95; and Sydney/5/97, we have reagents available. We are currently also distributing New Caledonia IVR-116 reagents from the Therapeutic Goods Administration in Australia, which are being used for testing of Southern Hemisphere vaccine. And our IVR-116 reagents will be available by February. If any other strains are chosen, those reagents would not be available until May at the earliest.

If there are any questions?

CHAIRMAN GREENBERG: Thank you very much. Panel have any questions? Okay. We're moving on to

manufacturers' comments and this is Dr. Slusaw.

DR. SLUSAW: Thank you. Roland noted I had 30 seconds so that he could get the agenda back on track.

(Laughter.)

I don't envy the task before the committee today of selecting the strains for the next influenza vaccine season. It's really, I guess, all about balancing and trying to find the best antigenic match for the strains you anticipate will be circulating during the next season, yet selecting strains that also have appropriate growth characteristics so that they are practical to use to make vaccine. And also doing that selection in a timely fashion which allows the manufacturers time to produce the required vaccine within the timeframe that it's needed.

There are several critical key pieces to the puzzle that have to fit together to support vaccine manufacturing. The first is egg supply. In the U.S., the flu vaccine manufacturers probably consume about a half million eggs per day during a six-to-eight month period while the monovalent concentrates are being manufactured each season. The good news is that this is a pretty predictable process and we have a fine-tuned and robust system in place

that ensures the availability of embryonated eggs for vaccine manufacturing.

Something that we're talking about a little bit more today is selection of seed viruses and also another component of that, preparation of high-growth reassortants. And it would not be possible to produce the numbers of doses we talked about for last year, for example, 80 to 90 million doses, without the availability of high-growth reassortants prepared by Dr. Levandowski's and Dr. Kilbourne's laboratories as well as laboratories in Europe and Australia.

And then, finally, the third critical piece is the availability of the potency test reagents. Until we have prepare the reference antiserum and the reference antigen and those reagents have been calibrated, we have several disadvantages. One is that we don't know precisely the amount of vaccine we're manufacturing. Although we can estimate that number, it can be off by quite a bit. So we run the risk of producing too much or not enough of a particular component. And, of course, until we can measure the potencies, we can't formulate the trivalent vaccine so the rest of that process is dependent on having the potency test reagents completed.

A bit of a timeline to illustrate a normal flu vaccine manufacturing season, if there is any such thing. Generally the process begins about a year in advance when the egg suppliers order their birds to support the egg supply for the following vaccine season. These pullets are housed usually in October or November, and this is really the only time during the year when an egg supply is not available.

An ongoing process that usually begins sometime in fall and continues through the early part of the year is receiving candidate seed viruses. And, kind of in parallel with that, the preparation of high-growth reassortants. Now this is, of course, one of the first stages where surprises can come up and things can begin to go wrong. An example is what we've heard this morning with the A/Moscow reassortant, for example. There's a bit of black magic involved and things don't always turn out as expected.

The manufacturers hope to come away from this meeting with at least the first strain selection at this time. Two would be nice, but I think in a typical year we expect one. And then following at about four week periods, the second and finally the third strain selection.

As the strains are selected, production of the monovalent components of the vaccine proceed. Many manufacturers, both in the U.S. and some in Europe, actually start production of the monovalents in January, before the official strain selection. And that's a bit of a risk. We can make educated guesses based on the latest surveillance data at the time, but it's a bit of a risk that must be undertaken in order to support the number of vaccine doses that must be manufactured in the time period.

The next surprise in the process, of course, can occur at the stage of producing the vaccine components. Although we receive the candidate strains and have an opportunity to evaluate and test them a bit, especially on small-scale, once those strains are scaled up to large-scale production, there may be surprises with the growth characteristics or the purification properties of the virus that can affect the yields and the final availability of doses. And then, of course, in the same timeframe, the preparation of the potency test reagents for SRID testing.

Then normally we would expect to bulk the first vaccine in the beginning of June and then after the appropriate testing and release is completed, the

license is generally issued the first week in July and vaccine distribution will begin. And that'll proceed through about the first or second week in October. And, especially in recent years, this has become kind of a hard cut-off date and any vaccine that's available after that time period generally either won't be sold or will be returned by the customers.

I wanted to try to put together a little bit of an illustration about some of the things that begin to go wrong if strain selection is delayed for any reason. And, of course, it pushes out the timeframes for the availability of the candidate viruses as well as the high-growth reassortants.

And in this illustration, supposing third strain selection is pushed out a months or so, one of the first bad things that happens is there may be a gap in production of the monovalent concentrates at this point. If a manufacturer has made all of the required first and second strain, rather than overproduce something that won't be needed, we may actually have to wait until the third strain is available and then resume production. The downside of that, of course, is that the chickens and the egg supply can't be turned off, so manufacturers and egg suppliers have to absorb that cost of, say, a half

million eggs per day, which are essentially just be discarded.

Then, of course, this gap in production here can translate into an extended production cycle at the end of the program. And, again, that can also delay the availability of the SRID testing reagents and pushing out the bulk vaccine preparation and perhaps the license issuing. And the really critical factor here is that we lose this window of opportunity for vaccine distribution and continue to distribute vaccine as normal, but rather than just simply pushing out the timeframe into the November part of the year, these vaccine doses essentially won't be used by the marketplace.

Any questions or comments?

CHAIRMAN GREENBERG: Panel? It's clear, a treadmill. Okay. If not, thank you very much. And now Roland's going to lead us in -- yes? There is a short break, but you just broke. You're strong. We don't need it.

DR. LEVANDOWSKI: Okay. I would like to lay out what we see as some options for the 2000 - 2001 influenza vaccine composition and just go over the different possibilities here.

Okay. Take that off. We're not ready yet.

that.

(Laughter.)

Influenza A viruses of the H1N1 and H3N2 subtypes and also Influenza B viruses have continued to circulate in human populations and there's been discussion here in the past about eliminating one or more of the components of the vaccine, but I think what we heard today is that all three strains that are currently in the vaccine and more are alive and kicking out there. Therefore, the first thing to consider is what the valency of the vaccine should be and I would argue that the vaccine should continue to be a trivalent vaccine.

As far as the Influenza A viruses, the H1N1 types, strains similar to the A/Beijing/262/95 strain have now been found in all areas of the world and what we've seen this morning is that those strains are undergoing antigenic drift. The human serologic responses suggest that the current vaccines are immunogenic, but that the predominant new A/Beijing/262/95-like viruses are poorly inhibited.

The vaccine candidate strains, such as the A/New Caledonia/20/99 are currently available and being used for production for vaccines for the Southern Hemisphere. So there is some manufacturing

experience with that strain as well. So options.

Now the first overhead, the options for the H1N1 viruses.

The first option would be to maintain the current vaccine strain. In favor of that is that the current vaccines appear to be highly immunogenic. And, in addition, manufacturing is well-defined and it's predictable at this point from having had the experience.

Against that are that the strains are demonstrating antigenic drift and those antigenic drift strains have been found in all parts of the world. In addition, heterologous serologic responses to the H1 deletion strains are clearly reduced.

So another option, on the next overhead, for the H1N1 viruses, would be to change the current vaccine strain to a more recent strain. And in favor of that, the more strain could possibly provide a better antigenic match with the current H1N1 strains that are circulating. In addition, there are vaccine candidate strains, such as this A/New Caledonia/20/99, that are available and they've been used for manufacturing vaccines for the Southern Hemisphere. Against that, we don't really have information on the immunogenicity of a New Caledonia-like vaccine.

So the third possibility would be, for the H1 strains, to defer this selection to accumulate some more data. In favor of that is that there may be some additional data that would further refine and clarify the position. But against that is that it doesn't appear that it's likely that there will be much more information coming in over the next several weeks because there have not been, except for Japan, there have not been a lot of H1 strains that have been isolated.

Okay. Overhead off.

For the Influenza B viruses, the strains of Influenza B in the Yamagata/16/88 lineage have predominated, with strains that are similar to the current vaccine strain, which is B/Yamanashi/166/98, islated in the Americas, Europe, Africa, Australia, Asia, and essentially the whole world. A new variant in that lineage has been identified just in the last week. And therefore its possible significance has not really been assessed completely. Strains of the B/Victoria/287 lineage continue to appear in Asia, as has been true for several years, but the relative frequency of these strains appears to be diminishing at this type.

The sera from people who are immunized

with the current vaccines inhibit some of the current B/Yamanashi-like viruses well, as previously current vaccines did not produce antibody responses to the B/Victoria/287-like strains. And I should add that some of the B/Yamanashi-like strains are also not well-inhibited by the current vaccines.

There's limited information at this time on other vaccine candidates, as we just heard. However, the strain that has been examined really does not appear to grow very well and, for that reason, would probably not be a very desirable candidate.

So the options for B, the first overhead here, the first option, of course, is to maintain the current vaccine strain. And in favor of this would be that most of the strains worldwide are similar to the current vaccine strain. The vaccines appear to be immunogenic and, again, manufacturing is well-defined and predictable. But against that is that recent Yamanashi-like strains are not clearly well-inhibited by the post-immunization antisera.

So the next option would be, again, to change the current vaccine strain to a more recent B/Yamanashi-like virus. In favor of that is that the vaccines could be antigenically closer to the current Influenza B viruses. But, against that, we don't

really know that there would be a clear advantage based on any antigenic characterization that's been done so far and there really are no superior alternate vaccine candidate strains at this time.

So option three is, again, to defer to accumulate more data. In this case, in favor of this option would be that there are more data that are likely to be available in the next two-to-three weeks, including analysis of these new Chinese Influenza B viruses that have been sent to CDC recently. Against that is that additional data may not really alter what the current considerations are, once all the information is in.

You want to take the overhead off?

For the Influenze H3N2 A viruses, there is antigenic heterogeneity that's continuing among these strains, as there has been in the past year or more. And approximately 10 to 15 percent of the strains are antigenically distinguishable from the A/Sydney/ vaccine strain. And, again, that heterogeneity has been found widely, not only in the United States, but in most areas of the world.

From that information, there is not a clear antigenic or genetic pattern to suggest a group of antigenic variance that might become

predominant one. The antisera to some of these newer H3N2 strains appear to inhibit many of the current strains reasonably well, but serologic responses are reduced against some of the recently emerging and antigenically divergent strains. Although vaccine candidate strains and high-growth reassortants for some of these are available, it's not clear that the vaccine candidates currently available will offer an antigenic advantage.

So, again, the options for the H3N2 virus. The first option would be to maintain the current vaccine composition and that was a strategy that was used last year in view of much of the similar kind of information. In favor of this would be that manufacturing is well worked out and the yield is predictable. But against that is that there is this antigenic heterogeneity and 10 to 15 percent of the new H3N2 viruses are distinguishable, readily distinguishable, from the A/Sydney/5/97 strain.

Some of these recent strains are not well-inhibited by post-immunization antisera. And the current vaccine strain has been in use for the past two seasons and the A/Sydney-like strains have predominated for the past three years, which is a distinctly unusual situation to be in, particularly

for the H3N2 strains. That's really unprecedented in the last 20 years or more.

So the options for the H3N2 virus. Again, the first option is that we could maintain the current vaccine composition and in favor of that is that manufacturing is well worked out and the yield is predictable. But against that, there is antigenic heterogeneity and 10 to 15 percent of the new viruses are distinguishable from the A/Sydney strain. The most recent strains are not well-inhibited by post-immunization antiserum and the current vaccine strain has been -- did I say this already? What am I doing? Sorry.

CHAIRMAN GREENBERG: It's okay. We're slow learners.

(Laughter.)

DR. LEVANDOWSKI: Pardon me.

So option two. This is what I really meant to say. We could change the current vaccine strain to more recent. And in favor of that, 10 to 15 percent of the recent strains are poorly inhibited. It could be possible to achieve a better antigenic match with the recent strains. And there are some alternative strains that are available for production.

Against that would be that the choice of

the strain could benefit from additional epidemiologic, serologic, and manufacturing information. We really don't have all the data in that we'd like to have. It's not clear that the available strains are superior to the current vaccine strain, however. And there is little information on the potential for vaccine production with any of these new strains, except for a very little bit of information for these Panama reassortants that's been mentioned.

So the final option of these four is number three, which is to defer to accumulate more data. And in favor of that, there will probably be significantly more data for these more recent strains over the next two to three weeks. And since the H3N2 strain is the one that's most likely to cause significant mobidity and mortality, this choice is one that should be really very carefully made. Against that, of course, is always that the additional data may not alter what we know from the current conditions, considerations.

So I'll stop there.

CHAIRMAN GREENBERG: Roland, that was a very clear, at least to me, delineation of options. Now I'm sure the committee will come up with some

other options, but that was very helpful to me. And I think we had planned for discussion after lunch, but I think we have some time now and I think it would be wise to see how far we get in discussion. So I'm going to open that up for discussion. And you can sit here, but I suppose most of the questions will be -- Dr. Estes first.

DR. ESTES: I have one question that hasn't been brought up yet today. We have a new potential factor in flu variation and that's the introduction of neuraminidase inhibitors this last year. And I wonder are there studies that are looking at flu coming out of areas where these inhibitors are being used extensively to be sure that we're not putting a new pressure, there will be a new virus that's now going to pop up in the next month or so? I'd just like to hear people's opinions. Others must be worrying about this.

CHAIRMAN GREENBERG: Anybody with expertise can answer that. Dr. Cox.

DR. COX: I can at least give a partial answer. This has been a concern because the viruses that are resistant to the neuraminidase inhibitors have been found to have mutations both in the neuraminidase itself and also in the hemagglutinin

and, of course, the concern is that you might be driving antigenic change. But it also should be stated right up front that it's much more difficult to generate resistant strains to the neuraminidase inhibitors than it is to the older antivirals, symantodyne and rhymantodyne.

So the manufacturers are now working together to set up a susceptibility network and they will be looking not only at field strains, which are collected by CDC and other WHO colloborating centers, but they will also be attempting to obtain isolates from individuals before treatment and after treatment to look at changes that occur. So I think that monitoring should be sufficiently good to give us a good idea of what's going on.

CHAIRMAN GREENBERG: Ms. Fisher.

MS. FISHER: This is sort of a general question, but to what extent does mass vaccination versus targeting high-risk groups contribute to antigenic drift of strains included in the vaccine every year?

CHAIRMAN GREENBERG: Again, anybody of the experts who wants to answer questions, I think Roland, do you want to tackle that?

DR. LEVANDOWSKI: Well, I don't think

have a good response for it, but when you're saying the term "mass vaccination," I don't believe we've used what's really mass vaccination in the United States at any point. Possibly the closest thing to that experience would be in Japan where all the children were immunized for some number of years, all the school children. But I don't know that there are, from any studies done there, that there was any impact on epidemiology of spread of influenza. I'm not sure whether Dr. Nerome would have any comments on that or Dr. Cox.

MS. FISHER: I wasn't speaking to children. I was thinking the increase in the elderly and in healthy individuals.

DR. LEVANDOWSKI: Yes.

MS. FISHER: Does it put pressure on the strains in the vaccine to change?

CHAIRMAN GREENBERG: Dr. Cox is looking like she wants to answer.

DR. COX: I don't think that there's any way to give a definitive answer. But such a small proportion of the world's population is vaccinated at the present time that we would not expect that vaccination could be contributing significantly to antigenic drift. Many of the new strains do emerge

from Asia and immunization rates in Asia, with influenza vaccine, are very low.

DR. LEVANDOWSKI: There may be some data from the pre-immunization era. We've only used influenza vaccine since the 1940s and there are studies looking back, seroarcheology, to see what had happened.

And I believe Dr. Daudle has published some paper describing one of the events that was originally thought to be an antigenic shift, that is a complete change in hemagglutinin being more like a substantial antigenic drift some time near the end of the 1800s, beginning of the 1900s. I don't remember the exact epidemic or outbreaks that are described from that paper but it has been described previously that there are major antigenic changes that occur, short of an antigenic shift that would cause a pandemic within influenza viruses in the past.

CHAIRMAN GREENBERG: I think, just for me, Dr. Cox's answer was a compelling one that the world is susceptible to influenza and the amount of vaccine given to the world at this point is very small compared to the amount of people who are infected. But it's an interesting question.

Dr. Daum and then Dr. Kohl.

DR. DAUM: I'm actually very interested in that question and would like to sort of push the envelope a little bit further. Leaving the world aside for a moment and focusing just on the United States where we're distributing 70 or 60, I don't know the exact number, million doses of vaccine a year and we have very little B activity, relatively speaking, very little H1 activity, relatively speaking and lots and lots of H3 activity, relatively speaking. We've had this Sydney-like H3 member of the trivalent vaccine in the last few years. And couldn't we make any inferences at all about the kinds of viruses that are circulating and the types of vaccines the committee has chosen in years past?

For example, one might say, in a naive way, the B vaccine works great; the H1 vaccine works great; and the H3N2 is not working because it's still circulating, despite 60 or 70 million doses of vaccine being circulated.

So I'm wondering, is there anything to be gained from what we've done with previous vaccines and what's actually been circulating in the community in spite of or in concert with this large vaccination effort?

CHAIRMAN GREENBERG: Dr. Cox.

DR. COX: I think that what we're seeing with regard to circulation of H3N2 viruses versus B and H1 is a reflection of what's occurring globally. I mean, if you remember the first slide that I put up for each of the different groups of viruses, what we were seeing in the United States or what we're seeing in the United States is pretty representative of what we're seeing globally. And the vaccine coverage in the United States is higher than it is in many other regions of the world.

So I think it's very difficult to say that we're not having H1N1 because the vaccine is working well or we're not having B because the vaccine is working well. It's a very complex interaction of the host, the immune background, and the virus itself, how transmissable it is, how different antigenically it is, and so on. And those host and virus factors are what determine which strains circulate.

I think we have a tremendous amount to learn and there are some very interesting modeling techniques that we'd like to use to try to help us understand the way viruses are changing and the epidemiology of the circulation of the different strains.

DR. HOKE: Thank you. One population that

is immunized in what might be called a mass way is the military recruit populations and they are universally immunized against influenza and carefully monitored for respiratory diseases rates. It has an important impact on training. And when rates exceed a certain threshhold, investigations are conducted.

We've long recognized that if there were strains of influenza that circulated that, for example, against which vaccine could not protect, that that would be a very good sentinel population in which that would happen. And, to my knowledge, the kind of instance that you inferred that there might be a sudden shift in that population, highly immunized as a sort of source of a new strain that emerged under pressure, I don't know that that's ever happened. I haven't combed back through the data.

But I should say, on the other side, that, through the use of influenza vaccine in association with adenovirus vaccine, that respiratory disease rates in military recruits are suppressed to very, very low levels. And this is really a population that would be highly susceptible to transmission of respiratory viruses. So that, you know, anecdotes of isolates from people who had been immunized notwithstanding, I think that the almost complete

suppression of influenza in military recruits under a universal immunization policy is rather compelling information about the effectiveness of the immunization.

CHAIRMAN GREENBERG: I would guess also that recruits are a somewhat isolated population, especially isolated to children more than the general population, which might help the vaccine work a little better.

DR. HOKE: Well, that would depend on where the training force post was, but generally they are embedded in communities.

CHAIRMAN GREENBERG: Dr. Kohl.

DR. KOHL: I don't know if this is premature, but I think I, for one, feel we can start focusing on some of these viral selections and, to use a phrase earlier, one is a no-brainer, I think. And the no-brainer is the H3N2. It looks like we should hold off on that selection pending, quote, "significant new data."

CHAIRMAN GREENBERG: I want to make sure that -- if the panel feels that they've asked enough questions to help Roland give recommendations, I'm not against moving ahead with that. Roland, is that okay with you? And we can start with each one.

Are there any further questions from anybody in the panel? Dr. Couch.

DR. COUCH: Well, mine was just a question for clarification that I neglected to ask Dr. Hampson. Just to be sure I understood that all of the Influenza B experience in Thailand and in New Zealand and in the Southern Hemisphere was the Yamanashi-like virus, not anything related to the B/Shenzhen that's now being considered as perhaps something different.

DR. HAMPSON: No, there we haven't any of the Shenzhen-like virus.

DR. COUCH: So those would fit with the previous classification of these.

DR. HAMPSON: Yes, the B viruses that we have found throughout our area of surveillance are the B/Yamanashi-like viruses. We're showing some percentage of them with a degree of drift, react about two to fourfold down with the B/Yamanashi antiserum. And more closely related to the B/Johannesburg is our current updated reference strain.

CHAIRMAN GREENBERG: Dr. Ferrieri.

DR. FERRIERI: I just want to second what Dr. Kohl said. We will have more data in about two to three to four weeks about alternative strains and so I don't know that we need extensive discussion on the

H3N2 status.

CHAIRMAN GREENBERG: Well, what I would, since I think everybody feels they're ready to go, I think I'll just move around and we can take one virus at a time. I'm going to switch to the left-hand side of the table here.

(Laughter.)

And I see somebody, an expert in influenza down there. So, Dr. Couch, why don't we start with the -- does everybody want to start with the big guy, H3N2? Because I've had two people say let's start with the H3N2 and our recommendation there. Is that okay with the panel? We'll start with that component and what we think?

I think we were presented by Roland three possibilities. One, to recommend staying with the current. Two, to identify a new candidate. And, as best I can tell, there's only one candidate that could be identified at this moment and that's the Panama reassortant that is there. Or, three, to wait some period of time while more serology and analysis of new viruses is done. And we were told that since -- and Roland clearly, I think, tipped his hand as to what he thought since he said this is by far the most important, usually the most important virus and the

most information we could have, the better-off we'll be.

So I will start with you as to what you're recommendations would be.

DR. COUCH: Well, I will do one and then let's move down the table on the left. How about that for the others?

Well, actually, I'd like to first of all compliment industry on their efforts, which those of us who've got institutional memories know that industry used to be relatively intolerant of not making all three decisions at this time. And that was always extremely difficult. And then they gave us one. And now they're giving us three. So we really only have to make one for sure at this time and they've set up a schedule that we've all certainly got to try and live by.

And so I think that's a major improvement over the way, if you want to go back 10, 15 years, the way these decisions were made in the past. And so I think they ought to be complimented for that accommodation to make this decision a little bit more definitive.

So if you want to start with the three, I guess I'd consider that --

CHAIRMAN GREENBERG: Could I interrupt for one second? I am told -- excuse me, this is my parliamentary naivete. But before we start voting from the panel, I was supposed to ask for public comment and I apologize to the public. This is purely my inability to follow schedule correctly. Please step up to a microphone and identify yourself.

MR. RUBIN: Yes, Mr. Chairman. I'm Fred Rubin. I've worked for Aventis Pasteur. We are one of the manufacturers of influenza vaccine.

I think one consideration that hasn't been mentioned here. I'm sure some people know it, but maybe not everybody and that's that the ACIP at its October meeting voted to lower the high-risk age group to 50 and that, I think, constitutes a sizeable additional population of people. And so the challenge is being put to industry to produce vaccine a little bit more than there's been in past years. So rather than this being a trivial piece of information, I think it's a highly significant piece of information.

If that policy, which they've voted on, is implemented, it's going to mean that we have to produce, in industry, you know between 25 and 40 million additional doses. I could be off by, you know, a million or two here or there.

So I think the putting off of the decision could have some impact. So I think it's important for you to keep that in mind. Even though you have to pick the right strain, we also have to provide enough vaccine for all these people. And if we don't have time to do it, a policy that's voted on and then you can't implement it has terrible repercussions.

CHAIRMAN GREENBERG: That's very helpful. And since I am now in the high-risk group --

(Laughter.)

-- sort of startling to me.

DR. COUCH: Did you get your vaccine this year?

CHAIRMAN GREENBERG: No. Are there any other comments from the public? If not, again, I apologize for not having done that before.

Dr. Couch, back to you.

DR. COUCH: Well, what I usually do -- I started it, actually, many years ago -- was what Roland put up there first. I put down my strain, epidemiologic vaccine, and availability and mark my crosses on these things. And I've been doing the same thing here I always do.

And he, of course, enunciated all of the considerations very clearly. And I've got a bunch I

question marks and only one plus across under H3. And it's a clear note and deferral is, as Dr. Kohl indicated, I suspect, based on where we stand right now, perhaps the last decision. And if we hold to the industry schedule, that will be an April decision. But we can decide whether one or the other is ready to go with the next decision.

It's not the only one I think we have to defer, but H3 should be deferred.

CHAIRMAN GREENBERG: Dr. Hoke.

DR. HOKE: Am I supposed to talk about H3 or pick another one?

CHAIRMAN GREENBERG: Yes, we're doing H3 into now moving along on that one.

DR. HOKE: Yes, I agree with that. I agree with that.

CHAIRMAN GREENBERG: So, for the record, Dr. Hoke agrees to defer decisionmaking for the time being on H3N2. Dr. Kilbourne.

DR. KILBOURNE: Well, I think we have a population that's saturated with H3N2 right now. I have not seen evidence today of any prospective strains that look as if they're going to be significantly antigenically different, so I think you have not only a well-vaccinated population, but one

fraught with the disease itself. So I suspect that even if one of those new strains were to come into the population next year and we stuck with Sydney, we'd still be okay. Because there's enough cross-reactivity among strains so I think we could be comfortable.

CHAIRMAN GREENBERG: So, was that a vote to use Sydney now?

DR. KILBOURNE: That would be my vote. Maybe I'm jumping ahead, but certainly it could be deferment as far as I'm concerned.

CHAIRMAN GREENBERG: So would you say to defer, pending new information? Or do you say we have enough information at this moment to choose?

DR. KILBOURNE: In my view, we have enough to choose.

CHAIRMAN GREENBERG: Okay.

DR. KILBOURNE: But others may not agree, so I don't want to --

CHAIRMAN GREENBERG: No, that's the whole point of voting. Dr. Couch.

DR. COUCH: Could I ask Ed a question? What if we get antigenicity data on the neuraminidase and there are major differences between Sydney and say a couple of the recent strains? Just in the

neuraminidase.

DR. KILBOURNE: Then you put in a new neuraminidase.

(Laughter.)

CHAIRMAN GREENBERG: I think Dr. Kilbourne has said that his vote is that there's enough information now to say that the manufacturers should go ahead with the current Sydney vaccine, that we do not have to wait. Am I putting it -- did I not interpret what you said correctly?

DR. KILBOURNE: You did.

CHAIRMAN GREENBERG: Okay. Thank you. Dr. Cox.

DR. COX: My view is that, because we have H3N2 circulating widely now and there's always a delay between the time the viruses are isolated and sent to the state health departments or the intermediate labs and then on to the international collaborating centers, it would really be prudent for us to defer this particular recommendation and accumulate as much information as possible.

CHAIRMAN GREENBERG: Okay. Dr. Ferrieri.

DR. FERRIERI: I support deferral and suggest that exploring not just the Panama strains, but the Shenzhen/510/99, although I may have missed

some point. But the antisera and inhibition of all of the new strains look superb for that, with a rare exception.

CHAIRMAN GREENBERG: Dr. Eickhoff.

DR. EICKHOFF: Well, I support deferral and yet I'm reasonably confident that, when we can defer no longer, we're going wind up with A/Sydney back in the vaccine.

CHAIRMAN GREENBERG: Dr. Daum.

DR. DAUM: I must confess to be having a difficult time with this. I'm persuaded that deferral for the period of time talked about would still give manufacturers enough time to prepare properly for the season. And, given that and the possible availability of new information in a timely way, why not have new information?

But I share Dr. Eickhoff's view. I don't think there's going to be likely to be a change here and I'm not sure we have enough confidence in what the new information's going to be that's going to drive that.

CHAIRMAN GREENBERG: Dr. Edwards.

DR. EDWARDS: I would vote for deferral.

CHAIRMAN GREENBERG: Ms. Fisher.

MS. FISHER: I don't feel comfortable

making this decision. I would defer to Dr. Cox and others. However, I do want to make a statement.

I do think some attention has to be paid to increased mortality among those who got flu this year, particularly looking at what their vaccination status was. And, also, you know, as flu vaccine coverage increases, especially among the elderly and healthy persons under 65 in the U.S., perhaps there should be an investigation of whether vaccinated persons are losing cell-mediated immunity acquired from natural infection and are becoming more vulnerable to both vaccine-strain flu infection and increased mortality from the flu complications such as pneumonia caused by other infectious organisms.

CHAIRMAN GREENBERG: Dr. Faggett.

DR. FAGGETT: Yes. I really appreciate the input from Dr. Couch and other experts and do vote for deferment. I would agree, though, that I would hope that the manufacturers do have enough inventory to take care of the 50, that new age group, as well. And I think it's probably, in our patient population in my community, we do have a lot more interest now, so I think we're going to have an increased demand. Now we're in for that age 50, other places are going to be wanting it, too.

CHAIRMAN GREENBERG: Dr. Kim.

DR. KIM: I also support deferral, although I respect Dr. Kilbourne's comment that we may not be able to see any considerable difference in that sense. I think since the Moscow strain was not, indeed, feasible, then, again, the strains like the Panama, you know, appear to be appealing and, again, in addition to Sydney strain. So I think those options need to be continued to be explored.

CHAIRMAN GREENBERG: Dr. Kohl.

DR. KOHL: Defer.

CHAIRMAN GREENBERG: Dr. Estes.

DR. ESTES: I support deferral. I also think it's prudent to get as much information as possible and I am concerned about the pressure of the use of the new antiviral as to whether that's going to end up changing this hemagglutinin, which would only affect the A strains.

CHAIRMAN GREENBERG: And Dr. Griffin.

DR. GRIFFIN: I think we need the maximum amount of information before this choice is made and so we should defer.

CHAIRMAN GREENBERG: Okay. And for the record, I also vote defer. And I think, in fact, I am heartened by the fact that, as Roland said, that the

A/Sydney there's two years of experience and we, I would assume, have some ability to defer because that is already in the bank, so to speak, and manufacturing can be done relatively efficiently. So if it ends up, as Dr. Kilbourne thinks, that that turns out to be the strain, we have it and we have a lot of experience making that vaccine. Not me, but --

DR. KILBOURNE: I'm not unhappy with this decision.

CHAIRMAN GREENBERG: Yes. And your point was clear.

DR. COUCH: Well, I might say that I think Ed is correct. I mean, the view that some of us might have been taking, which is in agreement with his that that may well be the decision, but I'm more comfortable backing into it rather than charging out there.

CHAIRMAN GREENBERG: And I think everybody understands that there is no real difference with Dr. Kilbourne. He was just looking into the future more than we were.

Well, I think we have time for perhaps at least beginning to talk about one other strain or even more. So, Dr. Couch, I know you said you didn't want to start off the next one, but, you know, you have

many years of influenza experience.

DR. COUCH: Oh, no. There are other people down here. You're pinpointing me a little bit too much.

CHAIRMAN GREENBERG: So I'm going to pick the strain.

DR. COUCH: Good.

CHAIRMAN GREENBERG: Let's go with the next one, with the H1N1 strain.

DR. COUCH: I was going to say, you know, let me select one and then let me try to defer the other one, if I may.

(Laughter.)

My H1 chart has plusses all the way across and that is what was once again highlighted and described very nicely by Roland and that is that we should change the H1 --

CHAIRMAN GREENBERG: Could you use your microphone a little bit more? I'm having a little trouble hearing you.

DR. COUCH: That my little chart I told you I make has plusses all the way across on H1 and so we need to recommend a change in the strain and the obvious change is to New Caledonia. And the reasons for that were enunciated very nicely by Roland.

CHAIRMAN GREENBERG: Okay. Fine. Dr. Hoke.

DR. HOKE: Perhaps I needed to hear Dr. Levandowski again, because I actually had not been so certain that -- but, of course, Dr. Couch always seems to, you know, sound definite. Sounds like he knows exactly what he's talking about.

I had written at the bottom of my chart to stay with the A/Beijing. And so I'll just say that I had written that down, because it wouldn't be right to change my mind just because you said that. But perhaps there will be some more discussion on that.

CHAIRMAN GREENBERG: So you can reconsider after you hear all of this. This isn't the SATs. Dr. Kilbourne.

DR. KILBOURNE: I think, all other things being equal, I would opt for the New Caledonia or something like it. I think there's enough evidence of a drift there so that we should be concerned about it.

CHAIRMAN GREENBERG: Dr. Cox.

DR. COX: I agree with going with New Caledonia. And I know that not everyone else in the room could see Dr. Nerome HI tables very clearly, but I happen to have hard copies and it was really gratifying to see that he has several pages of

recently isolated H1N1 viruses from their outbreak and they're all very well covered by the New Caledonia virus.

CHAIRMAN GREENBERG: And Dr. Hoke, I'm sure, is among us who couldn't see that data. Dr. Ferrieri.

DR. FERRIERI: Well, I support New Caledonia based on all of the data presented today, but what we don't have is immunogenicity data that should be generated within a relatively short time, so we need a backup plan if that data is negative and perhaps Roland can comment on that. But that's clearly the best choice for us to go to if everything works out.

CHAIRMAN GREENBERG: Dr. Eickhoff.

DR. EICKHOFF: I concur, based, I think in large part, on the data from Japan.

CHAIRMAN GREENBERG: Dr. Daum.

DR. DAUM: I concur and don't have anything to add to what's been said.

CHAIRMAN GREENBERG: Dr. Edwards.

DR. EDWARDS: I would vote for New Caledonia.

CHAIRMAN GREENBERG: Ms. Fisher.

MS. FISHER: I defer to the CDC.

CHAIRMAN GREENBERG: Dr. Faggett.

DR. FAGGETT: That New Caledonia has a good ring. I support New Caledonia.

(Laughter.)

CHAIRMAN GREENBERG: Dr. Kim.

DR. KIM: I support a New Caledonia strain, particularly with the data that Dr. Cox just shared. I think that's a real issue.

CHAIRMAN GREENBERG: Dr. Kohl.

DR. KOHL: I support the New Caledonia, but I'm a little concerned about isolates 16 to 20, the South American isolates that looks like we're not as well -- is that correct? That they weren't as well neutralized?

DR. COUCH: Yes. I've noted the same thing. But South America, so far, is A/Bayern-like.

DR. COX: Yes.

DR. COUCH: But that may be a result of the number of strains that you've had in hand and on your world chart, it stood out as the only one that had not seen the H1 change, the only major --

DR. COX: Peru had. Peru had, previously, had New Caledonia-like strains. And, in fact, those strains that you're mentioning are Bayern-like. And if you recall, the vaccination studies indicate that

viruses related to Bayern are well-covered by the Beijing/262 vaccine.

DR. KOHL: Well, then I'll withdraw that comment.

CHAIRMAN GREENBERG: Dr. Estes.

DR. ESTES: Well, I think the New Caledonia looks like a good candidate. Again, because of my concern about the new pressure on this virus, I just wondered if we would be wise to wait to be sure that we have typed other viruses that are just coming out now to be sure that there are no other changes. And maybe I'm being -- so I was actually going to suggest deferring this. But, obviously, depending on what the discussion is about the B component --

CHAIRMAN GREENBERG: You've got to do them in order, so what is your vote, Dr. Estes?

(Laughter.)

DR. ESTES: Actually, I vote to defer.

CHAIRMAN GREENBERG: Okay. Dr. Griffin.

DR. GRIFFIN: I think we have sufficient information. I think we have the most information on this; put it this way. We've got to make a choice on one of the three and so New Caledonia.

CHAIRMAN GREENBERG: Okay. And, for the record, I would pick New Caledonia as well. And I

agree with what Diane said, that this was the one that, for me, I thought we had the most information.

I would like a clarification on something that Dr. Ferrieri raised. And that is when a strain is switched, as we are recommending now, how frequently do we have immunogenicity data on what we are switching to at the time we make our decision?

DR. LEVANDOWSKI: Generally, it's very unusual to have access to any data before a vaccine is made. We've been in the position once or twice in the past 10 years where there have been some experimental vaccines that were made when some new variants had been identified at an early point. It's not so easy to get those vaccines made, but they would, if we could have them, would provide very important pieces of information, just to be sure.

Most of the time, I think we've been okay. And it seems like the vaccines are immunogenic, given the fact that measuring immunogenicity is sometimes a little bit tricky. But we, you know, we don't usually have that information.

I suppose it's possible at some point, as we're, both Southern Hemisphere and Northern Hemisphere are using the same vaccines, that it might be possible to get some earlier information, but

probably not in time for us to make a recommendation here.

CHAIRMAN GREENBERG: Because, of course, Dr. Ferrieri's question was critically important, you would hate to switch to a vaccine that was not immunogenic. I just was trying to figure out how, if you were making a new one, you would necessarily have that information.

Okay. It's now noon and, since this committee is hot, I think we should just go on to H3N2 while it's fresh -- I mean -- excuse me -- to B while it's fresh in some of our minds and make our decision. And so, Bob, despite the fact that you were, you know, I let you off the hook and then you bit, so do you want to start off with B again? Or should I --

DR. COUCH: I'll make a proposal then, because I -- the only concern that's been emphasized very well is -- well, let me back up a minute and say last year, you know, we do guesses, you see. And we thought, well, gee, we've had H3N2 two years in a row. We've got to start worrying about B.

And so we fine-tuned the B and it turned out that we had another H3N2 epidemic. And so now we've got three of them behind us and, unless H1 does something a little bit unexpected, B should be here

next year. So that we're back in that same position.

And do we need to fine-tune it? I'd say the data says we don't need any fine-tuning. So the question is whether we need to change the B strain. And I think Nancy emphasized very well that, gee, we've got a whole potload of new viruses coming in. Shenzhen's out in front of us. The epidemiologic data is not in-hand. And so the B information that we want for the definitive decision to stay with Yamanashi versus consider something else is not yet in-hand.

So it's another deferral. I actually suspect that that one will be the February decision and H3 will be the March, but they could be reversed. But I think it's in the deferral status also.

CHAIRMAN GREENBERG: Okay. Thank you, Dr. Hoke.

DR. HOKE: That is my choice also.

CHAIRMAN GREENBERG: Dr. Kilbourne.

DR. KILBOURNE: I would move for deferral.

CHAIRMAN GREENBERG: Dr. Cox.

DR. COX: I concur.

CHAIRMAN GREENBERG: Dr. Ferrieri.

DR. FERRIERI: I support that. And Nancy Cox said there would be more data from Chinese strains in two to three weeks or Roland said that.

concerned that the other candidates to date have demonstrated low yield in vitro, so we may end up having to go back to Yamanashi, though.

CHAIRMAN GREENBERG: Okay. Dr. Eickhoff.

DR. EICKHOFF: I concur.

CHAIRMAN GREENBERG: Dr. Daum.

DR. DAUM: Same.

CHAIRMAN GREENBERG: Dr. Edwards.

DR. EDWARDS: Deferral.

CHAIRMAN GREENBERG: Ms. Fisher.

MS. FISHER: No comment.

DR. FAGGETT: Dr. Faggett defers.

CHAIRMAN GREENBERG: You vote for deferral? Yes. Dr. Kim.

DR. KIM: Defer.

CHAIRMAN GREENBERG: Dr. Kohl.

DR. KOHL: Defer.

CHAIRMAN GREENBERG: Dr. Estes.

DR. ESTES: I agree.

CHAIRMAN GREENBERG: Dr. Griffin.

DR. GRIFFIN: I also agree.

CHAIRMAN GREENBERG: And, for the record, I also agree.

So I'd like to thank the panel for dealing in a very logical way with a very complicated system.

Of course we punted on two decisions, which was, I think, the logical thing to do.

So, because of scheduling issues, I'd actually like you -- it turns out that it would be easiest for us to continue a little while longer and hold your hunger in place. We're going to have 10 minutes of open public meeting which Nancy and Dwight, I just ask whether there's any public -- is there anybody in the public out there who wishes to say something? Okay. Well, in which case, then, there is nobody.

So, then, we're going to have 10 minutes of talk from Dr. Carbone and then we'll adjourn and we will have then ended the public component of this meeting. Kathy, come on up. So we're just switching gears here and Dr. Carbone is going to talk, describe to us the activities of the Laboratory of Pediatric and Respiratory Virus Diseases.

DR. CARBONE: Hi. Actually, today I'm going to describe the two subsections of the laboratory that I head. And that's the Neurovirulence Unit, which is my research group, and Dr. Judy Beeler's research group, the Antigen Immune Response Team.

Next slide, please.

Just to illustrate the two. This is Dr. Beeler's group in yellow. This is my group in yellow here. This is the rest of the laboratory. Of course, the noted Dr. Levandowski is part of our group; Dr. Atreya; and associated members. This group here is an academic group that's working in collaboration with my group at the FDA. I just want to point out that these two new candidates have just arrived in the laboratory, so the work that I'll be describing is really the result of Mr. Rubin, Dr. Pletnikov, Ms. Jones just arrived, and myself.

Next slide, please.

Just to give you a little introduction to the Laboratory of Pediatric and Respiratory Viral Diseases, we regulate the new research on vaccines that are innoculated into virtually every person in the United States, either as an adult or a child. That includes influenza, measles, mumps, rubella, rotavirus, and polio virus vaccines. That's, sum total, about 100 million doses per year.

Over the time since I arrived to head the lab in 1996, at the present time in 1999 or now 2000, we have had an increase in IND reviews of twofold PLAs and supplements of fivefold, but we've managed to increase our scientific publications by twofold. And

I'm very proud of the laboratory for that reason.

One of the reasons, despite about a 50 percent decrease in research funding for the laboratory, is that there have been successful applications for outside funding. And we have the National Vaccine Program Office. Dr. Zoon, the Center Director's Target Award. And we also have our collaborations with academia and the Office of Women's Health at the FDA to thank for these outside funds to continue our research.

Next slide.

So Dr. Beeler and myself, as an introduction, we deal with licensed vaccines. We have a new collaboration with Dr. Levandowski's group that I'll describe later. Dr. Beeler has been working on measles for many years. We've been working on mumps since my arrival at the FDA. We also work on two viruses there. Dr. Beeler and Dr. Atreya work on two viruses: RSV and human parainfluenza virus III. They're not currently vaccines, but they're in research program.

And then, of course, the laboratory has cross-cutting programs which include neurovirulence and human immune responses that we serve as references and act on these areas for the entire division.

Next slide.

So just briefly I'm going to describe in two minutes my program and follow with Dr. Beeler's. Time does not permit us, obviously, to get into much detail so I hope I don't leave everyone too much in the dark. But, in general, when I arrived, I had an interest in neurological disease and viruses. And virus vaccines, of course, have been associated with many neurological diseases. And part of our job is to determine which of those associations are causal and which are coincidence.

In some cases, there's clearly a causal association between certain types of mumps vaccine strains and meningitis; Ural B vaccine, Leningrad III, and Sophia, none of which were licensed in the United States. Polio vaccine has clearly been associated with the polio the disease. Measles vaccine has rarely been described in cases of encephalitis. There are issues of varicella vaccine and questions of latency for this virus in the nervous system.

And then there are several areas that are of great concern to the public and, as yet, the data are not available to know whether this is a causal or a coincidence and more work needs to be done to determine it, but publications have come from

outside, non-FDA and non-government publications, trying to associate the measles, mumps, rubella vaccine and autism; hepatitis B vaccine and multiple sclerosis; and a host of other neurological diseases.

Next slide.

So in my laboratory, we've developed a very multi-disciplinary group to study virus-induced neurological disease and brain development. Because if we're going to determine whether vaccines are safe for use in the population in regards to their infection and damage to the nervous system, it's important to understand how viruses affect the brain.

Because we deal with so many pediatric diseases, we do something that's actually very rare in the United States and that's we look at developmental milestones in terms of virus-infected brains. Now typically people have for years been looking at neurovirulence assays in adult animals. We actually look in the developing nervous system and look for developmental brain damage, which may be more pertinant to the pediatric and newborn populations.

We actually have data of neurochemistry, serotonin changes in the brain, neuroimmunology, we look at cytokines. We have indicates of brain developmental gene up regulation and infection. And

now we have some data which show that sometimes adverse events associated with wild-type virus infection in the brain are dependent upon genetic background of the animal. We use a rat model for these.

We also, in the rat model, have studied behavior as sort of an outcome. This is a very, actually a very sensitive outcome for developmental brain damage. And have determined abnormalities from wild-type virus infections with social/play behaviors, cognizant deficiencies, and anxieties and other emotional disorders. In addition, we've been able to describe anatomical differences.

We use all this information that we gather with the wild-type viruses to try and develop effective vaccine neurovirulence assays to make sure that the vaccines that we use are safe.

Next slide.

Thus far, the accomplishments specifically in the laboratory -- and I'm sorry I don't have time to show you data, so I've referenced them if anybody would like the references. With our emphasis on brain developmental damage, we've been able, with the strong involvement of Mr. Rubin in my laboratory, we've had several publications on mumps virus neurovirulence

assay development trying to get to a small animal assay and avoid the use of primates if possible. This was just returned with very favorable review, so I suspect this will be accepted. We are now starting influenza virus and an HPIV3 neurovirulence experiments.

Mechanism and pathogenesis of virus-associated developmental brain damage, as I described in the previous slide, has resulted in a host of publications coming directly out of my laboratory or collaborations with Dr. Katz and Dr. Plata-Salaman.

And we also have published early last year the first animal model for autism or autistic-like disease associated with neonatal brain damage due to a virus infection. We used Borna disease virus as our agent. And Dr. Pletnikov, a very talented instructor, has published several publications on this model, following our previous 10 years of work. He's has done some tremendous work.

Next slide.

So now I'll move into Dr. Beeler's program. She's also done some slides here and they're very abbreviated, but I'll try to do my best, due to time constraints. Dr. Beeler has an excellent program in virus-host cell interactions. And she is looking

at particularly a virus attachment, two RSV proteins F and G. They are important in attachment in cell fusion.

And the particular interest in this area is -- she's currently got an excellent post-doctoral fellow, Dr. Feldman, working in this area -- is that this is a look at antibody-mediated immune responses to prevent infection and spread of the virus. In other words, if we can find the RSV receptor and the virus attachment sites, there may be ways to target the vaccine to prevent, actually, the virus from even entering the cell or to block the receptor rather than neutralize the virus per se.

This is very exciting work and it's very unique. The RSV receptor has not been defined.

The next slide.

You'll see that this work has resulted in both collaborative and publications coming directly from Dr. Beeler's lab, as well as many submitted publications. And the work is continuing nicely. She also has a nice collaborative publication on human immune response to RSV.

Next slide.

Dr. Beeler has a program on measles as well and has just recently, with Ms. Audet in her

laboratory, published a paper in Biologicals. It was recorded by an international group that there was pestivirus contamination of measles vaccine and Dr. Beeler did a very nice careful study which demonstrates, no pestivirus contamination. It was a very well-designed study and, like I said, just got accepted into Biologicals.

She has a very interesting line of research that she's been working on when time permits on measles vaccine associated thomboytopenia resulted in a publication in '96 and another manuscript in preparation. It's a very interesting publication with very interesting work which suggests that certain factors in cell substrates may cause immune responses that result in anti-platelet antibodies. Excellent work.

Next slide.

She provided this slide and I put it up here to illustrate that in many cases we hear about leveraging resources, both inside and outside the FDA and through leveraging resources in these multiple collaborations that Dr. Beeler has initiated or been asked to participate in studies, it has tremendous impact in the research world through these collaborations as well.

Thank you very much.

CHAIRMAN GREENBERG: Thank you very much, Dr. Carbone. I'd just like to editorialize briefly. As all the panel knows over at least the last couple of years that I've been on it, the FDA-CBER research has been really cut to the bone as far as what their research support is and it's sort of amazing that you and your colleagues continue to be able to be productive in what is an inhospitable situation.

Are there any specific questions for Dr. Carbone before I ask you folks a question about how to proceed? Dr. Estes.

DR. ESTES: I'd like to ask Dr. Carbone, I mean, your laboratory has been very successful at leveraging resources. Do you have a specific mechanism that has helped you? Is there something unique about what you're doing that has been successful in this that would be of benefit for us to know about?

DR. CARBONE: Well, the applications to the NVPO, the Office of Women's Health, Center Director's Target Award are open to everyone. There have been some instances, because I came from academia and was permitted to maintain a part-time academic position at a university, then, through that

mechanism, I am able to be a collaborator on NIH-RO1 funding with approval of NIH and the FDA. They got together. And they have done this in the past. It's done at the CDC. It's done at veteran's hospitals. I can't serve as the primary investigator, but I can collaborate on grants. And that is a very helpful mechanism.

DR. ESTES: Thank you.

CHAIRMAN GREENBERG: Dr. Kohl.

DR. KOHL: Dr. Carbone, I want to congratulate you. I was very impressed by what you've been able to do in the last three or four years. I guess my question is is there anything you desperately need that would help you further in your efforts?

DR. CARBONE: Oh, boy.

(Laughter.)

Christmas. I think it's what we don't need. That's the problem. But I think that I would say that the one major problem has been the shrinkage in FTEs at CBER. And that has necessitated some very drastic measures. We've been lately discussing sharing technicians and rotating them through because there aren't sufficient technicians for everyone to utilize. And that makes it difficult because of the review work we do requires that there be support in

the laboratory.

So FTEs for technical positions would be very important. And this pertains to every laboratory in the division. This is not just my laboratory.

And the second thing would be a somewhat reliable or sustainable source of funding for the research. We've taken some pretty drastic cuts. And, unlike an NIH-RO1 mechanism, which I had an RO1 for 10 years, on the outside, we get funded year-to-year. And that makes it very difficult to maintain a program as opposed to the three-to-five year continuous funding you'll get from an RO1.

So, really, more funding and more personnel. I think that the CBER environment is extremely supportive and talented. The administration and management is very supportive of the research program. We're dealing, I think, with external issues.

CHAIRMAN GREENBERG: Ms. Fisher.

MS. FISHER: Yes, I'm curious because there is a lot of publicity about record amount of money that is being allocated to HHS for scientific research. Why is the FDA's research program somehow not getting a part of this pie? I mean, am I --

DR. CARBONE: That's a little above my

area.

MS. FISHER: Well, I mean, I don't understand.

CHAIRMAN GREENBERG: I think when Dr. Goldman addresses us in closed session, I think that's a spectacular question to ask him.

DR. CARBONE: Yes. That's a good person to ask.

CHAIRMAN GREENBERG: Dr. Carbone, probably doesn't -- if you have a speculation, feel free.

DR. CARBONE: No, I really wouldn't.

CHAIRMAN GREENBERG: I would invite you to leave it to the people who can take more heat.

DR. CARBONE: Yes. I'm down here looking up. That's all I am.

CHAIRMAN GREENBERG: Okay. Any other questions? I would simply say one thing that just because Dr. Carbone and her colleagues have been successful, that should not indicate that anybody I think on this committee thinks that the current level of support is appropriate. I would say this, if anything, your success has occurred despite what's happened to you, not because of it.

Okay. You have a choice here as a committee. We can move right now into closed session

and review the lab. Or you can go for lunch and come back and we can move into closed session and review the lab. I'm happy either way, but I want to give people on the committee the -- I think Dr. Griffin, who ran the review of this lab, says it will be quite expeditious to do that. So she votes closed session. The rest of you?

Okay. So I'm dismissing the audience and the consultants, with tremendous gratitude. And you all did a great job.

(Whereupon, the proceedings went off the record and resumed in Closed Session.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: Vaccines and Related Biological Products Advisory Committee

Before: DHHS/FDA/PHS/CBER

Date: January 28, 2000

Place: Bethesda, MD

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.