DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

VACCINES AND RELATED BIOLOGICAL PRODUCTS

ADVISORY COMMITTEE

OPEN SESSION

Thursday, January 30, 1997

8:12 a.m.

Holiday Inn Bethesda
Versailles I and II
8120 Wisconsin Avenue
Bethesda, Maryland

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Nancy Cherry, Executive Secretary

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Dr. Claudia Dade

Dr. Theodore Eickhoff

Dr. Arthur L. Reingold

GUEST

Dr. Edwin K. Kilbourne

FDA

Dr. Roland Levandowski

C O N T E N T S

P R O C E E D I N G S

DR. FERRIERI: Good morning, everyone. I would like to welcome all of you to our meeting of the Vaccines and Related Biological Products Advisory Committee Meeting. I think we can start by doing our introductions around the table, starting with Dr. O'Brien.

DR. O'BRIEN: Dr. Alison O'Brien, Uniformed Services Medical School in Bethesda.

DR. BELSHE: Dr. Robert Belshe, St. Louis University.

DR. GLODE: Dr. Mimi Glode, University of Colorado, Denver.

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

DR. COUCH: Dr. Robert Couch, Baylor College of Medicine.

DR. CLEMENTS-MANN: Dr. Mary Lou Clements-Mann, Johns Hopkins.

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

DR. HALL: Dr. Caroline Hall, University of

Rochester, New York.

DR. EDWARDS: Kathy Edwards, Vanderbilt University.

DR. MEIER: Paul Meier, Columbia University.

DR. DADE: Claudia Dade, Elmhurst Hospital, New York City.

DR. REINGOLD: Art Reingold, University of California, Berkeley.

DR. LEVANDOWSKI: Roland Levandowski, Center for Biologics Evaluation and Research.

DR. FERRIERI: Thank you very much.

I thought we would begin by paying a tribute to Jack Gertzog, who many of you knew and many of us here on the committee worked with Jack in our past rotations on the committee. Jack, who was director of the Scientific Advisers and Consultant Staff, died on December 13th.

He will be remembered by many of us for his devotion and activities on behalf of all of these advisory committees and how he interacted with us.

I would like you all to stand for a moment of silence in tribute to Jack.

[Moment of silence.]

DR. FERRIERI: Thank you very much.

I will turn the meeting over now to Nancy Cherry for some of the basic issues and administrative matters.

Call to Order

MS. CHERRY: My statement is short this time.

This announcement is made a part of the record at this meeting of the Vaccines and Related Biological Products

Advisory Committee on January 30th, 1997. Pursuant to the authority granted under the committee charter, the Director of the FDA Center for Biologics Evaluation and Research has appointed the following individuals as temporary voting members for the discussion of the influenza virus vaccine: Drs. Broome, Couch, Eickhoff, and Snider.

It should be noted that Dr. Dixie Snider, who we just named, could not be with us today.

Based on the agenda made available, it has been determined that all committee discussions at this meeting including the formulation of the influenza virus vaccine for the 1997-98 season, the review of a research program, and updates of recent activities in the Center for Biologics Evaluation and Research present no potential for a conflict of interest.

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

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

DR. FERRIERI: Thank you, Nancy.

As many of you know from looking at the agenda, we will be spending all morning on the influenza virus vaccine formulation. I would like to bring everyone's attention to the fact that we have a very tight agenda and everyone who is speaking must absolutely adhere to the time that has been allotted to them.

I will now turn the meeting over to Dr. Roland Levandowski from FDA.

Session 1 - Influenza Virus Vaccine Formulation

Introduction

DR. LEVANDOWSKI: Thank you, Dr. Ferrieri.

Dr. Ferrieri, committee members, ladies and gentlemen. I would also like to welcome you to Bethesda. I think most of you who are here have probably been here before and know what the agenda of business is for this morning.

What we need to do is to start the process of selecting the strains that go into the vaccine, the influenza virus vaccine used for the United States for the coming year. Just by way of a small review, I would just

like to remind everybody that we went through this process last January, began it.

At the completion of the process, the vaccine formulation that had been selected included the strains

B/Harbin/07/94, A/Texas/36/91 as the H1N1 influenza A component, and A/Nanchang/933/95 as the influenza A/H3N2 component.

Subsequently, those vaccines have been made, distributed, and are being used now, and as you will hear, we are in the midst of a fairly substantial epidemic of influenza.

The information that we will be addressing to try to make strain selections will include information on the antigenic properties of newly circulating strains. In addition, the surveillance and epidemiology of those strains with information about the spread and impact of them in human populations will be evaluated, and finally, information on the serologic responses of individuals who have been immunized with the current vaccines will be used to try to understand whether changes need to be made in the current vaccine formulation.

There are handouts that are available or may have been available. If there are individuals who would like to have those, who didn't get them, we will need to hear about that after the fact. We won't be able to make any more of

them at the current time.

Just by way of housekeeping, there will be a break that is taken, but as Dr. Ferrieri has already pointed out to us, the time is very short for us to do all of the

business that we have to do, and I would appreciate greatly if people would scurry back here. I will warn you that we may be starting without everybody present if they are not here at the time the presentation needs to begin.

I would also like to remind our speakers that we do need to be brief and to the point, and stick to our time limits in order to squeeze in what is a very full agenda of business.

This year we are very pleased that we have a number of international guests who will be giving us reports on what is happening in their own home countries, and I think that this information will be very important supplemental information to what we are hearing about for the United States.

So, having said that, we will get started. I will ask Dr. Keiji Fukuda if he will approach the microphone and get us started on U.S. surveillance.

U.S. Surveillance

DR. FUKUDA: Good morning. I am going to discuss U.S. surveillance in a few minutes, and I will try to be very brief.

The take-home message is that the influenza season or the influenza activity in the United States appears to have peaked in the latter part of December and the early part of January, and we are on the down slope of activity,

however, we have not yet peaked in terms of influenza-related mortality or death.

[Slide.]

As you can see from this graph here, we have three different parameters that we follow in the influenza surveillance system, the top one being isolates which are identified during the season; the second one being influenza-like activity reported by states; and the third one being influenza-like illness reported by sentinel physicians. I will go over these in a little bit more detail.

[Slide.]

As of January 18th of this year, approximately a little over 20,000 respiratory specimens had been tested for respiratory viruses, and of these, a little under 4,000 were positive for influenza. The vast majority, 97 percent of these, have been influenza A shown in the red and the white bars. Of those that have been subtyped, all have been influenza A(H3N2).

You can see capping the bars are these little yellow blocks, and these represent influenza B or 3 percent

of the total. You can see that these have increased a little bit in the latter half of the season, but it really makes up a very small proportion of the entire number.

[Slide.]

In terms of influenza activity reported by the states, again, you can see it really peaked around the latter part of 1996, and that at the peak of reporting, 38 states were reporting either widespread or regional influenza activity in their states.

[Slide.]

In terms of influenza-like illness being reported by approximately 140 sentinel physicians in the United States, this peaked at about 5 to 7 percent again during the latter part of December and early part of January.

[Slide.]

Now, unlike the measurements for morbidity, we have not seen mortality peak yet. This typically lags behind morbidity by about two to five weeks or so, and right now or as of January 18th, influenza-related mortality, P&I mortality, was at about 8.6 percent.

You can see or some of you can see that there is a sort of sinusoidal wave, and this represents the expected number of pneumonia and influenza-related deaths if there is not an epidemic, and you see from the bold yellow line that it has exceeded that threshold.

The previous peak over here represents the 1993-94 season, which was also predominantly an H3N2 season.

[Slide.]

Now, in terms of geographic distribution,

influenza really has been widespread through the country. This map here shows influenza activity reported by the states, and this was as of November 9th. The yellow represents regional activity, red represents widespread activity. So, you can see that in mid-November we really had little influenza-like activity being reported.

[Slide.]

By a month later, in early December, early mid-December, we can see that activity had begun picking up largely all over the country and no particular concentration in one geographic region.

[Slide.]

Then, around the week of January 4th, which was about peak influenza activity, you can see that it was really being reported all over the country at fairly high levels.

Anyway, I think that I will conclude there. I don't know if you take questions now or after, however you want to do it.

DR. LEVANDOWSKI: If the committee has any questions, they certainly should raise them at a convenient

time, which might be now.

Dr. Couch.

DR. COUCH: Actually, it is relatively minor, just a clarification question. How do you define the states as

regional or sporadic or widespread?

DR. FUKUDA: The states basically have a menu on how they can report influenza activity, and it is four different levels or three different levels: no activity, sporadic activity, widespread activity, or regional activity, which is defined as influenza-like illness being reported in counties making up less than 50 percent of the entire state population, and then widespread activity is reported as influenza in counties representing more than 50 percent of the state population.

DR. COUCH: To what extent was the physician network set up to try and be representative of the entire country, the sentinel physician network representative of the entire country?

DR. FUKUDA: Well, I wish I could say that it really was. It probably really isn't. It is 140 physicians, and that is insufficient to cover the country. What we would like to see is that number increase, so it is a little bit more representative.

DR. COUCH: But they are widely dispersed in the country.

DR. FUKUDA: They are widely dispersed throughout the country.

DR. LEVANDOWSKI: Thank you, Keiji.

We will move on. Dr. Helen Regnery from CDC will

give us some information about world surveillance and strain characterizations.

World Surveillance and Strain Characterization

DR. REGNERY: I would like to join Roland in saying welcome to come of our international visitors today. I think it is really great that we can have international visitors at this meeting to give us an emphasis on local influenza.

Today, I will update you on the antigenic analysis of influenza viruses, the recent strains that we have gotten, and the frequency of isolation both in the U.S. and worldwide.

I will start with influenza B and then I will go to H1 and then H3. The handout has all the transparencies that I will be using today, and for those folks who are in the back, I think we have a large number of handouts this time, so everyone should be able to follow the HI tables in the handout, because I know you are not going to see them from up here.

[Slide.]

The frequency tables that we have put together

began in October 1995 and span through the influenza season and going through the summer months of the year and ending up with our current time period.

In the U.S. last year, we had sporadic isolations

of influenza B pretty much all year except for one month here in July. We had an outbreak reported at a university and a nursing home during this period of time.

In Canada, there was a minimal amount of influenza B, as well as in Europe, there was some outbreaks, but very little influenza B. Europe is reporting now sporadic and outbreak material. In Romania, we have an outbreak of influenza B, as well as in Spain, we have an outbreak of influenza B.

South Africa, Australia, and New Zealand have been reporting sporadic isolations of influenza B during their flu season, as well as Central and South America.

Asia, we have again sporadic occurrence of influenza B throughout the year with a couple of epidemics. The B outbreak here in December is in China.

[Slide.]

We will go next to the HI. What I would like to do this year, so that the visual is a little bit larger, all of the HI results that I will be showing were done on the same date, but I am splitting them up, so that perhaps we can see them a little bit better.

This is our reference battery for the influenza B viruses. B/Guangdong/05/94 is a B/Victoria-like virus. We have included Guangdong/05 in our reference battery for a couple or three years now when there was an increase in

isolation rate in China and also in Hong Kong.

We have not identified any B/Victoria-like viruses to date outside of China and Hong Kong, but we do keep it in our battery. We keep also the B/Panama/45 vaccine strain, the Beijing/184 recommended vaccine strain, as well as the vaccine strain itself B/Harbin/07.

We also have included recently B/Nanchang/24/96. This is a recent isolate from China, and was picked for serologies to have an updated strain. We have not been seeing a lot of antigenic variation with the B viruses, but to be able to understand what is going on, we will usually pick a recent strain for the serologies, and also put it into ferrets for your HI comparison with your current strains.

B/Russia/22 is another recent virus, as well as the last B virus -- well, not the last -- but B/Alaska/12 is representative of the U.S. strains for this year.

You will see that Victoria viruses are very distinct from the Yamagata lineage B viruses. We have been having most of our viruses in the Yamagata lineage for several years now. You can tell the differences between

Panama and Beijing and Harbin in that the homologous titer is reduced with Panama antisera.

In all of our tests, Beijing/184 and Harbin were essentially identical. The Nanchang that we used this year

produced a high antibody titer in the ferrets, but it still is very much like the Harbin strain. If you compare Harbin and Nanchang/24 antigenically, they are pretty much identical.

The Russian strain did not produce as well antibody in ferrets, and the titers are a little bit lower, but again, the Russian strain is antigenically like our Beijing/184 and Harbin/7. The same is true for Alaska/12.

Now, on all of my slides, I will have one star indicating the serological antigens that you will be hearing about later on, so Guangdong, Beijing, Harbin/07, Nanchang were included in the CDC serologies.

In addition, as we discuss the viruses, Nancy Cox will be presenting the genetic data for these viruses, and we put two stars by this, so that you can relate the antigenic character to the genetic tree.

[Slide.]

This shows the group of test viruses that we used for demonstration for the influenza B viruses. We have this group of viruses from the U.S. collected May, June, and October and December, and you can tell that they are well

inhibited by the Beijing/184 antisera with the homologous titer of 640, as well as with the Harbin/07 antisera.

We have one recent strain that we received from Maria Zambon in England, and it is Beijing/184, Harbin/07-

like also.

The recent strains that we have been looking at from Asia, that we have received, and were collected in June, September, and June again from China, Hong Kong, and Taiwan, again are very similar strains and are very well covered by Beijing/184.

The summertime brings us to the Southern Hemisphere for epidemic activity, and this group of viruses is from this past year, in September and August for Brazil, as well as the 1996 season in New Zealand. Again, the viruses are homogeneous.

Now, we still are receiving viruses that are clearly Victoria-like. These are some of the latest ones that we received on May and June. Here, you can see that the Hong Kong/70 is reduced from a homologous of 64, and leads us to believe that these viruses are constantly evolving, just as the Yamagata lineage is evolving.

[Slide.]

If we take a look now at the B viruses that we characterized in our laboratory last year, it is on page 11, you can easily see that there is not as many influenza B

viruses hardly at all that we have been able to characterize this year. Only five isolates actually have been included in our tests from the U.S. However, we have got quite a few viruses coming in now for influenza B, just as Keiji was

showing a little bit of a blip for flu B.

Last year, most all of our viruses except for one were Beijing or Harbin-like, and during the summer months, we still had, as you saw on the worldwide activity, we had quite a few sporadic isolates in the U.S., and it totaled 66 that we analyzed during the summer months this year.

Europe, again, is Beijing-like viruses, and Asia, the one isolate of Victoria and then 26 isolates of B/Harbin. Most of the Victoria-like viruses have been coming from the southern part of China, and we had 18 Victoria-like viruses collected during April to September of 1996 last summer in comparison to 19 of the Beijing-Harbin lineage.

Central and South America, we only had 9 isolates. Again, they were Beijing-Harbin-like, and as well in the Southern Hemisphere, only 2 isolates.

I think the influenza B viruses are straightforward antigenically. We are not seeing a lot of changes, and the activity level is fairly moderate to low worldwide.

Are there any questions on B viruses?

DR. BELSHE: Could I ask you a question on B?

DR. REGNERY: Sure.

DR. BELSHE: We have worried about the B/Victoria persistence in China. Have you actually seen B/Victoria

viruses outside of China?

DR. REGNERY: Hong Kong. Hong Kong keeps reporting some B/Victoria-like viruses.

DR. BELSHE: And over the period of time, it wasn't clear what was China out of the Asia set. What is happening to the balance between Victoria and B/Harbin viruses in China with time? Is it turning to more B/Harbin?

DR. REGNERY: It is still primarily B/Harbin.

DR. BELSHE: In China?

DR. REGNERY: In China. The numbers are higher for B/Harbins.

DR. BELSHE: B/Victoria is just there persisting somewhere.

DR. REGNERY: It is still there circulating.

DR. BELSHE: Do you know anything about the age of patients that are circulating in?

DR. REGNERY: For B/Victoria viruses?

DR. BELSHE: Right.

DR. REGNERY: No, I don't actually. I do have that data, but I haven't looked at it carefully. I am not sure whether it is primarily children or adults.

[Slide.]

Influenza H1N1 surprised us last year after having a period of time when we did not have H1 viruses. We thought they may disappear, but in the U.S., it was our

predominant virus for the season last year.

There was also H1 activity in Canada, as well as Europe, and then in South America, Australia, and New Zealand, there was scattered activity of H1 viruses. Central and South America reported more H1 activity than South Africa, Australia, and New Zealand, but not at tremendous levels.

The one epidemic bar for Central and South America was from Guyana, French Guyana, and then the second epidemic bar occurring in June, was from Chile. So outbreaks and sporadic activity.

In Asia, there was a fair amount of H1 activity also, in Japan, and Israel also had reported outbreaks in January. The summer months of the year saw just sporadic activity occurring in Asia.

[Slide.]

For our battery on the H1 viruses, it looks like a very large battery, but most of the viruses were recently added to look a little bit retrospectively because we haven't had any H1's to look at recently. So, all the data for the H1 viruses are primarily collected several months

ago to last year.

We keep Taiwan in our battery. It is an '86 virus. We use this one in our battery because it helps us to identify the Texas/36-like strains. Texas/36, our

vaccine recommended strain, and Texas X-113, the recombinant used in the vaccine.

We also have Moscow/01, which is a virus that is an egg isolate. It matches the consensus sequence for the H1 viruses, and was chosen as an alternative to look at if we decided that the H1's were starting to drift enough to consider updating the vaccine.

The Bayern/07/95 is also an egg isolate, and it was a representative isolate from Europe last year. Shanghai/07/96 is a virus that we have looked at recently that appeared to have a pattern that is similar to a few other H1 viruses that we have seen in that from the Taiwan, the Taiwan antisera, if you look down at Taiwan antisera, you can see that the Shanghai/07 is reduced from the homologous titer, as well as the Texas/36 is also reduced only twofold, but we have had several viruses that have been reduced with Taiwan, as well as being reduced with Texas/36. Shanghai/07 was picked more or less as a representative of that, so that we could analyze the reactions in ferrets and also choose for the serologies to determine if there is indeed any differences in the viruses.

If you look at the Shanghai/07 ferret antisera, which is No. 7 across the horizontal row, and compare it to the Texas/36 and Texas/X-113, there are very good comparison between those antisera, so it is not significantly different

from our most prevalent viruses that we see.

The other interesting fact about H1 viruses is in the last year, about July, there was an H1 virus that was identified who gave this terrificly low titer reactions to all the reference antisera that we had. When this was analyzed further, it was truly an H1, and last year was presented as Wuhan/371. It is a deletion mutant, and it has very little cross-reactivity with the currently circulating strains.

[Slide.]

Now we can go and look at some of the test viruses that we have for H1's. The viruses that we had last year as H1/s, December 1995, and one that was collected during the season, as well as in January. All conformed to being Texas/Taiwan-like. We also have Canadian virus that is Texas/Taiwan-like.

During the summer months, the H1's that occurred in Brazil and South Africa and China were again fairly homologous, nothing really exciting to look at necessarily. The Shanghai/08, the last antigen on the chart, that is included in some serologies, as well as being sequenced, has

the differences we were talking about with being reduced with the Taiwan antisera, as well as being reduced with the Texas antisera, so we are seeing a few of these viruses, and whether that indicates that we might start seeing a drift

from the Taiwan-like viruses is not yet clear.

When I reviewed the data, I found that out of the number of U.S. viruses that we characterized last year for the Shanghai/08-like reaction pattern, there was about 11 percent, and on the foreign level, there was about 12 percent.

[Slide.]

Now, the deletion mutant variants, the Wuhan/371 and the Beijing/262, which is representative for this year, are still being identified in China and Hong Kong, and this is a very clear reaction pattern over on the righthand side of the chart, and these particular isolates were collected in July, August, and September.

I think we can actually go to the frequency table now.

[Slide.]

So all the Taiwan/Texas-like viruses in the U.S., North America, Europe, Central and South America, and the Southern Hemisphere worldwide. If we look at the Beijing/262 deletion mutant viruses in Asia during the wintertime last year, there were 21 viruses for a percentage

of 5 percent of the ones that we tested.

During the summer months, there was an increase to 39 viruses, and this calculated out to be 55 percent of the viruses that we have characterized from Asia.

That total number is 115 that were characterized in Asia.

Down at the bottom is a pie chart that shows the worldwide frequency for H1 strains, the Taiwan/Texas being the majority with 95 percent last year from October to March, and the Wuhan/171 being about 5 percent, and then in the summer months, the increase of Wuhan to 54 percent compared to 45 for Taiwan, and that is not a lot of viruses, but that is the percentages that we are seeing.

As we were leaving CDC yesterday, Nancy Cox got information from Mill Hill that they had their first Wuhan/371 isolate from Switzerland, and it was an adult who was hospitalized, and there are seven other possible Wuhan/371-like viruses to be determined that they would be Wuhan/371, but definitely one confirmed, there has been no history of travel to Asia at this time, and the information is a little bit sketchy, but it seems to be firm.

DR. COUCH: Helen, the same question I had a while ago, and you partly answered it there, but is A/Wuhan outside of China in Asia, is it in Japan?

DR. REGNERY: This is the only one.

DR. COUCH: That is the only one outside of China?

DR. REGNERY: That we know of and that we have tested, and, of course, we don't get all the viruses like, you know, I don't have a good representative sample from

like Japan, Singapore, sometimes, and in some of the other neighboring countries. We have a fair amount from Korea, but, you know, we could improve our surveillance outside of China.

DR. COUCH: How about Hong Kong?

DR. REGNERY: And Hong Kong.

DR. COUCH: It's in Hong Kong.

DR. REGNERY: Yes, it's in Hong Kong. Hong Kong is running right neck and neck with China.

DR. BELSHE: Helen, could you refresh our memory on the nature of the deletion mutations?

DR. REGNERY: Yes. I think Nancy will go over that when she gives her talk.

Let's talk now about our H3 viruses.

DR. LEVANDOWSKI: Helen, before you go on, Dr. Kilbourne, who is here as one of our consultants, but isn't up at the table, has a comment that he would like to make. There is probably a space for him up here somewhere. I know it has been tight, but please come up here.

DR. KILBOURNE: I would like to remind everybody that there are two surface antigens on this virus. Thus far

we have been talking about serologic reactions, but on the hemagglutinin. We have looked at the Beijing/262 with respect to the neuraminidase, and our preliminary serologic information would indicate that there is very little

inhibition by the Texas or Taiwan antisera of that neuraminidase, so that is something to take into account if you are making any kind of decision.

DR. REGNERY: Thank you, Dr. Kilbourne. That is very useful information.

Dr. Couch, I just remembered I had one of the collaborators in Hong Kong recently look at her H1 viruses that she had collected over the last year, and out of that, there was about 17 percent of her viruses were the Wuhan/371-like.

[Slide.]

H3 keep us busy never mind H1. Last year, of course, H3 circulated worldwide with considerable activity in the U.S. and Europe, as well as in Asia, and during the summer months we also continued to have outbreaks and sporadic isolations throughout the summer in the U.S., and now we are experiencing the epidemic of H3 viruses in the U.S.

Canada is also reporting outbreaks of H3 with sporadic isolations, as well as Europe is experiencing H3 viruses. During the summer months, the H3 viruses were very

prevalent and very popular in the newspapers in various areas, too, for a lot of increased activity especially in New Zealand and Australia, as well as South Africa, and Alan Hampson, I am sure is going to be telling us more about

those viruses.

In Central and South America, it is seemingly that their season skipped over a couple of months this year, and didn't actually end up until probably November with still outbreak activity.

One of the things that was interesting this summer to us at CDC was some of the South American countries are not up to date necessarily on diagnosing influenza, and there was a lot of increased activity and a lot of concern about what was going on, and in particular, Colombia contacted us at CDC, concerned about the epidemic they were having. Colombia had not done influenza laboratory work for 10 years, so consequently, we were very pleased to be able to send one of our people to Colombia to identify the virus and bring it back and characterize it, and it was Wuhan.

In addition, there was Wuhan-like activity in French Guyana and several other places that don't -- they say they don't normally have flu, so it was severe enough to make them look about what was happening.

Asia is just blocked up with H3's, a lot of H3 activity last year, as well as this year, in China.

It is going to take me just a little bit of time to go over the H3 battery, but I think it is important to do so slowly. We have Johannesburg/33, which is our previous vaccine strain. We have Alaska/10. Alaska/10-like viruses

started showing up in the U.S. last year. In most of the HI tests, Alaska/10 is twofold lower than the Johannesburg, not in this particular test, but invariably, it is two and sometimes fourfold lower.

So, we started seeing quite a few viruses that were reduced to Johannesburg, and then would react to a high titer with Alaska/10, and this is that group of viruses here.

The Wuhan/359/95 cross-reacts with Alaska/10, but it is distinct in most of the tests here. It is pretty much twofold across, but it is definitely distinct, the viruses, as you will see some of the viruses will be different.

The Nanchang/933 is the antigenically identical virus that was chosen for the preparation of the vaccines last year, and if you compare the antisera, you will see that they are very closely identical.

The New York/37/96 was an outbreak virus, and you can see that this particular virus -- and also was put into our serologies -- is Wuhan-like or Nanchang-like.

Fujian/47/96 is a recent Fujian virus from China, and we put this particular virus into serologies and started

including it in our HI test as an alternative egg isolate for vaccine production if necessary. By sequence, it is very close to Wuhan/359 and Nanchang/933, and as you compare antigenically across the row, it has the same antigenic

profile as Wuhan and Nanchang.

The Fujian antisera again confirms its relatedness when you compare its reactions to the Wuhan and 933.

The South Africa/1147/96 virus is a virus that we have received recently in our laboratory from Mill Hill, and this virus, Nancy will show you forms a subgroup, genetic group, that is distinct among itself, however, it may be a little bit low reacting in our HI test, but it is still pretty much Wuhan.

The antisera for the South Africa is a little low, which makes it sometime difficult to really see if there are differences, and there are differences when you point these out, but overall, the South Africa viruses have been considered to be related to the Wuhan-like viruses, and maybe the small differences we see might be attributed to some of their amino acid changes.

The Auckland/05/96 is a representative strain from New Zealand from their epidemic season, and it is truly Wuhan-like. The Nanchang Resvir-9 is the reassortant that is used in the vaccine this year. More recently we started including some of the reassortant viruses to run with our

test antigens. We haven't done this a lot, about three tests or so. The Resvir-9 is identical to Wuhan/Nanchang, as well as the X-125, and then Auckland/5 reassortant IVR-99, likewise is Wuhan.

The homologous titers for the reassortants is 320 for Resvir-9, which is a little bit low. It is 112/80 for X-125 and 640 for IVR-99.

[Slide.]

If we look at some of the viruses that we have tested this year, the first overhead, we are going to take you back actually to last year, February 1996, to start to look at the Wuhan spread story, which has really been quite rapid.

When I was here at the meeting last year, we had a few Alaska/10-like viruses identified. We had no Wuhan-like viruses. February, there was a ship outbreak, the USS Arizona, so severe that they brought the ship back into port. The people onboard the ship, almost 100 percent, were ill, varying degrees of severity of illness, but ill. These folks were vaccinated, being in the military, with Johannesburg.

The Alaska/02 was an isolate in July. It is from a sporadic case, and it has been sequenced, and will be on the sequencing tree. Hawaii in July had a nursing home outbreak and increased activities in July.

Wisconsin, at a university, had an outbreak in September. New York/43 is from an HIV-positive patient in November, and a New York/50 is a nursing home outbreak that occurred in November, and the population had been previously

vaccinated in October.

Indiana/01 is a sporadic isolate, and New Jersey/08, in December, is an outbreak, and then the Texas/09 is also a sporadic isolate, but if you look, all the titers are very homogenous and within two of Wuhan and Nanchang, so they are definitely Wuhan-like viruses.

The Resvir-9 with a homologous of 320 covers these viruses, inhibits these viruses pretty. With X-125, we saw some reductions with some of the test antisera, and then with Auckland, other IVR-99, there was reduction with the Texas, not consistent.

DR. LEVANDOWSKI: Helen, I am sorry to interrupt, but we will need to move on. If you could summarize the next tables fairly quickly for us, please.

DR. REGNERY: Okay.

[Slide.]

We have the group of viruses from China, recently collected from July, August, and May. Again, all the viruses are fairly homogeneous with a few viruses that are reduced from the Wuhan and Nanchang. Again, coverage is good with IVR-99.

[Slide.]

Viruses that were received from Colombia, French Guyana, and Guadeloupe, Brazil, and Trinidad, are the first group in October and November, are Wuhan-like viruses. We

had one virus from Brazil that is low-reacting. This particular low reaction pattern is also seen in some other viruses, in fact, I think it is about 6 or 7 percent that we have seen a low reaction pattern.

Also, Alan Hampson will be talking about Auckland/108, which is a low reactor. Victoria virus from Australia is Wuhan-like, and with South Australia, there is some reduction with the Wuhan/Nanchang.

In France, we have another virus that is a low-reacting virus, as well as having other viruses that are more clearly Wuhan-like.

[Slide.]

This is an HI table with the most recent H3 viruses that we have from the U.S. We have a few that are reduced with the Nanchang, and one that is reduced with Wuhan, but overall, the viruses are Wuhan-like. As far as coverage with one of the reassortants, we get good coverage with X-125 except for one and except for two with IVR-99.

[Slide.]

So the trend has been and it has been very dramatic with Wuhan/359 because of its initial

identification in July probably of 1995, and then spread to the U.S., most of the H3 viruses have taken about two years before they reached the U.S., and this one was much quicker. Last season, by the time we had all the viruses in the lab,

we had 26 Wuhan-like viruses.

During the summer months, we had Wuhan viruses, and today, the majority are Wuhan-like virus.

North America, we don't have too many viruses to analyze from North America, and Europe, by the end of the season, had a small number of Wuhan-like viruses. In Europe so far, their viruses have also been Wuhan-like.

Asia, the same repeating pattern of being increasing or consistently a larger number of Wuhan-like viruses. We haven't had that many viruses yet from Asia. We have a large shipment coming from China, and we will probably fill in this gap. Hopefully, not another variant will be found.

Central and South America, again, Wuhan-like viruses. The pie charts at the bottom just emphasize what we have here on a worldwide basis from October being 59 percent, and 30 percent Johannesburg and Wuhan, and then increasing amounts of Wuhan-like virus in the summer months, and then finally, presently.

[Slide.]

A quick summary of the influenza B viruses world

activities at low levels. There are some influenza B viruses being submitted to us currently for analysis. The majority of the strains are well inhibited by Beijing/184 and Harbin/07. To date, the strains currently match the

vaccine and B/Victoria-like viruses continue to circulate in China and Hong Kong only.

H1 viruses. There is few reports of recent activity. There is few, if any, current strains available for us to analyze, and to date, most of the strains are Taiwan or Texas-like.

The deletion mutant/262 or Wuhan/372 have not been seen outside of China until recently identified in Switzerland.

Influenza H3 viruses. Epidemic level activity in most of Northern Hemisphere countries. The majority of the strains are well inhibited by Wuhan and Nanchang, and to date, the epidemic strains match the vaccine strains, and I feel it is pretty important for us to analyze the current strains that we will be receiving from China, and also to continue monitoring the low-reacting strains that we have seen in South America and Australia, and a few in the U.S.

DR. LEVANDOWSKI: Thank you. We are a little bit behind, but if there are some particularly important question from the committee, we should entertain that now probably.

If there are no questions, we will want to move on, and I will ask Dr. Maria Zambon from the Public Health Laboratory Service in London if she will give us her information.

International Reports

DR. ZAMBON: Good morning, ladies and gentlemen. Thank you very much for inviting me here to speak today, and I hope to update you on the situation in the United Kingdom and, where possible, reference any parallels that exist in the U.K. with the European situation.

[Slide.]

My first slide is a summary of the epidemiological situation and the way that we collect data in the United Kingdom. We have a number of indices which we use to inform us of influenza and influenza-like activity in the United Kingdom analogous to the situation here in the United States.

One of the most informative indices that we use is the Sentinel Physician Index, called the RCGP consultation rate, which is derived from an index of consultations to 100 general physicians scattered throughout England and Wales, and because the denominator population is known, we therefore derive consultation rate per 100,000 population.

For nine months of the year, this consultation rate remains below 50, and we are agreed, based on the past

10 years worth of experience in looking at this index, what we can describe as influenza-like activity in the United Kingdom.

We are agreed that a level of over 200 represents

moderate influenza activity, and a level of over 400 represents major epidemic influenza activity in the United Kingdom. The situation of major influenza activity in the United Kingdom has only arisen once in the last 10 years, which was in 1989.

So, this year our activity could be described as moderate, peaking in weeks 1 and 2 of 1997, although there was probably some reporting after the fact over the Christmas period. So, this is shown in this pink line here.

The dotted line here represents the number of isolates which we have received and analyzed in the Virus Reference Division, which is the national influenza laboratory for the United Kingdom, and the histogram blocks represent the surveillance scheme which we also run directly from the Virus Reference Division in Colindale, representing swabs taken from sentinel physicians, and the lower blue line representing the positivity rate for influenza.

So, all of our indices indicated influenza activity commencing in mid-November, rising to a peak in the first couple weeks of January, and then just as in the United States, we are on the down slope. I suspect that is

also the situation in the U.K.

[Slide.]

Our isolates, we have currently looked at 300 or so from throughout England, Scotland, and Wales, and the

majority of the isolates that we have looked at have come from the south and central regions, which does not reflect necessarily clinical influenza activity, but rather the density of hospitals and density of populations, which are the source of many of our isolates.

[Slide.]

If we look at the number of isolates week on week in the '95 and '96 season, we can see that this season here has been predominantly H3N2 thus far, although we are starting to see a little bit of B activity in the early weeks of this year.

Last year was also predominantly H3 activity, although we saw some H1N1 activity towards the end of the season, which was February and March. The green line here is the clinical index, the RCGP index, so our peak activity here correlated with H3N2, but interestingly, the H1N1 activity that we saw was not translated into clinical activity.

[Slide.]

Just to prove that China is not the only source of interesting potential pandemic strains, our excitement last

year came from the isolation and detection of an H7N7 virus recovered from a human being, which was the result of a direct avian to human transmission. I am pleased to say we have no evidence of transmission of that virus.

[Slide.]

Now, if we look at the age distribution of the isolates that we have looked at this year, we can, because of the surveillance schemes that run in the United Kingdom, separate them broadly into two categories: those which we receive directly from the community, and those which we receive from other laboratories within the United Kingdom, and that allows us to say something about community-based illness and the illness represented by these isolates here, which is largely hospital-based illness. So, that says something about the age groups which are actually being hospitalized with influenza.

Interestingly for us, and in contrast to the last season, the majority of the isolates that we have received this year from our community scheme have come from individuals aged 16 to 65.

We also see a fair percentage of hospitalized isolates coming from the same age group, but what we have here is that the majority of the isolates coming from hospitalized patients have come from children under five, which is not reflected in the community particularly.

The reason that is of interest is because last year I presented here at this meeting some information about levels of antibody in the population derived from a serum bank taken randomly in July 1995, which indicated that the

major gap in serum antibody to a Wuhan/359/95 actually laid within this age group here. That is where the lowest antibody levels were, and that appears to have been reflected this year in the number of people actually getting Wuhan/359/95, as we will see.

[Slide.]

I will take analysis of the strains in order, H1N1, H3N2, and influenza B. So, this season we haven't seen any H1N1 activity, but this is a recap of the H1N1 activity from the end of last season.

Our ferret antisera battery contain many of the sera which Dr. Regnery has just presented to you, most importantly Taiwan/01/86, Texas/36/91 are not included in this battery or on this table here is Wuhan/371, which is the deletion mutant, and we had absolutely no evidence of any Wuhan/371-like strains in England last year.

The thing to say here is that the antisera that we have indicate that our strains can be described antigenically as Taiwan-like, showing good activity with Taiwan, but a rather variable reactivity with Texas/36/91, which is also indicated here, with our Sichuan antisera, and

in general, the comment that I could make is that perhaps our ferret antisera for H1N1 are not very discriminatory.

[Slide.]

The genetic level, what we can actually say is

that there is a fair amount of genetic diversity in our strains, which is not particularly reflected antigenically. This is based on sequence analysis of the HA1 portion of the hemagglutinin of England strains here.

The deletion mutant Wuhan/371 is represented in our table by this virus here, and the vaccine strains are shown here, so this represents the diversity of England's strains that we have actually seen over the last 18 months.

[Slide.]

If we move on now to the H3N2 situation, that is a little bit more complicated in England. England/217/96 was the last H3N2 virus that we had in January, towards the end of the last season, and from this you can see that it could be described antigenically as Johannesburg-like with a poor reactivity, at least a fourfold reduced activity to Wuhan antisera, thus, causing date characteristic of all the H3N2 viruses seen last season.

So, our H3N2 activity was entirely Johannesburg last season, and it was therefore with some trepidation that we awaited the first H3N2 this year, since we had no evidence of Wuhan/359/95-like viruses in the United Kingdom.

However, our first H3N2 virus this year, England 272, was indeed Wuhan-like with a reduced reactivity to Johannesburg. So that, from the point of view of matching circulating strains to vaccine composition was somewhat of a

relief.

However, we have seen some heterogeneity antigenically in the viruses that we are looking at currently in the United Kingdom, and this picture is by no means complete in the sense that we still have many more viruses to isolate, and we are some way away from the end of the season.

What we can already say is that there are at least two circulating types. 272, the first virus this season, has got a good reactivity with earlier strains of influenza. The dates here indicate the years in which these reference strains were actually isolated.

Then, there is a second sort of isolate here, represented by A/England/279/96, which has got a rather poorer reactivity against earlier viruses, but still good against Wuhan.

Rather more alarmingly, recently, we have seen some isolates represented by Scotland/41/96, which have very poor reactivity against earlier viruses, and reduced reactivity to Wuhan, which these viruses may be similar to the one which Dr. Regnery just described A/France/187/97.

So, we have some sequence analysis for 272 and 279, which I will go through. We don't have sequence analysis available yet for this sort of isolate, and we also have European egg isolate, which in many ways is

intermediate between these two sorts of virus.

[Slide.]

One of the interesting features of the England isolate this year has been that they all contain a receptor-binding change at position 226 from isoleucine to valine, and this may or may not be contributory to the fact that we have been unable to make any primary egg isolates from the clinical material that we have.

Also of some interest has been the generation of a novel potential glycosylation site here at position 120 to 124, and interestingly, one of the differences between 272, which is the first strain with high reaction against earlier antisera, and 279 and later strains, is a position, a glycosylation site created here at position 46, which is not shown here because when I made that slide, that sequence information was not available to us.

Lisbon/296, which is the egg isolate that I have indicated to you, does not have this potential glycosylation site, and it also does not have the change to leucine here at position 194, which may be contributory to its growth in eggs, i.e., Lisbon/296 is an egg isolate whereas the rest

are tissue culture isolates, and as I have already indicated, we have been unable to grow any of the England strains in eggs.

[Slide.]

So, phylogenetically, then, all of the England viruses which we have sequenced so far come out very close to Wuhan 359/95. This group here represents the Johannesburg/33/94-like viruses which were circulating last year along with these Thessalonica-like viruses in the United Kingdon, and to the best of my knowledge, these viruses and these viruses, apart from single reports from Switzerland, have actually disappeared from Europe, so that the majority of European strains are antigenically and genetically closely related to Wuhan.

[Slide.]

Now, the situation with influenza B is really fairly straightforward. We have seen very little influenza B in England, although we are starting to see some coming through now, and it is possible that by the Geneva meeting in two weeks time, I will have considerably more information, but quite straightforwardly, we can say that our England strains are B/Beijing/184/93-like, although they do show some heterogeneity in their reactivity to Harbin antisera, and whether this is a trend or really coincidence, I can't yet say. We will have some more information on that

in time to come.

We do not see any of Victoria lineage in the United Kingdom, and equally, from the point of view of genetic analysis, our sequence analysis of the

hemagglutinin, one portion of our England strains indicates that they are quite closely related to Beijing/184/93.

So, in summary, then, we have late activity in the United Kingdom. We have predominantly H3N2 viruses circulating, and there is some considerable heterogeneity in there, although, broadly speaking, we would describe them all as Wuhan-like.

We have no evidence of Johannesburg-like strains, which are those H3N2 strains from last year. We have had limited influenza B activity, and the influenza B isolates that we have had, have all been B/Beijing/184/93.

With respect to H1N1 activity, we have had no H1N1 viruses circulating this season in the United Kingdom, and what we saw in the spring of last year were all Taiwan/186-like with no evidence of deletion mutant-like viruses circulating.

Thank you.

DR. LEVANDOWSKI: Thank you, Dr. Zambon.

Are there any questions from the committee?

If not, then, we will move on. I will ask Alan Hampson from the WHO Collaborating Centre in Melbourne,

Australia, if he would give us some information on what is happening there.

DR. HAMPSON: Thank you very much. Thank you for the opportunity to talk to you today. I am just going to

give you a very brief overview of the findings of the WHO Collaborating Centre for Influenza located in Melbourne. We undertake some surveillance and collect virus specimens from the southern pacific region and from South Africa.

[Slide.]

During this last season, we had viruses submitted from New Zealand, Australia, from New Caledonia, and from South Africa, and what I have given here is just a very brief overview of the distribution of strains that we had for the year.

In fact, we had moderate to severe activity throughout the regions that we were responsible for, and the great majority of this activity was, in fact, H3 influenza, very, very little H1 influenza A, and some influenza B. Most of this has been, in fact, quite late, and in fact, this appears to be continuing at the moment in Australia with some late, unusual summer outbreaks of influenza B. It may be biased a little bit by one which was on an oil rig, which caused considerable outbreak amongst the workers on the oil rig.

[Slide.]

In fact, New Zealand I think was the country that had the most severe outbreak in the region, and what I have just done here is to show the weekly consultation rate, the sentinel practice rate in comparison with 1995.

New Zealand introduced a new surveillance scheme in 1990, and in fact, this last year is the most severe that they have had since the introduction of that scheme, but it is also the most severe winter they have had for many years preceding that.

What you can see is a very, very sharp outbreak. It was countrywide in New Zealand, and it started in June with a very rapid rise. The previous season was much lower, much more typical, although in 1995, it was atypically late.

[Slide.]

The sentinel practice reports in Australia, you will see are very similar to the preceding two years, and, in fact, we have had moderate to severe influenza over the past three seasons now.

The rates don't necessarily look remarkable, they are not exceptionally high, but we had quite significant levels, and these are rates per 1,000 consultations at medical practices. I can't give you a baseline, because unlike the U.K., we don't have population baselines for the individual practices.

[Slide.]

Now, in comparison with the sentinel practice report, what you will see for this year, the laboratory isolations were, in fact, quite high and a very sharp peak of laboratory isolates. Most of our laboratory surveillance

is based on hospital laboratories. This is probably an indication of the severity of the disease this year, so while the number of reports to sentinel practices were very similar to the preceding year, we have a very sharp peak, a very high peak of laboratory-reported disease this year.

[Slide.]

Now, when we had a look at the strains that were available, as I said, there were very few influenza H1. In the handout that I prepared, I have shown separate tables showing the South African H1's, which were very typically A/Texas-like in the case of South African strains.

What I have shown here is that the Australian strains, the very few strains that we did have were showing some reduced reactivity with Texas. In fact, the characteristic of two isolates from the preceding season, when we had a very large H1 influenza outbreak, two strains which varied a little bit from the A/Texas, and as you can see, these new viruses from this current season are very similar to these Perth/01 and Perth/13 viruses. So, that may be a little bit of an indication to some antigenic drift going on with the H1 viruses, the very few isolates that we

did have.

[Slide.]

Now, just moving down to the characterization of the H3 isolates that we had for the season, which was the

majority of our strains, quite surprisingly, the A/Nanchang and A/Wuhan viruses constituted almost -- well, the very great majority of strains that we isolated this year.

This is, in fact, a very rapid emergence of this new variant because we had expected, if anything, the majority of our strains would have been Johannesburg-like. In fact, there were very few Johannesburg-like strains, less than 5 percent.

I have marked on here Auckland/5, which was shown in Dr. Regnery's slide, as being maybe a little different from the Nanchang-Wuhan-like viruses, a further variant Auckland/108, and a small group of strains here, which do appear to be variants, possibly Auckland/108-like, but we have only just derived an antiserum against Auckland/108 to give us a chance to analyze these.

[Slide.]

Now, this is a summary overhead of the strains for which we have antisera, and I have not put individual isolates in here. What you will see, for Auckland/5, which Helen also showed, it is just discriminated from the Nanchang-Wuhan type of viruses. There is a slightly reduced

reactivity against the Nanchang antiserum.

It is more discriminated by the reduced reactivity against early antisera, such as the Beijing/32. Again, Dr. Zambon showed this for some of the recent U.K. isolates, and

we also discriminated quite well with monoclonal antibodies. This panel of three monoclonal antibodies showed that there is, in fact, a change in that virus.

Auckland/108 is showing maybe a more distinct change, and when we produced antisera against these, unfortunately, I have lost the age of this particular line here, but this is an Auckland/108 antiserum, Auckland/5 antiserum.

What we find is the Auckland/5 antiserum behaves very similar to the Nanchang serum. Maybe it is giving us slightly better cover against some of our more recent strains. The Auckland/108 is distinct. It gives us reasonable cover most of our recent strains, but a result, which we obtained just yesterday indicates that the Auckland/108 is, in fact, a different variant than that currently circulating in South America. It does not cross-react well with the South American strains.

[Slide.]

The type B strains, these are characteristic of the sporadic isolates that we had throughout the season and of the most recent isolates we have had from later in the

summer and from the oil rig outbreak.

Quite typically, our strains are well neutralized by Beijing/184 antiserum or Harbin/07 antiserum. They may be a little close to the strain B/Indiana/01/95, which we

can discriminate from the B/Harbin series, mainly by reaction with monoclonal antibodies, but at the moment certainly the current antisera or the current strain antisera seem to react quite well with essentially all of our type B isolates.

So, in summary, H1, we have very little isolates of H1 influenza. What we did have from Australia maybe showed a little bit of ongoing antigenic drift characteristic of light isolates from our 1995 season.

For H3N2, these certainly are strains which are showing low reaction with the current Resvir-9 or A/Nanchang antiserum, and from the type B strains these appear to be quite consistent and reacting quite well with the current B/Harbin-B/Beijing antiserum.

Thank you.

DR. LEVANDOWSKI: Thank you, Alan.

Are there any questions or comments from the committee?

If not, at this time we will move on again, and I will ask Dr. Nerome, who is visiting us from the NIH in Japan, in Tokyo, if he would come to the podium and share

with us his information.

DR. FERRIERI: I might remind all the speakers that there is a timer with a light on the platform. When it turns red, you must immediately bring your presentation to a

conclusion.

DR. LEVANDOWSKI: Thank you for that reminder.

DR. NEROME: I am very pleased to be here to exchange our understanding of scientific results regarding viral surveillance of the influenza viruses.

[Slide.]

In my first slide, I describe the activity in Japan from the third report. Large outbreaks of influenza caused by A/Hong Kong viruses still tend to increase throughout Japan based on influenza-like illness, absentees and class closure and school closure up to mid-January.

As a reflection of these reports from local governments, a number of influenza A and B viruses were isolated in many parts of Japan. This season was particularly characterized by a great number of adults infected with N3N2 viruses and the deaths reported in the elderly over 65 years of age in nursing homes. TV and newspaper reported daily the above damages by influenza.

From virus isolation and characterization as of January 17th, 39 and 47 prefectures reported to us virus

isolation of N3N2 viruses. All isolates are characterized by post-effection ferret sera in each prefectural Institute of Hygiene and, as a result, 1,278, about 98.3 percent, were identified as N3N2 viruses.

The remaining 22 viruses, 1.7 percent were B viruses although more so the N2N3 isolates were similar antigenically to a Japanese vaccine strain, A/Wuhan/359/95. A small number of H3N2 viruses seem to be different from the above vaccine strain. For example, antiserum to the Wuhan strain reacted to a low titer, a small number of N3N2 viruses, and some viruses did not react to the antiserum to Wuhan strain.

We are now confirming their antigenicity by different tests.

[Slide.]

This is a Japanese map. This is distribution of isolates between October 1 and December 15, 1996. You can see here most of the N3N2 viruses, indicated by a shadow, were specifically in the north part of Japan, and the western part of Japan. From this report, many elderly people were dead in the north part of Japan and the west part of Japan.

This early morning, the Japanese government called me at 3 o'clock. Already, more then 30 elderly people were dead in one prefecture, in my hometown, Kanagawa.

[Slide.]

This tendency reaches all over Japan. Still, in Hokaido, until December 15, only B viruses were circulated in Hokaido, in the north part of Japan. Now, Hong Kong

viruses also have caused an outbreak. And then in several prefectures, N3N2 and B viruses cocirculated.

Now, in Japan, other prefectures also reported to be based on an outbreak based on an influenza-like illness. So I can say that all over Japan now has experience with big outbreak of influenza since 1989.

[Slide.]

This is a transitional virus isolation in Japan since October 1996. Our Japanese activity starts in mid-November and then they exactly increase and reach the first wave of our outbreak in the mid or end of December and a decline with the start of winter vacation in school.

Then, early this year, again starts even the activity now increasing rapidly, pointing to a second big peak that was usually observed in early February.

[Slide.]

From the present communication, I eliminated data regarding the evolutionary analysis, molecular analysis. This is described as N3N2 viruses analyzed by post-infection season. As you can see here, 90 percent of all N3N2 viruses are identically similar to our vaccine strain,

A/Wuhan/359/95. But a small proportion, such as 10 percent, of our N3N2 viruses reacted to a low titer to antiserum to our Japanese vaccine strain, Wuhan.

This morning, it was also reported to us. So

three N3N2 viruses were isolated in the Kyoto area did not react with antiserum to Wuhan strain and we are getting those analyzed much more in detail from a different point of view.

[Slide.]

So the HI test using post-infection ferret sera or other animal sera is only as a preliminary screening to understand antigenic characteristics, to understand in much more detail the antigenicity of the antibodies to two vaccine companies to immunize two groups of people. One group, A, the mean age is 50 years old. The second group, B, the mean age is over 65 years old, and living in nursing homes.

As can be seen, our three antigenetic variants isolated in Japan such as Nagasaki, H3N2 Fukishima, B/Sappore. You can see both of the tables are right above Tokyo. Particularly, I would like to point out that B viruses such as Tokyo/942/96 reacts to low titer in older people indicating that it is a new variant.

And then our Japanese H3N2 viruses seem to react to low titer with Wuhan/395/95 strain.

In conclusion, the following points should be considered. Most of N3N2 isolates in Japan were similar antigenically and evolutionarily to the vaccine strain Wuhan/359/95. Really, about 10 percent that were isolated

reacted to low titer with antiserum to Wuhan viruses. These results must be analyzed in much more detail by HI, neutralizing tests and immunogenicity in the mouse model system as one of the vaccine candidate strains.

Secondly, even though B viruses were isolated in a lower proportion, several strains appeared to react to extremely low titers with our vaccine strain which is B/Harbin/07/94 or Beijing/184 strain. These strains must be evaluated from different points of view.

Third, in the last season, two types of H1N1 variants were isolated in Japan. The first group was antigenically and evolutionary related to the Wuhan/296/96 but the second group seemed to be different based on the plaque neutralization and phylogenetic analysis.

On the whole, it is evident that we have to consider carefully the recommendation of vaccine strains in the coming season.

Thank you very much for your attention.

DR. LEVANDOWSKI: Thank you very much, Dr. Narome.

Are there questions from the committee for Dr. Narome?

If not, at this point, we will move on again, and I will ask Dr. Nancy Cox if she will present information on the molecular analysis of strains.

Molecular Analysis of Strains

DR. COX: I will be fairly brief this morning because we are a bit pressed for time and because many people in this room have become much more accustomed to looking at the sequence analysis that we present and are much more familiar with the ways in which we examine this particular data.

[Slide.]

I will just briefly touch on which viruses we choose for sequencing. We sequence all variant viruses. In other words, we sequence every strain that is down fourfold or greater with a number of our ferret antisera in the panel, so that we can find out what amino acid changes are responsible for this variation.

We also sequence typical epidemic viruses, and we look particularly for viruses that will give our sequence database a broader geographic distribution, and as well a broad temporal distribution.

In the last year or so we have been selecting viruses based on the RFLP results. Last year, I talked about how we had begun to do restriction fragment-length polymorphism screening in order to be able to pinpoint which

genetic group each virus was in.

[Slide.]

Once we have the sequence data, we use it to compare the antigenic analysis with the specific amino acid

sequence data to determine if there is any correlation between specific amino acid changes and changes in antigenic reactivity.

We look at computer-generated evolutionary trees or dendograms, and these are sometimes very informative. We look at computer-generated consensus sequences, which are actually average sequences, and of course, our consensus sequence evolves with time, and the older viruses, the older HA sequences are dropped off and we move with the newer strains, so our consensus sequence for each of the three groups of viruses is made up of '95, '96, and '97 sequences.

We examine the location of the specific amino acid sequence changes in the three-dimensional structure of the HA to look to see if the changes are actually in the antibody-combining sites that have been defined.

I will remind you that there are five defined antibody-combining sites in the HA. These antibody binding sites are made up of noncontiguous sequences, so we do sequence the entire HA1 domain, so that we can see what is going on overall.

We also want to determine if we have a number of

sequence changes and then a correlation in an increase in influenza activity.

[Slide.]

As I just mentioned, we have begun screening the

HA genes of all of the viruses that are tested in HI tests by restriction fragment-length polymorphism or ITPCR testing, and we developed the screening method based on our past sequence data, our need to distinguish genetic lineages of viruses when HI tests fail to do so, and we also wanted to devote fewer staff to routine sequencing.

So, we now apply RFLP screening to all viruses, and in the last year or so, we have screened over 1,500 viruses.

[Slide.]

We will start with the influenza B viruses. In order to orient you, these are the Yamagata lineage viruses that others have spoken about. These are the Victoria lineage viruses here.

I won't discuss these viruses very much because, as you know, they have not been detected outside of Hong Kong in China, however, I would like to mention that they have continued to evolve as they have sequenced in primarily southern China and Hong Kong.

The viruses on the upper part of this dendogram have predominated. Here was the old vaccine strain Panama.

Our current vaccine strain B/Harbin/07/94 is located here. We can see that the majority of the viruses that have been isolated and sent to us during the last year and a half fall into this group here.

If we look at what happened during the summer months, as Helen mentioned, we did have B/Victoria viruses being isolated in China, and we can see that they make up approximately 16 percent of the viruses in terms of their genetic makeup.

We have a small number of viruses represented here, and they are all in this group that we call the Chinese lineage. I would like to remind you that just a few years ago, we were not able to distinguish these viruses from these viruses antigenically, and so it was very important for us to be able to distinguish them genetically.

[Slide.]

We used the computer-generated consensus sequences to look at the number of amino acid changes between various strains and the consensus. We can see here that we have five to eight amino acid changes between the Beijing/184 and Harbin strains and the consensus.

We have nine amino acid changes for the Nanchang strain. The representative U.S. strain has only two amino acid changes from the consensus, and the B/Russia/222/95 strain also has two changes.

[Slide.]

So, in summary, most recent influenza B viruses fall into one of the two genetic groups which we have called Chinese or B/Harbin. B/Harbin has just three additional

amino acid changes.

The B/Harbin vaccine strain is actually the smaller of the two related genetic groups. We cannot distinguish these two groups antigenically. The HA sequence of B/Harbin has eight amino acid changes from the HA consensus sequence, and, of course, B/Victoria-like viruses are continuing to evolve as they circulate in China.

[Slide.]

The H1N1 viruses are really quite interesting. To orient you very quickly, this group, shown in green and termed "Chinese" here, is made up of two groups of viruses which look different antigenically.

Part of these viruses have a deletion mutant, and they are very clearly distinguished from other viruses in this group and from all of the viruses in this group. The viruses in this group, which do not have the deletion, look Taiwan-like in spite of the fact that they have a fair number of amino acid differences.

The viruses in this group are fairly homogeneous in terms of their sequences. We have the Moscow/01/95 strain up here, Shanghai/08 up here, Shanghai/07 right here,

and I think those are the primary viruses that have been pointed out and will be spoken about when we move on to the serologic analysis.

So, what we can see is that the majority of

viruses during this time period were the Taiwan/Texas-like strains. During this time period, during this late spring and summer, we had a significant number of viruses in this group, and during the current time we are seeing very few H1N1 viruses, but they are Taiwan/Texas-like.

DR. KILBOURNE: Nancy, excuse me. Does the deletion involve an antigenic site?

DR. COX: I will go over this a bit later, as well, but it is in site A, and it is at amino acid 134.

[Slide.]

The Texas vaccine strain X-113 has six amino acid differences from the consensus sequence. Moscow/01/95 is very similar with only two amino acid changes from the consensus sequence. Shanghai/08 has three changes, Bayern only one, Vermont, one which is a representative U.S. strain, only one, and the Beijing/262 deletion mutant has 11 amino acid differences from the consensus.

[Slide.]

Of the two distinct genetic groups of H1N1 viruses, one group predominates worldwide, and the second has circulated only in China, that is, until we heard the

report in the last couple of days from the U.K. indicating that an isolate was made in Switzerland.

The HA genes of H1 viruses have continued to evolve and viruses analyzed in the past year have between

one and 11 amino acid changes compared with the consensus sequence.

The molecular correlate of the reduced HI titers to the Wuhan/371-like or Beijing/262-like viruses is a single amino acid deletion at position 134. It is a deletion of a lysine. This particular deletion was also observed in a series of isolates obtained from a severely immunocompromised child who shed Chile-like viruses back in the mid-eighties. We also have seen this particular deletion in an H1N1 virus, which was isolated during the early era of circulation of the H1's.

[Slide.]

The H3N2 viruses have been somewhat more heterogeneous in general. Last year, just to recapitulate what was occurring last year, we knew that the group of viruses shown here in blue, in both colors of blue, the darker blue and the lighter blue, were predominating worldwide, however, we were not able to distinguish at that time many of the viruses that were in this group.

They, of course, have fallen out of the dendogram because they are older strains, but, nevertheless, they did

fall into this genetic group and they were indistinguishable antigenically from the Johannesburg genetic group of viruses represented here in red.

So, last year the RFLP analysis was extremely

useful because we knew that this group of viruses was predominating even though we couldn't tell that on an antigenic basis.

Then, we started detecting the viruses, the Wuhan-like viruses that we could distinguish antigenically, and they formed a group of viruses within this blue group, and, of course, those viruses have predominated worldwide, so that now from October of 1996 to the present, about 97 percent of the viruses that we have examined have fallen into that genetic group.

The Resvir-9 reassortant has three amino acid changes from our current consensus sequence. Fujian/47/96, which has been mentioned a couple of times, has four amino acid changes from the consensus.

[Slide.]

The South Africa virus, which is representative of a newly emerging genetic group, and we probably need to go back to the previous dendogram, so that I can point that out to you -- the South Africa virus actually isn't on here because we had only the amino acid sequence, and this dendogram is based on nucleotide data, but it falls into

this group right here, and it appears that this is the most rapidly growing genetic group of viruses, and we will be looking at adding new restriction enzymes to our testing, so that we can distinguish this group very readily without

sequencing.

[Slide.]

The Auckland/5 reassortant IVR-99 has five amino acid changes from the consensus, and the Texas/9/96, a representative U.S. strain, has seven amino acid changes from the consensus, and it falls into that South Africa group.

[Slide.]

So we were able to distinguish four genetic groups of influenza A viruses, and, of course, the group represented by Wuhan predominates worldwide. The HA genes of H3 viruses have continued to evolve, and the HA of the current vaccine strain A/Nanchang has only three amino acid changes from the consensus sequence.

I mentioned the growing South Africa genetic group of viruses, and the signature changes that indicate that viruses belong to this group are at amino acids 121, 124, 133, and 142, and as Maria pointed out, two of these changes encode additional potential glycosylation sites.

Are there any questions?

DR. LEVANDOWSKI: If there are no questions from

the committee, at this point, I will ask Dr. Ferrieri if this seems like a convenient time for a break.

DR. FERRIERI: Yes, this would be a wonderful time for a break, and we should reconvene precisely to start at

10:20. We are right on time.

[Recess.]

DR. FERRIERI: We are into the vaccine responses. I will turn the program back now to Dr. Levandowski.

Vaccine Responses

DR. LEVANDOWSKI: Thank you, Dr. Ferrieri. At this point, I would like to ask Dr. John Wood, who is from National Institute of Biological Standards and Control in London if he would present a summary of information on responses of people to current vaccines.

DR. WOOD: Thank you, Roland, and thank you for inviting me to attend your meeting.

[Slide.]

What I am going to do is to try and summarize the serology studies that have taken place over the last few weeks. There have been four different serology centers, two here in the states, at CBER and at CDC, one in Australia at CSL, and one in my lab at NIBSC in the U.K.

The vaccine panels that we have been looking at are down the lefthand side here. A trial at the University of Wisconsin in adults and elderly; Rochester, adults and

elderly; a nursing home in Virginia in the elderly; and a pediatric trial at Vanderbilt University, all of these trials in the U.S.; one trial in Europe, which is called the NIBSC trial, and lastly, a trial in Australia, which we call

the CSL trial, and both of these are in adults and elderly.

Three of the trial sera were redistributed to the other serology labs, so here we have the Wisconsin sera tested in each of the labs. This is very important because of the inherent variability of hemagglutination tests. There are technical differences in all of the serology labs, and these lead to differences in HI titers.

So, it is quite important to have a variety of labs looking at these sera, so if you find a difference, you ask the question do other labs see that difference, as well.

[Slide.]

The vaccines that were tested contain these strains. In Europe and in the U.S., we have the H1N1 Texas strain, Nanchang and B/Harbin. In Australia, the only difference was that the H3N2 strain was Guangdong/25/93, which is antigenically the same as the previous vaccine strain in the Northern Hemisphere like Johannesburg.

[Slide.]

What we have done is to test the pre- and post-vaccination sera for antibody which cross-reacts to the variant viruses that we have been hearing about, and we have

established panels of viruses with the help of the three WHO influenza centers at CDC, Mill Hill, and in Australia, but not all of those viruses were examined in all of the labs, so it is a little bit complicated.

But what I have done is to try and give you a snapshot of what the results were, and then at the end I will try and pull them all together.

[Slide.]

So, let's start at influenza A H1N1 Wisconsin adult trial. The results analyzed at CBER and at CSL. This is the vaccine strain in each case, Texas/36/91, the X-113 reassortants, and in all of the tables we are looking at the pre- and post-vaccination geometric mean titers and the percentage of individuals with significant antibodies, and that is defined there, before and after vaccination, and the percentage with fourfold rises.

For the purpose of this presentation, I am really going to concentrate on the post-vaccination antibody responses. What I have done is ringed in red where there is a reduction in HI titer of greater than 30 percent just to give you an idea of which are the significant drops.

So for CBER's results, we are seeing a significant reduction in HI titer to Bayern/07/95, Shanghai/08/96, and most of all to the deletion mutant, Beijing/262/95, a reduction from 99 to 18.

When these sera were analyzed in Australia, we are seeing quite similar patterns, reduction to Bayern/07, Shanghai/07, which is I think a close cousin of Shanghai/08, Vermont/01/96, and again a great drop to Beijing/262.

[Slide.]

Here we have the Australian adult vaccine trial, analyzed in Australia and at CDC. Very similar strains are being picked out as being different, a little bit different antigenically: Bayern/07, Shanghai/07, Vermont/01, Beijing/262, the biggest drop; and analyzed at CDC, Bayern/07, Shanghai/08, not Vermont at CDC, and Beijing/262.

[Slide.]

Now we go on to two representative trials in the elderly. First of all, NIBSC, elderly, analyzed at CSL and at CDC. Again, we are seeing the same viruses picked out as being antigenically a little bit different with post-vaccination sera this time in the elderly.

CDC again, don't recognize the difference in Vermont.

[Slide.]

Here we have the Wisconsin elderly analyzed at CBER: reductions to Bayern and Shanghai/262; and at CDC: all reductions to Beijing/262 and 262 here. But I should say that this trial produced very low post-vaccination titers.

[Slide.]

What I haven't shown you so far is my results with the H1N1 viruses, and that is because they are a little bit different from the other three centers. So there is an

error here. This should be Wisconsin elderly. I am showing the results from NIBSC in two trials, NIBSC adult sera and Wisconsin elderly sera.

First of all, you see the much higher HI titers than the other centers, and secondly, the only virus we see as being different is Beijing/262. We are not seeing differences with Bayern, Shanghai/07, Vermont. So, it illustrates the variability of the results.

[Slide.]

Now, let's move on to H3N2. Again, these viruses you have heard antigenic analysis and genetic analysis in the talks earlier, and this trial is NIBSC adults analyzed by CDC, and NIBSC.

Here the differences are seen with the South Africa 1147, which you have heard was on a slight different lineage from Nanchang, and Fujian/47 and Auckland/05, which are more Nanchang-like than the South Africa lineage, but they are all showing reductions in past immunization titers.

At NIBSC, we saw differences with South Africa/1147, Fujian/47, and a representative European H3N2, Lisbon/02/96.

[Slide.]

The Wisconsin adults tested at CSL and NIBSC. At CSL, they introduced the Auckland/108 virus, and they found significant reductions in post-vaccination titers. At

NIBSC, we found differences with the South Africa virus, Fujian, and both European viruses, Lisbon/02 and Genoa/09/96.

[Slide.]

A similar story in the elderly. First of all, the NIBSC elderly analyzed at CDC and at CSL. Drops to South Africa, Fujian, Auckland/05 tested at CDC, and at CSL, a reduction in the South Africa virus and Auckland/108.

[Slide.]

Wisconsin elderly tested at CSL and NIBSC. Reductions to Fujian, Auckland/108, reductions to South Africa, Fujian, Lisbon, and Genoa.

What I haven't shown are the results from CBER for H3N2, and that is really because they were difficult to interpret because the post-vaccination titers to the vaccine strain, Resvir-9, were very low indeed. In fact, they were higher to the variants, so I deliberately avoided talking about those results.

[Slide.]

Influenza B. The vaccine strain is B/Harbin/07/94. This is the NIBSC adult trial, tested at

CBER and at CDC. This is the B/Victoria lineage, and it is being seen by the post-vaccination trials as being different in both the lab at CDC and CBER.

[Slide.]

This is the Wisconsin adult trial, tested at CSL and NIBSC. Again, Guangdong is seen different here at CSL, and in our test, we found that Nanchang/24 had a reduction from the homologous titer to B/Harbin.

[Slide.]

Wisconsin elderly, tested at CDC, B/Guangdong was the only virus that was reduced in titer, and at NIBSC, none of these viruses were significantly different.

[Slide.]

The last data slide I am showing is CSL elderly, where they were tested at CSL and at CDC, and again Guangdong is the only virus that is different, so there is not a lot happening with the B viruses.

[Slide.]

So, in the last three slides, I have drawn all these results together, and a way of illustrating this is to just single out the viruses that are seen as being antigenically a little bit different by post-vaccination sera.

So, for H1N1, these are the viruses - Bayern/07, Shanghai/08 and /07, Vermont/01, and Beijing 262, and these

are the labs that did the serology, and this is the incidence of results that show a low titer for this particular virus.

So, for example, Bayern/07/95, all of the tests at

CSL saw this as different, five out of seven at CDC, eight out of eight at CBER, and none of the tests at NIBSC, so overall, 19 out of 25 tests saw this as being a little bit reduced, and the typical reduction was about 50 percent reduction.

The other viruses, Shanghai/08 and/07, and Vermont, they were seen as being a little bit different in some of the labs, but not all of them, but Beijing/262 was seen as being different in all of the labs, and quite large reductions, nearly 80 percent reductions in titers.

[Slide.]

Let's move on to H3N2. The viruses that were identified as being different were Fujian/47, 10 out of 19 tests, all of the tests at NIBSC, all of the tests at CDC, and one of them at CSL. South Africa/1147, four out of 14 of the tests; Auckland/05 and Auckland/108, four out of 19, four out of four. This was only tested at CSL, and all of the tests showed this as being significantly reduced.

Then, the two European viruses, they were only tested in my lab at NIBSC, but in nearly all of the tests they seemed to be different.

[Slide.]

Finally, the B viruses. This is the B/Vic lineage, B/Guangdong, and nearly all of tests showed a reduction on the order of 63 percent, and B/Nanchang/24/96,

we are seeing in just a few of the tests, four out of 25 tests conducted as being different, but not very great reductions.

So, that is a summary of the serology lab results.

Thank you.

DR. LEVANDOWSKI: Thank you, John.

At this point, you have summarized a huge amount of information there in those tables in a very short period of time, and done it very nicely.

I don't know if the committee members want to ask any questions about serologic results at this point.

If not, I would ask John Treanor. we have additional information from studies that were done at the University of Rochester, which we really didn't have time to add here, if he might want to make a comment, as well, from studies being done there.

DR. TREANOR: I just wanted to point out that you may or may not have a handout of the results from studies that we did along with Bill Gruber at Vanderbilt, and we did try and make enough handouts, so everybody could see that.

There are tables also of reactivity at different

groups of populations against the H3H1 and B antigens. Although we didn't test quite as many different viruses as John did, we got very similar results.

The responses in the H3 group to the Fujian and

Auckland viruses are slightly less than the responses to the Nanchang, which is in the vaccine. I am not sure how significant they are, but the one difference that we did see that does seem to be consistent in all the different groups that we tested were the responses to the South Africa virus, which are significantly less than the responses to the other members of the group.

With the H1 antigens, again, there are slight decreases in the responses to the Bayern and Shanghai, not really seen in every single group tested, but very significant decreases in the responses to the Beijing/262 in those who got the Texas vaccine.

For the B, again, we are seeing slight decreases in some of the viruses in some of the group, but the only really consistent change is that the people who were vaccinated with Harbin had very poor responses to Guangdong as expected.

So, those are really the most striking differences in the things that we saw.

DR. LEVANDOWSKI: Thank you. At this point we will move on.

Availability of Strains and Reagents

DR. LEVANDOWSKI: If I could get the first overhead, I would like to give some information about the availability of strains and reagents, and there may be

others here in the room who could or would comment on this also either now or at the appropriate time.

[Slide.]

In terms of the influenza B viruses, the B/Harbin/07/94 virus, of course is available. That is last year's strain. That is a moderate- to high-yielding seed virus in terms of what most manufacturers are finding. Of course, seed viruses for that strain have been approved for vaccine production.

At this point, you will note that I have indicated that we really don't have any other serious vaccine candidates for production.

[Slide.]

For the H1N1 viruses, the A/Texas/36/91, X-113 reassortant is the one that was last year's strain. It is a moderate- to high-yielding reassortant, and seed viruses for that strain have also been approved for vaccine production.

At this point, we have distributed to manufacturers the A/Shanghai/08/96 strain and also the A/Bayern/07/95 strain, but those were sent out just this week, so that I doubt that there is any information that is

available. It is really unknown whether these wild type strains would be appropriate for manufacturing or not, and at this point those strains, nothing has been done in terms of making reassortant viruses for those.

In terms of the A/Beijing/262/95 strain, however, there are two high-growth reassortants that have been produced, one in Dr. Kilbourne's lab, the X-127, and one from our lab, Resvir-10. We have not distributed those yet either because we did not have, up to this time, all the information that we wanted to have about the reassortants, but those could be made available fairly shortly.

[Slide.]

For the H3N2 viruses, of course, the A/Nanchang/33/95, Resvir-9 strain, is available. That is last year's vaccine strain. It has been a moderate- to high-yielding reassortant, and there are vaccine seed viruses that have been approved for production.

There are additional strains that are available at this time. There are two wild type strains that have been distributed to manufacturers, but again only within the last 10 days, the A-Fujian/47/96 and the A/South Africa/1147/96 strains. I do not have any information on the growth characteristics of those strains, but the manufacturers may be able to supply some information to us.

There are, in addition, other high-growth

reassortants that are available, and I see that I have left one off the overhead. There is the X-125, A/Nanchang/933/95 reassortant from Dr. Kilbourne's lab.

There is also an A/Auckland/05/96 strain that is

designated IVR-99, which was produced at CSL in Australia. That strain also is available, but again, we don't have information on the growth characteristics of that one.

[Slide.]

In terms of the potency reagents, of course, we have reagents for potency determinations for all of the strains that were used in last year's vaccine. We have sufficient material for that. If there are new strains that are selected, however, the reagents will not be available until sometime in May, and during that period of time, if there are other strains that are selected, manufacturers would, of course, have to rely on the old reagents, which may be give falsely high values in terms of yield for vaccine viruses.

I think I will stop there, and if there are any questions, take them.

If not, leading right into that, we always reserve some time for the manufacturers to give us comments on their view of the manufacturing season, either both last year and the coming season.

I would ask if there is anyone in the audience

from the vaccine manufacturers who would like to share some information with us or some thoughts that you would please do so now.

Would you also please identify yourself for the

recorder.

Comments from Manufacturers

MR. THIBOUTOT: Roth Thiboutot from Wyeth Labs. I guess I am representing the influenza vaccine manufacturers and that I guess we would like to ask the committee if they could expedite any decisions on strain selection.

I guess as you are all aware, influenza vaccine is an egg-based product, and we have all turned the chickens on, if you will, and we have approximately a couple of 100,000 eggs coming into our facility every day, and really no mechanism to shut that off if we have any break in the strain.

Specifically, I guess we would really like to have two strains named today as in about three weeks I believe we are going to start to have some problems as far as our manufacturing capacity being exceeded on one strain for the entire year. The effect of that will be pretty disastrous financially to us.

In addition to that, there is also going to be a tremendous effect on the number of doses that are going to be available at the end of the year as it extrapolates to

about a couple of hundred thousand doses every day if we don't have a decision.

So, leaving it at that, you can plug that into your equation.

Thank you.

DR. LEVANDOWSKI: Thank you.

Do any of the manufacturers have information about the growth characteristics of any of these strains that have been distributed, anything that you are willing to share with us?

Please identify yourself.

MR. SLUSAW: Greg Slusaw, Pasteur-Merieux Connaught.

We have had an opportunity to do some seed passage with the H3 candidate viruses which were distributed, and they appear to be moderate growers.

One point I would like to make is that for a virus candidate to be suitable for production, generally, we do need a high-growth reassortant, and several of the H3 candidates which we have received are prototype strains.

Also, one thing I would like to add is that we generally need about a month from the time we receive a candidate virus until we can go into production, which gives us time to do seed passage and prepare seed virus cultures for production and do the appropriate testing, and so on.

So, at the point that a candidate virus is distributed, there is some lag time before we can actually begin production with that.

DR. LEVANDOWSKI: Thank you. I should mention

that in several laboratories, there are efforts being made to produce high-growth reassortants with both the A/Fujian/47/96, the A/South Africa/1147/96 strain, and also the Lisbon/02/96 strain, so that there are some efforts going on to produce those, and they are in various stages of completion, I guess is a good way to say it.

DR. KILBOURNE: How about H1?

DR. LEVANDOWSKI: At this point, this information that we are looking at has literally only come to us in the last several days, and we had really not contemplated this event, so we had not started to work on any of these strains in terms of high-growth reassortants, but it is something that we are starting to think about to try to select those that might be the most valuable.

DR. KILBOURNE: We have the X-127, the Beijing/262 prototype.

DR. LEVANDOWSKI: Yes. I am sorry. I am not trying to exclude the Beijing/262/95 strains from the H1N1's, but those are very much different from what have been the predominant strains out there, and the strains that we might be somewhat concerned about in addition to those

Beijing/262/95 strains.

But it is correct, there are two reassortants already available that have just not been distributed yet for the Beijing/262/95 variants. Sorry for the confusion.

If there are no further comments from the manufacturers at this point, then, I will go ahead and we will discuss or I will present some information that I would like to have considered in terms of what the options are for making the strain selections.

Options for Strain Selection

DR. FERRIERI: Is there anything in our packet, Dr. Levandowski, that was distributed on this particular point now?

DR. LEVANDOWSKI: No, there won't be anything in any of the packets on this. I have some overheads that I have put together.

First of all, before we go to the overheads, of course the influenza A viruses of both the H1N1 and the H3N2 subtypes have continued to circulate along with the influenza B viruses, so the first option or the first proposal for an option would be that the vaccine should continue to be a trivalent vaccine at this point.

We have had discussions about this at several of the meetings in the past about what the desirability of having some changes in that would be, but as all three

strains seem to keep circulating, and just when we least expect it, the one that we think might die out becomes predominant, it seems like it would be a good idea.

In terms of the influenza B viruses, influenza B

viruses isolated during the last year in the United States and everywhere except China have been clearly in the Yamagata/16/88 lineage with most of those strains very similar to the current vaccine strain, which is B/Harbin/07/94.

In China, the strains in the B/Victoria/02/87 lineage have continued to be found, and as we have heard, there seem to be some antigenic alterations occurring in those strains even though they are not predominant.

Although a few strains that are like B/Victoria/02/87 have recently isolated, a large cohort of children, mostly those under 5 years old, have had no immunologic experience with those strains, and that is true not only in the United States, but probably elsewhere and may represent a population for future rapid introduction of those stains.

In addition to that, there are reduced antibody titers that we are finding in adult populations, as well, which has been increasing as time goes on.

The serologic responses of vaccinees have been uniformly good to the recent influenza B virus strains of

the Yamagata lineage, which includes with some few exceptions I would say recent strains, such as the B/Nanchang/24/96, and we have no new vaccine candidate strains at this point.

[Slide.]

So, for influenza B, going through this overhead, the first option would be to retain the current vaccine strain. In favor of that, the current vaccines appear to be immunogenic. The most recent strains are well inhibited by the post-immunization antisera, as we have seen, and manufacturing is well defined and predictable, as we have also heard. Opposed to that, I don't really have anything.

[Slide.]

The second option would be to change to a more recent strain, and in favor of that, I don't have anything, but opposed to that, there really is no predictable advantage if we change to another strain that would be like the Harbin/07 strain at this point, and we have found those superior alternate vaccine candidate strain.

Before we go to the next overhead, I will summarize for the H1N1 strains. There are genetic changes that have continued to accumulate in the H1N1 influenza viruses. The predominant strains in human populations are antigenically closely related to the A/Taiwan/01/86 and A/Texas/36/91 reference strains, however, there are changes

that are occurring, and amino acid deletion mutants, represented by the A/Beijing/262/95, have been isolated in China, and now we have heard potentially in Europe, as well.

Although activity of the H1N1 viruses has been

generally low in recent months, significant activity during the 1995 and 1996 season indicates that there is a continued potential for spread of these strains in human populations.

Human serologic responses suggest that the inhibition of some recent A/Texas/36/91-like strains may be reduced compared to the vaccine strain, which is different from the experience in recent years.

Although some strains isolated from recent outbreaks, such as those similar to the Shanghai/07 and 08/96 strains may not be as well inhibited by antibodies, it is unclear how generalized that reduction might be.

The potential vaccine candidate strains similar to A/Shanghai/08/96 are currently available, at least in wild types, but there is really insufficient data to predict what the suitability for vaccine use might be.

[Slide.]

Options for the influenza A H1N1 vaccine component. The first option, of course, would be to retain the current vaccine stain, and in favor of that, the current vaccines are immunogenic. Again, manufacturing is well defined and it is predictable, and there has been a lot of

experience with the strain that is in the vaccine currently.

Against this, there are continued genetic and antigenic changes occurring, and the current vaccines may be inadequately protective against these newly circulating

strains. As we have heard, sometimes those strains can spread very quickly, maybe surprisingly so.

[Slide.]

The second option would be to change to a more recent strain, and in favor of that would be that we might get better antigenic matching between what is in the vaccine and the strains that are causing infection.

Opposed to that, it is not entirely clear at this point that the results for A/Shanghai and other strains are truly representative, and the strains related -- well, I shouldn't say this any more, this is different now, isn't it -- the strains related to A/Beijing/262 might be spreading. So, I guess that would be a pro, wouldn't it, to move that one up.

[Slide.]

The next overhead is the third option, which is to defer the recommendation on this strain to accumulate more data, and in favor of that would be the continued genetic and antigenic changes in the strains that are circulating. The current vaccines might not be adequately protective against those strains, and additional data might help us to

clarify exactly what direction we should go.

Against that is that there may not be any difference in the data that we get. It may be the same as what we are seeing how. Also, it may not be possible to

identify suitable alternate vaccine candidate strains depending on which direction might be chosen.

Now, for the influenza A, H3N2 viruses, there has been continuing antigenic drift among the H3N2 influenza strains, and there is a group of strains suggesting a new genetic group appearing, as exemplified by strains, such as the A/South Africa/1147/96, however, a majority of the recent viruses which have been analyzed are very clearly in the A/Wuhan or A/Nanchang antigenic lineage.

Although some strains recently responsible for human infection are well inhibited by sera from people immunized with the current vaccines, the serologic responses appear to be reduced against some of the most recent viruses.

We do have a number of potential vaccine candidate strains, and there are several high-yield reassortants for some of those strains which are already available.

[Slide.]

The first option for the H3N2 vaccine component would be to retain the current vaccine strain, and in favor of that, most strains seem to be reasonably well inhibited

by the ferret antisera to the current vaccine strain. There are exceptions to that.

Against that, some of the recent strains are less well inhibited by the post-immunization antisera, and the

significant epidemic with the current vaccine strain this year makes it more likely than a drift variant will predominate in the next H3N2 season.

[Slide.]

The second option would be to change to a more recent strain. In favor of that, some recent strains are poorly inhibited by post-immunization antisera. A change would also potentially achieve a better antigenic match with the recent strains, and a number of alternative strains have the potential for being useful for production.

Against that, the choice of the strain could benefit from additional epidemiologic, serologic, and manufacturing information, which we really haven't had time to collect at this point.

[Slide.]

So that brings me to the third option, which is to defer to accumulate more data for this decision. In favor of that, more data are likely to be available as some more strains are examined. Since the H3N2 is likely to be a cause of significant morbidity and mortality, as it has in the past as we would expect in the future, this choice

should be made particularly carefully.

Against that, again, the information that we collect may not really be any different from what we see currently.

I will stop there, and if there are any questions or comments, take them.

If not, I will turn the meeting back to Dr. Ferrieri.

DR. FERRIERI: Thank you, Dr. Levandowski.

Committee Discussion/Recommendations

DR. FERRIERI: Well, you present some real challenges for us this year, and counterbalanced with that is the request for manufacturers to try to provide information as fast as possible. We may or may not be able to please everyone here.

Who would like to start out the discussion? Is everyone satisfied that they have as much information as can be provided today? Yes, Dr. Hall.

DR. HALL: Can I just ask what is the actual absolute deadline for deciding this in terms of manufacturers? We always go through this and everybody would always like more information, and we have to obviously balance the two. I would appreciate more guidance on what is the real deadline.

DR. FERRIERI: Dr. Levandowski, could you start to

address that?

DR. LEVANDOWSKI: I will, and the manufacturers may wish to comment on that also. The longer the decision is postponed, the more difficult it is for the manufacturers

to produce vaccine, as it has already been stated. I think we all agree that that is true.

It is difficult to not only make the vaccine, but it is also difficult to get the standardization reagents produced in a timely fashion. I would say that we are late this year in terms of starting to consider some of the strains that might be used. If we would make a strain change, we would be very late in terms of trying to get information both for manufacturing and also for production of reagents.

But in terms of an absolute deadline, I don't know that there ever is an absolute deadline. Things are always in relative terms with influenza, and we are always trying to balance whether there is a vaccine produced at all or whether the vaccine contains the antigenic composition that most closely matches the strains that are likely to be causing infection.

DR. FERRIERI: Realistically, Roland, how many weeks do you think you can really -- how much longer do you think it would take to come up with substantially more data, four weeks, six weeks, or is it completely unpredictable?

DR. LEVANDOWSKI: I will give an answer and then maybe Nancy Cox would like to give an answer. I think that it would probably be a period of weeks. We have been scurrying for the last three weeks to get this information

together, and even now it is not complete. If we had more time, we would probably have more information, but I think a period of a few weeks would give us an opportunity to collect quite a bit more information and to amplify the results or the differences that we found already in terms of serologic responses and antigenicity, and maybe Nancy Cox would like to address this also.

DR. COX: I would like to make a couple of comments about coordination of flu vaccine strain recommendations worldwide. As many of you in this room know, the WHO makes vaccine strain recommendations usually in mid-February, and in general, a significant amount of data are developed between our own national meeting and that February meeting.

Although the time period is short, we are really cranking out data at full speed, and so there is no question that we will have a significant amount of new antigenic and genetic and potentially serologic data available by February 17th through 19th, when the WHO meeting occurs.

I think that given the amount of worldwide travel that occurs, and so on, it is very important to coordinate

the decisions because we get many, many questions at CDC about what travelers should do if the European recommendations are different from the U.S. recommendations, we get calls from the military about whether the military

stationed in Europe should receive a different vaccine, so it is very important to have coordination and clarification of the strains that are used in vaccines worldwide.

DR. KILBOURNE: Could I comment?

DR. FERRIERI: Yes, please.

DR. KILBOURNE: I can't speak for manufacturers. My understanding from previous discussions through the years have been we have been faced actually with several deadlines.

If a definite choice could be made on one of the three strains, they can immediately stick their virus into those eggs, so they don't go to waste, and my reading, my own personal reading of what is going on is that most likely they will stick with the B, and maybe some decision could be made on that pending further information from the Geneva meeting.

DR. FERRIERI: Thank you. Yes.

MR. THIBOUTOT: Roth Thiboutot again. Our choice, I guess our need is for the second strain, not the first. Between all the manufacturers, between two weeks and 20 days, if we don't have a second strain, we have an I Love

Lucy movie occurring. We would have a lot of eggs coming in and nothing to go in them. So, those are the exact facts.

Some manufacturers it is two weeks, some manufacturers it is 20 days for the second strain, not the

first strain. So, that is the reality, and the reality is, it is not only, as I said, financial.

What will occur at the end of the season, we will not manufacture enough vaccine because we have had this break, we are counting on every single day, and between all the manufacturers, we are cranking out a couple of hundred thousand doses a day, and there will be no making up for them, because of the fact that flu has to be sold in August and September, if you will, so it will be available.

Those are the horrible facts, I guess, but those are the facts.

DR. FERRIERI: Would you refresh our memories, Dr. Levandowski. Last year I thought we had only make one recommendation at the committee meeting, and then the other two came later, is that not true?

DR. LEVANDOWSKI: Yes, but I think we probably had a firmer direction at the beginning of the year last year than we really do now. The discussion really was, for the most part, centering around the H3N2 component of the vaccine, which was not very clear at all.

DR. FERRIERI: Dr. O'Brien.

DR. O'BRIEN: Actually, listening to your summary versus what I had heard before, I would have said that it was the H1N1 that was the most problematic in this worry about a potential for the Beijing isolate to move further

than Europe, and I wouldn't, in listening to you, have predicted that we would be in such a dilemma about the -- I mean the other people -- the H3N2, and yet you presented it as actually that is the most problematic.

What am I missing here?

DR. LEVANDOWSKI: I may ask for some help from Nancy Cox on this also, but I think we are concerned by the results that we have seen from the serologic responses to current vaccines.

We have heard that there is antigenic heterogeneity, and there is a new genetic group which seems to correspond to a group -- at least one of the strains that was used in the serologic procedures -- where there may be some reduction in the antibody responses. If that is a group that is expanding rapidly and may have the potential for being the predominant strains in the future, I think we would want to try to get more information that would help to make that clear.

Is the expansion of the A/South Africa/1147-like strains such that it would warrant consideration for changing that strain?

Maybe Nancy Cox would like to answer that.

DR. COX: Only just briefly. What Roland said about that genetic group expanding is true, and we want to have time to look at additional viruses in that group in

cross tests and in serologies, and to do a good bit of sequencing. The reason that we considered the H3N2 candidate so carefully is that it is responsible for a lot more serious illness.

DR. FERRIERI: I think it might be helpful if you could redirect us to some of the data that would permit us to understand cross-neutralization data from the ferret antisera to the emerging new H3N2 strains, or is there just not enough data? I can't put my finger on it instantly, Dr. Cox. That might help us in our deliberations to be able to now target some precise information rather than our having seen everything laid out.

If we could take a few minutes, if you don't mind. Would others of the committee agree that this might be valuable? We have had to digest this information quite recently and fast.

I would like to state that everyone on the committee is committed to trying to arrive at the very best decisions possible with the information at hand, appreciating very much the problems the manufacturers are presented with, but it would be very rash of us to neglect

anything critical that is emerging, as well.

DR. COUCH: If I could while we are waiting, I just have two or three general comments I was interested in making before you maybe come to grips with specific

decisions.

DR. FERRIERI: Yes, please.

DR. COUCH: By the way, over the years since I have been sitting here, the amount of data that is provided for these decisions has grown almost in logarithmic proportions. I decided when I looked at that packet last night, I am going to make me start taking an earlier plane, so that I can spend more time kind of digesting some of that data. I think we ought to say how nice it is to have the global perspective presented more completely than I think we have heard in most years, and to have Britain and Alan Hampson visiting us with that data, too, I think that is interesting.

Just from the point of view of trying to come to grips with it a little bit, one of the deficiencies -- let me just call it a minor rather than a major deficiency -- we have really got a lot of strain information now, almost more than we can digest, and you are really doing a complete job of serologic responses in all age groups scattering around pretty well.

In trying to assess these things, that third

ingredient is the epidemiologic significance of the strains we are looking at, and that is not clearly given to us each time. I think Helen gave some -- this is a sporadic isolate, this is an outbreak isolate, so we have got a

little better feeling of it is still restricted to China, it is a sporadic isolate, or it is a clear-cut outbreak. That sort of information is also important input to the decisionmaking, and that wasn't clear in the data.

So that would be one of my requests, that in the future, perhaps that information be more clearly presented to us, as well.

The last comment before you go on to the decisions that I wanted to make was support for the concept of deferral, not to make the manufacturers have a hard time, but because I think that from my point of view, that is the one introduction since I have been sitting here that has probably accounted for more of the recent vaccines having the perfect match or the almost perfect match by the epidemic than most of the decisions that we have made around here.

So that it really is a give and take I think, as Roland has said, with the manufacturers, not to be punitive to the manufacturers, but to make the best decision and to move when we have to, but that ability to defer rather than all three strains today, which is the way it was when I

first came on this committee, I think has been a major help in the matches.

DR. FERRIERI: Thanks, Bob.

This was not intended for us to rapidly get to the

decision, but in my opinion to amplify and having us more targeted.

Dr. Cox.

DR. COX: Yes.

[Slide.]

What we really would like to be able to do for the H3N2 strain is gather more information on those viruses that are fourfold or greater down with the Wuhan and Nanchang strains with the antiserum to Wuhan and Nanchang, and find out are these viruses in one specific genetic group or not. That is the primary use of our sequence analysis, to determine whether the viruses which are antigenically different from the vaccine strain are all in one group or predictably in one group because of the antigenic profile or if they are scattered around.

If we can determine the trends more precisely than we are able to do at the moment, I think we will be much clearer in our thinking about where we need to go, if we need to change directions with the H3N2 vaccine strains.

DR. FERRIERI: What do you view as representative of the new strains, the South Africa/1147/96?

DR. COX: The South Africa is one representative, and so what you can see in this test is that the ferret antiserum to Wuhan inhibits the South Africa virus fourfold less well, and we consider fourfold differences to be -- if

they are reproducible -- to be important or potentially important.

As Helen pointed out, the South Africa homologous titer is rather low, and so we don't therefore see a two-way difference, and sometimes when we have seen one-way differences in the past, they have not been very important, and sometimes they have turned out to be more important as the viruses continue to move.

So this is a somewhat ambiguous situation. If we had only the ferret data, we probably wouldn't worry all that much, but we have the post-vaccine serology data, and that gives us pause.

DR. FERRIERI: That is a very important point because I wasn't impressed that these differences were perhaps major enough regarding what the biologic significance might be than in humans is really the issue that we must consider.

Dr. Reingold.

DR. REINGOLD: Can I just understand a little more clearly, when you say that you would like to understand better whether these are genetically similar or genetically

different to ones where there is less antibody, how would that influence the decision? I mean could you take me through the thinking of that in terms of each of the scenarios, what the implications would be for the selection

of the vaccine candidate?

DR. COX: Perhaps I can do that best by recapitulating what happened last year. We had seen some antigenic drift, actually it was more dramatic than this for the Wuhan strains, and we wanted to find out if that group of viruses was really expanding and growing.

If we see that the viruses that are different antigenically are falling into one of the genetic groups, that is a clear indication that that group is really growing and going somewhere both antigenically and genetically.

On the other hand, if we see viruses that are located in the evolutionary tree in very different positions, all being down, there is not such a clear evolutionary trend even though you may see it reflected in the antigenic analysis. The genetic analysis tells us that the viruses are simply very variable, and there is no particular direction that they are going. If there is an indication of a direction, it tells us where to go with the vaccine.

DR. KILBOURNE: Nancy, what you are saying is the phylogeny really is very important in terms of the

epidemiology, and it is an epidemiologic question.

DR. COX: That's right, and although we haven't presented it very clearly today, we do try to sift through and look to see what information we can gather worldwide

about the extent of influenza activity that was occurring at the time the particular virus isolation was made, and that also is taken into consideration.

So, we will try to present that information more clearly.

DR. KILBOURNE: Just a quick comment on the South Africa again. The differences you are seeing, although they are fourfold, you are not sure of the other direction, they are in the worrisome direction.

DR. FERRIERI: Dr. Glode and then Dr. Belshe and Dr. Apicella.

DR. GLODE: This would also be a question for Dr. Cox.

I just want to ask a question about vaccine efficacy. If we now have -- this was my understanding and someone can correct me if this is wrong -- some 80 million doses of influenza vaccine produced, but still a large epidemic of H3N2, and at least in some of these tables, a strain that at least in the elderly and children doesn't look very immunogenic in humans, then, is there also a part of this that either is being done by other individuals each

year, some sort of case control study that gives an estimate of vaccine efficacy?

I guess I am wondering if we are sure we have an efficacious vaccine that we are widely distributing, because

the epidemic curves aren't really going down, you know, maybe it was going to be huge, but is that part of it? Do we have any information on that?

DR. COX: That is a very good question, and we have fielded similar questions almost every year at this meeting. Unfortunately, we haven't had funding and so on to do some of the vaccine efficacy studies that we would like to have done over the past few years.

There is an effort underway to look at least in Medicare populations at vaccine efficacy against hospitalization on an ongoing basis, so we will have comparative data.

We know from past experience that it is very important to compare H3 in two years, and not compare H3N2 with B years, because it is simply not a valid comparison. So we hope that in the future, there will be historical data available at least on hospitalization.

There are some smaller ongoing trials. Unfortunately, some of the trials that are going on with the live attenuated vaccine have not had an inactivated vaccine arm. I was hoping that those trials would have, so we would

have that data.

We have a small trial in day care population. We will have some data probably in about six months' time. Kristin Nickle is going to be developing her information

from her HMO population. She is primarily looking at healthy individuals 65 and older. So, there will be some data available later on.

There has actually been rather a lot of concern about vaccine efficacy this year, and it certainly for us has been difficult to understand, because the vaccine match has been good, as we have shown you.

We think that perhaps part of this is due to the fact that there are a lot of other respiratory viruses circulating at the same time, but we also feel that there are an unusually large number of reports to us of vaccine failures, and we don't quite know how to interpret this, so we are looking forward to the data that will be available in about six months' time.

It is true that the post-vaccine serologic titers were rather low in many populations.

DR. FERRIERI: Thank you.

Dr. Belshe.

DR. BELSHE: I actually wanted to followup, Nancy, on that particular point, and clarify regarding these children down at Vanderbilt. These are two doses of vaccine

given to children an average age of 13 months, so presumably, they are not previously infected, is that right? And the striking is that H1 and B antibody responses look quite good, but the H3 antibody responses look quite low or

absent.

DR. LEVANDOWSKI: Which tables are you looking at? Is that John Treanor's tables?

DR. BELSHE: I am looking at the tables in the CBER document.

DR. LEVANDOWSKI: As was pointed out, our results for the H3's were atypically low compared to other of the laboratories that we are looking at, at vaccine responses this year. John Treanor might want to describe the results that he got in his laboratory, because I think their H3 results are more typical than we have.

DR. TREANOR: Those are kids that Bill Gruber vaccinated who are in a clinic, and largely are children, I think, with bronchopulmonary dysplasia, and they received two doses of 0.25 ml of vaccine separated by a month, and this is before the first dose and a month after the second dose.

When we did the titers on this, we got an 84 percent response rate to the Texas. This is in the handout that I don't have overheads for, a 94 percent response rate to the Harbin, and 69 percent response rate to the Nanchang.

In the H3 group, those kids -- and there is 30 of them in this group -- 69 percent responded to Nanchang, but only 16 percent responded to South Africa, and the mean GMT is 29 to Nanchang post-vaccination, and only 8 to the South

Africa virus.

DR. BELSHE: I would say that is pretty good data in humans, that if there is a change in the strain circulating in the world, then, we need to mirror that in the vaccine. We will come back to the epidemiology data on what H3 is going to circulate next year.

DR. FERRIERI: Dr. Apicella.

DR. APICELLA: I just want a clarification. A/ Auckland/05/96 is a reassortant?

DR. LEVANDOWSKI: The IVR/9 strain is a high-growth reassortant.

DR. APICELLA: It is a high-growth reassortant. So that is available. That would fit in the South Africa group?

DR. LEVANDOWSKI: No. That would be more in the Wuhan/359- Nanchang/933/95 group.

DR. FERRIERI: Dr. Couch.

DR. COUCH: I think the kids come closer to being like ferrets. That is what we are looking at.

DR. FERRIERI: Every parent will thank you.

DR. EDWARDS: Spoken like an internist.

[Laughter.]

DR. FERRIERI: Dr. Adimora.

DR. ADIMORA: This may have already been mentioned, but I seem to have gotten lost here. I wanted to

ask about the frequency of isolation of some of the -- well, both the H3N2's and the H1N1's with low post-vaccine GMT's, just to get sort of an idea of what their importance is, if that is possible.

I mean were they just sporadically -- I just have gotten lost in all this data about the frequency of isolation of some of these particular viruses with low GMT's.

DR. LEVANDOWSKI: Is the question about why choose those particular strains to do the serologies and how representative are those strains for all the strains that are circulating in terms of the serologic responses of people? Nancy Cox and Helen Regnery will have to answer. I think they were discussing it.

This is a question for you and Helen, Nancy, about the frequency or the representativeness of the strains used for the serologic procedures.

DR. REGNERY: The South Africa/1147 that we were discussing is a different genetic group, we actually just started testing that virus recently, and the data I have from South Africa itself is limited. Alan Hampson has more

information on what the viruses circulating were actually characterized as, and they were Wuhan-like, but South Africa, I don't know what percentage and how testing was done in South Africa to show that 1147 might be more

prevalent than the 359. We haven't had the virus long enough to run a large set of sera antigens against it to really know what kind of percentages you would have and frequency of isolation.

As we test more viruses -- and there are a lot of H3 viruses to be tested -- might be able to get that information from our own U.S. isolates or either from China.

DR. FERRIERI: Other questions from members at the table? Dr. Reingold.

DR. REINGOLD: If I could follow up on Dr. Glode's question just a little bit. It seems to me that if this is a bad epidemic year, there are obviously a number of possible explanations. One is that the formulation of the vaccine is not a good match this year. The second is that it is a good match, but it is not opened.

A third is that the coverage is very low. A fourth is that most of the disease is not caused by flu virus, but it is caused by something else, and I would just like to say that we don't have some sense of which of those is the right answer.

Are we looking, for example, at the data from the

U.S., it looks like an average of about 20 percent of the specimens submitted for influenza testing turn out to be influenza. I mean is that the figure we would expect in any given year, is that high, is that low? I guess I am baffled

that we don't have some sense of which of these is the most important factor.

DR. ZAMBON: I can say a little something about surveillance data as carried out in the U.K. and Europe. Good surveillance data based on good clinical acumen usually yields a specimen positivity rate of the order of 25 to 33 percent positive for influenza at the peak weeks of the peak season.

Overall, you might expect to see something of the order of about 20 percent positivity, and I don't think you ever see very much in excess of about 35 or 40 percent of surveillance data based on culture of virus.

If you look detection for detection of virus by molecular methods, let's say, by PCR, you may go as high as 50 percent, but in most surveillance schemes I am aware of in European countries, the positivity rate for flu by whichever method you use is never more than about 50 percent, which means there is always going to be a substantial component of respiratory illness not detected elsewhere.

I think at the beginning of her talk, Dr. Regnery

actually indicated that, or one of the American talkers, indicated that some 20 percent of surveillance specimens submitted in the United States was of the order of 20 percent positive. So, I would say that is at least

comparable with the European data.

DR. FERRIERI: Thank you, Dr. Zambon.

Does anyone else wish to address some of Dr. Reingold's point, though, regarding the epidemiology of respiratory illness?

Dr. Clements.

DR. CLEMENTS-MANN: I can't remember which figure was cited, but there was an age group distribution I thought for hospitalization, but I could be wrong, which demonstrated the higher peaks were actually in the younger age group, the 18 to 64 age group, and also in the less than 5-year age group, and typically, those would probably be age groups that are not routinely vaccinated for influenza.

So, there clearly is a good influenza epidemic in many of the younger age groups, and so we would really need to look more directly at age groups that had been vaccinated to really get an idea of the vaccine efficacy, because the epidemic seems to be somewhat -- at least that is the only data that I remember seeing by age group, but that would suggest that a lot of the epidemic is occurring in unvaccinated age groups.

DR. FERRIERI: Dr. Couch.

DR. COUCH: For this kind of discussion, it seems to me it is important to appreciate that the policy for vaccine use in this country is not to prevent epidemic

influenza; it is to prevent hospitalization and death, and while we are making real inroads in approaching that high-risk population, the last figures I heard were still between 50 and 60 percent, so roughly half of the population that is the major target is still unvaccinated.

So, there is a task yet there in front of us, and even if you take the 180 million doses, and let's say it was all delivered, you know, we are about 250 million people. We are talking about a third of the people were vaccinated and if it is 70 to 90 percent effective, we have only done something for 20 to 25 percent of the population, and the population that is less likely to respond than those healthy individuals.

So, this is not for epidemic control. We can't be surprised at that part of it. Then, when you look at what you do get, you see, you are looking at the vaccine failure, at the person that got sick, so those are the persons who would yield the strains that only when we can begin to do the kinds of things Nancy was saying we need to do can you then begin to answer the questions that are being raised around here, and that data is not available right now.

DR. REINGOLD: My only point would be to P&I death data where now 8 percent of the deaths are being from pneumonia, influenza, being substantially above the 95 percent confidence intervals and what is expected, that that

obviously is an indication that either this is a bad epidemic year or something --

DR. COUCH: Or they weren't vaccinated. We don't know is the major point.

DR. COX: One of the things about the P&I mortality data, it is always very attractive to look at P&I mortality curves and say, oh, the vaccine is doing something or the vaccine isn't doing something, but it is only when you look in vaccinated and unvaccinated populations that you can really see what influenza vaccine is doing, because the different strains cause very different effects in the population.

DR. FERRIERI: Yes, Dr. Eickhoff.

DR. EICKHOFF: I think it is important that we all realize that influenza vaccine is an imperfect instrument at best. Even under ideal circumstances when there is a very close match with the wild virus and the vaccine strain, and in healthy young adults, the best that can be achieved in terms of efficacy is somewhere around 85 to 90 percent.

That figure deteriorates as you get into older adults and deteriorates still further when we talk about

elderly adults. So, I think what happened this year is not a huge surprise, and certainly does not necessarily indicate that there was not a good match between the wild virus and the vaccine strain. The vaccine may not have been all that

potent.

DR. COUCH: Or that there was a significant reduction in mortality --

DR. FERRIERI: Dr. Couch, would you repeat what you just said into the microphone for the transcriber?

DR. COUCH: Just a final phrase at the end of Dr. Eickhoff's comment, that we don't know that there might not be significant reduction among vaccinated individuals.

DR. FERRIERI: Correct.

Dr. Clements.

DR. CLEMENTS-MANN: I just wanted to say that the H3N2 strain is typically more virulent and results in more illness than either the B or the H1N1, so I think what we are seeing is the effects of a virulent H3N2 virus, and whenever it circulates, and there are enough susceptibles, we see a lot of excess illness.

DR. FERRIERI: Dr. Kilbourne.

DR. KILBOURNE: Well, taking off on the last point, I would agree. I think the evidence is that H1N1 tends to be the milder cousin in terms of population penetrants and in terms of individual case morbidity,

22 although having been alive in 1947, there were lots of

23 people that had temperatures of 104 with H1N1.

24 It seems to me that we have a peculiar dilemma

25 with the H1N1 this year because on the one hand, I think the

evidence is from the last few years that the virus is kind of struggling to survive in the presence of the more effusive H3N2, and you could make a case that since we did have an H3N2 year, and also a fairly big one last year, that maybe there would be a vacuum in which the H1N1 can now emerge.

On the other hand, if the incidence, as it appears to be, is sort of dwindling, the virus may die, and the subtype may disappear, but I think it is wise not to make any assumptions of that sort about any flu strain, so I think we should use judgment there.

I am struck by the data from Nancy Cox on the genetic characterization, in which Beijing/262 seems to be such an outlier, and seems to go along with its antigenic differences.

I was pointing out earlier it is not only with the hemagglutinin, but there is evidence now that the neuraminidase is less related, as well. So, it could be a potentially dangerous virus in terms of epidemic emergence, but having said all that, I think we can't forget the ability of H3N2 to keep continually changing and the South

Africa strain data would indicate that significant changes can occur there.

I don't know whether you want a recommendation from me or not, but those are just comments.

DR. FERRIERI: We will defer that for a few minutes perhaps, Dr. Kilbourne, there is a need for a little more discussion.

Dr. O'Brien.

DR. O'BRIEN: Actually, it is a little dated now, the discussion has changed, but back to how do you tell whether the vaccine is efficacious, and we really can't tell because not all the elderly are immunized, but we do have a population that is always immunized, and that is the military, and they are young and healthy.

Assuming they get immunized on time, which was a discussion point that came up earlier in private, we should be able to get some data from them.

DR. FERRIERI: In terms of efficacy.

Dr. Apicella, did you have your hand up also? Other points?

Yes. Could you give us your name, please.

MR. HOKE: My name is Charles Hoke, and I am in the Army, obviously. This issue of efficacy is obviously one of great concern to the military. We certainly don't have any kind of control data, but surveillance is conducted

on basic training posts for acute respiratory illnesses, and as a general rule, rates are very, very low no matter what else is going on in the community.

That surveillance is conducted by the Center for

Health Promotion and Preventive Medicine, the CHPPM. I don't know if anyone is here from there and can comment on current data or not, but I would say, as a general rule, these people are immunized, they get influenza vaccine, they get adenovirus vaccine, and in an attempt to keep respiratory rates low, because when they become ill, they have to recycle through their training, and that is expensive and difficult to do.

As a general rule, as I said, the rates of respiratory disease in these populations are very, very low year after year regardless of what else is going on in the community. So, although this is somewhat anecdotal data, it certainly suggests that you are doing the right thing in general with your selections.

DR. FERRIERI: Thank you.

MR. HOKE: If I could make one more comment about that, that also is a population that is a very valuable one potentially for detecting outbreaks of influenza due to viruses that are not well covered by the vaccine, so this is one of the reasons we are looking, because we feel that since it is a universally immunized cohort, that outbreaks

of disease there would be very significant potentially.

DR. FERRIERI: As many of you have gathered, we are not taking a second break this morning. The momentum is too good to give up on. So we will just keep going and then

come up with our recommendations.

Dr. Broome.

DR. BROOME: I am struck by the discussion on assessing effectiveness of the vaccines. This is something we could discuss forever and be no closer to the truth. Either we have to decide this is something that is worth knowing, in which case it is going to take some very focused, very carefully designed work to get the answers, are we trying to get a better comparison of titers with protection, and that would suggest certain ways of going, but I think the anecdotal data is essentially useless for the reasons that have been mentioned, and therefore, it is at best misleading to speculate about this being a poor efficacy vaccine just because of the inability to have a precise case definition, the lack of knowledge about vaccination rates when you look at overall surveillance data, et cetera.

I must say I would favor -- I think it would be important for us to know a little more about the efficacy of these vaccines, which essentially do change each year. We are making big assumptions that we can predict vaccine

performance based on titers, and it may well be worth thinking about some focused studies to recheck that hypothesis, but I think it is going to take resources and a well-designed effort to do it.

DR. FERRIERI: Thank you.

Dr. Hall.

DR. HALL: May I just ask Nancy or Helen a technical question in terms of the HI, particularly for the H3N2, and that is, when you noted that the South African was low against itself, and it was down onefold, I guess, against one other virus, does that in and of itself have any correlate in terms of what produced immunogenically in a human? I mean as you look at this, it looks like the Nanchang would do just as well. It was down onefold to two of the viruses. So, is there any correlate we can take from that?

DR. COX: We don't believe that there is a correlate, that the homologous titers produced with the post-infection ferret sera are probably not indicative of the immunogenicity of the strain in humans, unfortunately. It would be extremely nice to have an animal surrogate for immunogenicity in humans and have a bit more time to actually look at the new strains, but we are always so pressed to make the recommendations that we have very little time to develop animal data, but nevertheless, I think it is

worth looking at this.

DR. FERRIERI: Do we all have enough information at the table, have we taken the questions and discussions far enough now that we can address what our recommendations

would be? Dr. Edwards, do you have a point?

DR. EDWARDS: I had a question in terms of since there are so few H1N1 strains that are being isolated, will there be additional data gleaned from more isolates over the next several weeks or not. I was a little confused by that.

DR. COX: I think there will be limited additional information, however, I think it is very important to followup on the observation in Switzerland, and as Helen mentioned, there are another seven influenza isolates from the same hospital, and it is important to find out if they are Beijing/262-like or if they are simply Taiwan-like isolates, or if they are H3N2.

DR. FERRIERI: Dr. Eickhoff.

DR. EICKHOFF: Can I follow that up with a question to Nancy? Well, more broadly than Nancy, to all of us. If those seven viruses in Switzerland were found to be the variant, the Wuhan-like H1N1 viruses, which heretofore have been previously limited to China, would we on the basis of that information be ready to recommend changing the H1N1 component to that screen? That is the only reason, justification to defer a decision.

DR. FERRIERI: What more would we need then, Dr. Cox, I mean, realistically, how much more would be available in two weeks, and then if that were the case, as Dr. Eickhoff indicates, could we come up with a recommendation?

We have to get off the dime at some point on H1N1.

DR. COX: I was hoping that question would go away.

DR. FERRIERI: I am afraid not.

DR. COX: I think it is a good question for all of us, and I think that in addition to having the information about the other seven isolates, we would have some sequence data that have not been developed yet, where we would be looking at some of the isolates that react a bit lower to the Texas antiserum, and so there will be additional information in spite of the fact that there won't be a lot of new isolation information.

DR. FERRIERI: And the prototype has not been distributed yet even to the manufacturers.

DR. COUCH: Another part of this is whether CBER will have reagents and the viruses to even back that up.

DR. FERRIERI: Exactly.

Dr. Clements.

DR. CLEMENTS-MANN: There is information and things that would need to be done to have a contingency plan to select an alternate strain, you know, to narrow down the

possible strains to a few, and to see what kind of growers they are, and then to see what can be done about reagents, because it seems like if we are deferring, we would like to have some of that backup, so that then we could go into full

gear making the vaccines.

DR. FERRIERI: Dr. Levandowski.

DR. LEVANDOWSKI: Yes. Of course, we try to get that information as expeditiously as possible, and, of course, the manufacturers supply a lot of the very valuable information in terms of understanding what the different strains will do.

They are very good at getting things to grow. If anybody can do it, they will, but it does take them time. It takes them two to three weeks to have some good indication as to whether a strain really is going to be a good grower or not.

It takes several weeks, it takes at a minimum three weeks if one is lucky, but more likely, six weeks or more to make a high-growth reassortant and have a clone that seems to be the right one that you can be confident about the hemagglutinin and the neuraminidase.

So, we do try to distribute and try to get the reassortants going as soon as we recognize that there may be a need for those, but there are some limitations. The manufacturers also cannot work with that many strains. We

try to get them the ones that seem to be the most different and the most interesting in terms of new changes, and I believe we have done that for the wild type strains at this point.

We have not necessarily done that with high-growth reassortants because we don't have those yet for the strains that may be the most interesting.

DR. FERRIERI: Any other points? Art?

DR. REINGOLD: If I could just followup on Dr. Eickhoff's question, I think, Nancy, you got to just a little bit. I think that the fundamental question is that once you know everything you could possibly know about those H1N1 strains, is there a scenario you could conceive of where those data would dictate changing the formulation of the vaccine?

I mean is there a scenario you could envision once you have all of those data, where that would make for a compelling reason to change the vaccine this year? I mean isn't that the question?

DR. KILBOURNE: The scenario is that it will spread very rapidly.

DR. REINGOLD: But I am saying two weeks from now, if you have finished doing everything you can possibly do to those isolates, you know everything you could possibly know about them, could you have a set of data on those isolates

that would say, aha, we should change to a different strain?

DR. FERRIERI: Dr. Cox.

DR. COX: I am not sure I can answer it very clearly, but what I would say is that if it turned out, for

example, that a number, five of the seven strains were the H1N1 deletion variant, and we found out that the patients were really quite ill because we know that these isolates came from a hospital so presumably the patients were hospitalized, we would really be quite worried.

I am sure that there will be a lot of attention on this observation in Europe, and that there will be a lot of scrutiny of any H1N1 isolates that come through, and data can develop very rapidly. So, I think that we would be wise to wait and see what comes up in the next three weeks.

DR. FERRIERI: I might add, though, that in many European countries, as well as even here, outpatient samples are submitted to virology diagnostic labs, so one cannot make the assumption that these were very ill patients who were hospitalized. You would need precise data.

Other points? Dr. Couch.

DR. COUCH: Just repeating a point I made earlier, and that is that with what Nancy is saying, that in the past, this has worked very well to actually defer that decision rather than -- I guess we had the option here of decision now or decision based on certain contingency

information -- is delay that decision until all of the data is in hand, a little time goes by, you think about it more, you consider it more, and then there is a big conference call, and I think in general those have worked quite well.

DR. FERRIERI: Well, they have worked very well in my more recent experiences, as well as the previous time I was on committee, so I am a little bit perplexed this year about the urgency. Well, there is urgency from the manufacturers' point of view, but I still think that it would be best to have the information.

DR. KILBOURNE: I worry since we are talking now about mild versus virulent strains, they are all virulent, and I think that to get anecdotal or insufficient information or even complete information about a few hospitalized cases, it certainly should not influence our decision.

DR. FERRIERI: I agree.

DR. KILBOURNE: It is either a flu or it isn't, and it is going to spread or it isn't. So, I think the epidemiologic considerations, and Nancy's phylogenetic considerations, which is part of the epidemiology, should prevail in making a decision.

DR. EDWARDS: Not exactly related to the choice of agent, but I think we probably or at least I would like to hear a tiny discussion about the issue regarding the lot of

vaccine with decreased immunogenicity, and has the difficulty with that been identified, so that is not something that we need to worry about subsequently or that is not really cogent to the selection choice, but it is

certainly cogent to the efficacy question.

DR. FERRIERI: Well, someone needs to address that. Dr. Levandowski, do you have someone who can speak to that point? It is a compelling point, and it can be very briefly addressed.

DR. COUCH: It was the single manufacturer, so they are the ones that would have to address it.

DR. FERRIERI: Yes, I know, but we can't force anyone to get up and speak to the point.

DR. LEVANDOWSKI: While we are waiting for that possibility, I don't mean this facetiously. There has been a lot of effort that has gone into evaluation of the lots of one vaccine manufacturer's vaccine that had decreased potency and what the implications of that might be, and, first of all, I should say that it does not seem to be something that would be generalized to all manufacturers or any manufacturers.

There was information that was developed subsequent to identifying the reduced potency, and I should emphasize that the reduced potency only occurred after the vaccine had been released and had full potency at the time

of release. It was something that was occurring on storage.

When that was identified, there were some studies that were done to try to determine what the extent of that might mean for immunogenicity of the vaccines, and others

will probably want to comment on this, but there were studies which were done by CDC, and perhaps Keiji Fukuda should comment on this, and there were studies that were done by the company themselves to look at immunogenicity, and this information has been published in Morbidity and Mortality Weekly Reports, so that everyone can look at it if they want to, but the bottom line for it was that there did seem to be some mild reduction in the potency or in the immunogenicity of the recalled vaccine for the lot that was used for the studies as compared to another comparative vaccine which had full potency.

The extent of that was on the moderate side. It was something that was statistically significant, but yet it was of a level that made interpretation somewhat difficult. The manufacturer also did a study comparing their recalled vaccine to non-recalled vaccine, and did not see any difference between the results in populations they looked at.

The two populations were different. The CDC study was done in nursing home patients. The company study was done in health care workers. So, they are not immediately

comparable, but I would say that I think those data are still somewhat difficult to interpret, and are not viewed as something as a cause for great alarm.

In fact, the recommendation that was made as a

result of reviewing those studies very carefully was that immunization should continue, emphasizing those people who had not previously been immunized up to this point in the year, and then those individuals who had received the recalled vaccine could consider being reimmunized, but it wasn't considered as a first urgency to do so.

There are others in the room here who perhaps should comment on what I have just said.

DR. FERRIERI: Any takers on that? If so, come forward now.

MR. BOSELLI: Bruce Boselli representing Parke Davis.

I think Roland Levandowski had summarized the situation fairly well. I think we agree with basically what he said. We are still evaluating the situation, and at this point in time, it is unclear to us that this has any necessary bearing on the decision that is going to be made today.

DR. FERRIERI: Thank you very much. I think that is about all we can say on this point today, if you don't mind, and we are in a position now where I think we need to

have a recommendation made from the advisory committee, and I would entertain anything that would be in the form of a recommendation motion.

This is regarding the components of next year's

influenza vaccine. It can be made in any form, making a single recommendation or it could be made in any number of variations.

Dr. O'Brien.

DR. O'BRIEN: I would just get the ball rolling by suggesting we retain the current B component.

DR. FERRIERI: That is a simple recommendation. I would like to have a quick vote on that. Those at the table who, according to Ms. Cherry, are not able to vote today, would be Drs. Kilbourne, Dade, and Reingold.

Dr. Adimora, yes or no?

DR. ADIMORA: Yes.

DR. FERRIERI: Dr. Apicella?

DR. APICELLA: Yes.

DR. O'BRIEN: Yes.

DR. FERRIERI: Dr. Belshe?

DR. BELSHE: Yes.

DR. FERRIERI: Glode?

DR. GLODE: Yes.

DR. FERRIERI: Eickhoff?

DR. EICKHOFF: Yes.

DR. FERRIERI: Broome?

DR. BROOME: Yes.

DR. FERRIERI: Couch?

DR. COUCH: Yes.

DR. FERRIERI: Clements?

DR. CLEMENTS-MANN: Yes.

DR. FERRIERI: Dr. Hall?

DR. HALL: Yes.

DR. FERRIERI: Edwards?

DR. EDWARDS: Yes.

DR. FERRIERI: Meier?

DR. MEIER: I suppose so, yes.

DR. FERRIERI: Thank you. For the record, my vote is yes also, so that was easy, the easiest thing we have done in a long time.

Now, is there any recommendation we can make on the H1N1 and H3N2 virus components?

DR. COUCH: I will make a recommendation on H3.

DR. FERRIERI: Pardon me?

DR. COUCH: I will make a recommendation on H3.

DR. FERRIERI: Please.

DR. COUCH: That is that I would like to defer it as much as possible. The manufacturers have suggested that we don't have much leeway there, and the general view I took, which I don't think has changed to date from the

information I have, is that H3, we probably would be all right continuing with Nanchang.

If we change it, it would fall in the category of what I would call fine-tuning, but we would like to fine-

tune the H3N2 viruses, but a part of that is that this will have to be I think the next decision in line would be the H3, and that may be forced by a strain we have and the reagents we have when the manufacturer has got to have another strain to come on line, and I think it is much more important to have H3 vaccine in adequate quantities on time than it is to fine-tune it.

So, it is a recommendation for as deferral as much as possible, but not being unhappy with having to go with the current strain if that becomes necessary.

DR. FERRIERI: Is this a consensus of the advisory committee members? Could I have a show of hands, those in support of deferring on H3N2 for everyone who is eligible to vote? Put your hand up, please, so that I can get a head count here.

[Show of hands.]

DR. FERRIERI: It is unanimous to support Dr. Couch's recommendation that we defer a decision on influenza A(H3N2) choice. All right.

Let us move on to A(H1N1).

Yes, Dr. Eickhoff.

DR. EICKHOFF: I will recommend that we defer acting on the H1N1 component until such time as further information from Switzerland is available and interpretable.

DR. FERRIERI: Any opinions on this? Who would be

in agreement with deferring, then? A show of hands, please, those eligible to vote now.

[Show of hands.]

DR. FERRIERI: The recommendation is unanimous to defer on A(H1N1).

DR. COUCH: I don't know if the pecking order might be worth considering, but my own view would be that H1 is the one that should, if we have to choose between, would delay the H1 is the one with more consideration, and if we are forced to go ahead, I would go ahead with H3 first.

DR. FERRIERI: I agree completely. Are there any dissenting opinions on that, that the hierarchy then would be to move with the H3N2, and then the problematic decision based on information coming in on the H1N1? Dr. Levandowski and others here from FDA, CDC, would you be comfortable with these decisions for today?

DR. LEVANDOWSKI: I think we would be able to live with your decisions today, yes.

DR. FERRIERI: I am sorry we can't make everyone happy today. I regret that.

DR. COUCH: I would assume we made Dr. Levandowski

happy with that B decision.

DR. FERRIERI: Yes, but this is the best we could do today, I am afraid. I think that the data you provided were wonderful and in no way should our decision on deferral

reflect on any lack of credibility or any doubts about the rapidity with which you produced data for today's meeting. I think that all of you who presented did a marvelous job, and we appreciate the pressure you were under to do this.

We have to move on to other issues now, and we have a lab report that we will move to approximately nine minutes ahead of schedule. We will keep to it. This is an open session, and it is an overview of the Laboratory of Mycobacteria.

Session 2 - Lab Report

Overview of Laboratory of Mycobacteria

DR. FERRIERI: We are ready to start the open session, the Overview of the Laboratory of Mycobacteria by Dr. Michael Brennan from FDA. Mike

DR. BRENNAN: Thanks, Dr. Ferrieri.

In this ideal time slot here, I will try to be very brief. I am representing the Laboratory of Mycobacteria, which is in the Division of Bacterial Products, which is headed by Dr. Anthony, who is here in the audience, and we are in the Office of Vaccines Research and Review.

I would like to just summarize the organizational structure of our laboratory and briefly also summarize the research programs. I believe most of you have received a packet, sort of a large tome, that describes in detail the

research program. I will just summarize in generalities the major focuses of the research programs.

Dr. Apicella chaired an expert scientific committee, which also included Dr. Barry Bloom, Dr. Thomas Shinnick, Dr. Thomas Gillis, Dr. Larry Schlesinger, Dr. Josephine Clark-Curtiss, and Dr. Russell Carlson.

They visited us November 6th last year. We liked them, we think they liked us, and we had a very good time.

[Slide.]

The first slide here, this summarizes the scientific staff that has been in the Laboratory of Mycobacteria since the last lab review, which was in April of 1992.

Above the line is the current scientific staff in the laboratory, and I will talk about two additions that have recently occurred since last October. Dr. Sheldon Morris and Dr. David Rouse are the only two which have been here the whole time. They are in the Molecular Microbiology group, which I will summarize.

I came over in October of 1992 from the Laboratory of Pertussis and took over as the chief of this laboratory.

Dr. Zhongming Li, who is a Visiting Scientist, transferred in with me, as did Julie Rouse, who is a research biologist. Julie moved into Dr. Anthony's office late last year, and is no longer with us.

Dr. Frank Collins joined us from the Trudeau Institute as a distinguished visiting scientist, and he is here in the audience today.

Dr. Joe DeVito is an NRC fellow who works with us. Dr. Mohammed Alave, a staff fellow, and Cynthia Kelley is a research biologist working with Frank.

[Slide.]

Just briefly, the regulatory responsibilities of the laboratory include reviewing submissions that are related to vaccines for the prevention of tuberculosis, and we are in charge of the currently licensed BCG vaccine, and we are beginning to receive a number of submissions on the newer innovative TB vaccines based on subunit antigens on DNA vaccines, recombinant BCG products where the BCG is used as the recombinant vector for genes from heterologous organisms like Borrelia.

One of the largest uses of BCG live is as a treatment for bladder cancer, as most of you know, and we also have submissions for alternative therapies like superficial bladder cancer and interstitial cystitis.

We are responsible for review of the skin test

reagents like the tuberculins, histoplasmin, coccidioidin, and we do other bacterial products like Lyme disease, and we are responsible for the lot release of all of these vaccines and skin test products.

So we try to keep our research as best we can related to these regulatory responsibilities that the laboratory has.

[Slide.]

The laboratory is divided into three major groups. The Laboratory of Molecular Bacteriology is headed by Dr. Sheldon Morris with David Rouse and Dr. Zhongming Li in this group.

[Slide.]

This just summarizes the major focus of the research activities in their laboratory, which include a number of exemplary studies they have done looking at trying to define the genes that are involved in the molecular mechanisms of drug resistance. They have done work on defining the gene changes for the streptomycin drug resistance for Rifampicin, and mostly for the isoniazid with their work on the relevance of the catalase gene and also on the new INHA gene.

Secondly, their program has looked at the identification and characterization of mycobacterial antigens, and this is mostly from their previous work on the

M. avium organism. Currently, they are focusing on this bottom section here, which is more related to vaccine development and on the identification of new virulence factors using molecular techniques.

They have recently identified a trip gene, which they are using to make an aromatic amino acid auxotrophin mycobacteria, and the most exciting new development is the work they are doing now on DNA vaccines. I would just like to point out that what we try and do in the laboratory -- and I hope we made this point to the Review Committee -- is to try to work together among the three groups.

For instance, DNA vaccines is a good example where Sheldon is using his molecular expertise to make the DNA constructs from genes, for instance, such as the one that I identified from the putative mycobacterial adhesion, and then working with Frank Collins and his immunological models to look at the protective efficacy of these DNA vaccines.

So, in a nutshell, that is the program, and the details are provided in the packet.

[Slide.]

The second is the Laboratory of Immunopathology headed by Dr. Frank Collins with Cynthia Kelley.

[Slide.]

As most of you know, Frank was responsible for developing the aerosol mouse model for tuberculosis, and he

is using that model to focus on these research objectives, which include looking at host immune responses, in this case the mouse, to new virulent and attenuated mycobacteria, and also into auxotrophs.

He is collaborating here with Bill Jacobs of Albert Einstein to look at new, innovative, novel auxotrophic vaccines made from M. tuberculosis strains and also looking at unique recombinant mycobacteria where virulent genes have been put into avirulent strains, and he can compare the protective and immunological response in his mouse model for these.

He is also using similar techniques to try to define virulence-related genes in vivo in the mouse, and, lastly, working in an in vitro macrophage system to see what the bacterial host cell reactions are inside the macrophage.

If there are any specific questions, Frank is sitting in the audience.

[Slide.]

Thirdly, my Laboratory of Mycobacterial Pathogenesis with Dr. Joseph DeVito and Mohammed Alave.

[Slide.]

We mainly focus on trying to identify adhesions that are mediating the interactions between the microbacteria and host cells. So, we are trying to identify and characterize new surface cell antigens on the

mycobacteria that mediate host cell interactions.

We have found one which we published on last fall, which is a hemagglutinin, and we are focusing a lot of effort on the biochemical, molecular, and immunological

characterization of that adhesion.

We have two other projects, one headed by Joe DeVito, which is on cell division, cell division which is related to the important question of latency in mycobacteria, the question that we hope will be addressed in future clinical trials on reinfection versus reactivation.

Lastly, we have a collaborative project with Dr. Mann at the Red Cross. I am looking at a novel defensin-like antimicrobial peptide that is derived from lactoferrin and measuring its bacteriocidal effects on mycobacteria as a potential therapeutic especially in the area of drug-resistant mycobacteria.

[Slide.]

We have a new addition to the laboratory, who is Dr. Karen Elkins, who is kindly running the slide projector back there, and her research biologist, Tonya Rhinehart-Jones, and Karen was previously in Dr. Anthony's Laboratory of Enterics and Sexually Transmitted Diseases, but the work she did is very relevant, and we are very glad to have her. We hope that it will integrate very easily into the mycobacteria projects, because she worked on the

intercellular pathogen Francisella tularensis.

[Slide.]

This shows the major objectives of her work, which has been mostly immunological, so she will be part of the

immunology group.

These are her major aims, which has been to determine the basis for survival of her Francisella strain and that she uses in her mouse model work, and she, as you have noted in the packet, has found some novel immunological responses especially early as of yet undefined immunological responses that are protective to the infection with Francisella, and also lastly, to determine the bacterial antigens responsible for the generation of this protection, and she hopes to move some of the similar techniques she has used with Francisella into the mycobacteria arena.

That is it. I know it has been brief. I am sure you want to get to lunch, but if you have any specific questions, I believe Dr. Apicella is going to lead a closed session discussion of his findings after lunch on this, but Dr. Collins and Dr. Elkins, and myself are here if you would like to ask any specific questions.

Thanks.

DR. FERRIERI: Thank you, Dr. Brennan.

Committee members, this is a good chance if you have any questions for any members in this division.

Yes, Dr. Edwards.

DR. EDWARDS: I thought this was a wonderful document. I really enjoyed reading it, and also how a pertussologist becomes a TB-ologist, and I thought that was

very exciting.

I wanted you to perhaps comment a little bit on obviously, these model systems that you have established or that Dr. Collins has established are very important in terms of helping to evaluate these complicated products, and maybe he or you could just outline sort of does industry work with you on these, or do manufacturing companies all have their own types of these model systems, or sort of how does this work practically in terms of making things available quickly to study these important vaccines?

DR. BRENNAN: Perhaps Frank can comment also, but I will just start by saying that we hope this kind of works like it did like you mentioned pertussis, because I think we have a nice track record with what happened with pertussis.

Some of the antigens that we worked on, like pertactin, for instance, and the hybridomas that we developed, for instance, I think were a very nice tool, those monoclonal antibodies that have been used by most of the institutes and manufacturers in helping to develop the pertussis vaccine.

For instance, we have now a couple of monoclonals

against this new hemagglutinin, and we have Frank's model. I think one of the things -- and he will probably address this in a second here -- is that we hope to really work at this correlates question, which is on everybody's mind, and

that helps us so much when we get into the future clinical trials that I believe we will soon, in the next couple of years, on TB.

So, we hope to use Frank's model and his expertise in the immunological responses to develop some correlates, so that at FDA, we can use that for our potency assays, and much easier as we have with pertussis.

Frank?

DR. COLLINS: Yes. We have had or I have had a number of people approach me as to the use of the aerosol challenge method. The beauty of this is that it is essentially as parallel as you can get to the human infection as you can reasonably get.

The down side is that it is a P3 pathogen mycobacteria in TB, and so this has to be done under very carefully restricted conditions, and particularly when you are using an aerosol, so that a number of people have been very concerned as to where they can get their vaccines tested, and, in fact, of course the NIH has at least two labs that are primarily concerned with this.

I have been asked on several occasions to give

seminars with regard to the model itself, so that, in fact, I can see what is involved, but we have not been testing other people's vaccines. We have got enough problems and enough vaccines of our own to do so.

It is clear that there are only a few P3-restricted labs which have the necessary aerosol machine which can safely infect with M. t.b., so this is in a way a bottleneck which is concerning quite a lot of people, and naturally we are concerned, too.

DR. BRENNAN: I will also point out, Kathy, that we are also working closely with NIAID and the WHO, who has a working group including Dr. Ormen McMurray and the guinea pig model to look at these new candidate vaccines.

DR. COLLINS: I might just add that we are not discouraging people from doing collaborative studies. We have on the NIH campus several groups who, in fact, we have been collaborating with.

DR. EDWARDS: I guess one other thing that is distressing is that when the rate of TB stopped going up, it seems that the amount of money that the government was interested in paying for this most important infectious disease also stopped going up, and I guess that is reflected in some of your budgetary figures, as well.

DR. COLLINS: Yes.

DR. BRENNAN: But it is interesting that we sit on

an advisory committee at the CDC, and which has in the past been mostly interested in drug treatment, and lately they have been turning more to an interest in vaccine as has the WHO. I think that is good news.

DR. COLLINS: There is one other point, that although the rate of tuberculosis in the United States has flattened off, and presumably, hopefully, will turn down again, the incidence of tuberculosis worldwide is increasing steadily, and there is no question that until they find some way of controlling TB worldwide, it will be impossible to eliminate TB in this country, simply because of the number of people that come into the country who are already infected, and you have got to control that source before you go any further.

DR. FERRIERI: Thank you, Dr. Collins.

Dr. Anthony.

DR. ANTHONY: Dr. Collins showed a lot of forbearance. He didn't complain about how long it took him to get his P3 facility after he joined us, but as Frank said, he does collaborate and will continue to collaborate, not only with our colleagues on the NIH campus, but with the people in academia and industry to the extent that we can.

Incidently, this lab has been around a long time, and for many years I believe was the only mycobacterial research facility on the NIH campus. So, it has a long

history.

While I am on my feet, I would like also to comment that Dr. Brennan and his colleagues, I think represent the model of one of the prime credos of the Center

for Biologics, and that is the researcher/reviewer model. Research at CBER has always been under siege because that is not our primary mission, and it has been threatened as long as I have been there, and it is threatened once again as the Prescription Drug User Fee Act is renegotiated.

The industry negotiators intend to specify that those dollars that come into the Agency, even though they have accomplished every single goal of the Act, which was passed in 1992, they now wish to specify that those dollars cannot be used for research, and it has sent a chill through our organization. We hope we will survive as a research organization. That is why I went there, because that is one of the things that makes it so much fun to be there.

But I simply wanted our friends, you, the advisory committee, to know that we have some problems right now.

Thank you.

DR. FERRIERI: Any other points from the committee?

Otherwise, we will adjourn under the following proviso. The audience, guests, and consultants can return at 2:30, but the current members of the advisory committee

must be back at 1:30, so we will go into closed session, and we will be hearing the formal report from Dr. Apicella.

[Whereupon, at 12:30 p.m., the proceedings were recessed, to be resumed at 1:30 p.m. in closed session.]

AFTERNOON SESSION

[2:32 p.m.]

DR. FERRIERI: We are privileged to have Dr. Novak, who will be presenting an update on the Oncologic Drugs Advisory Committee, or ODAC, she will be spending about 15 minutes briefing us on things.

Dr. Novak.

Update on ODAC Meeting

DR. NOVAK: Good afternoon. Again, my name is Jeanne Novak and I am from the Division of Vaccines Applications.

[Slide.]

The reason I am here today to update you on proceedings at the Oncologic Drug Advisory Committee was because at the December 16th meeting, the TICE BCG product was taken to the advisory committee in order to discuss requests for new indication, and that was for intravesical use for superficial transitional cell carcinoma of the bladder.

[Slide.]

I should say at this point there were actually

five questions posed to the committee, and I will discuss those towards the end of this briefing just to give you an idea of what was discussed and the outcome of the meeting, but of the five questions, one was mainly concerned with

infectious complications as a result of the use of intravesical BCG treatment. In order to address those issues, we did ask that we have additional members join the ODAC session.

We had two urologists from the Center for Devices Advisory Committee for Gastroenterology and Urology Devices Advisory Committee. We also invited three infectious disease specialists from academia.

[Slide.]

The product was TICE BCG (BCG Vaccine), and it is produced by the Organon-Teknika Corporation. I know this committee is familiar with that product. It has been licensed since 1950 as a vaccine, and was approved for carcinoma in situ in August of 1990.

The standard form presentation is an ampule presentation of lyophilized organism at approximately between 1 and 8 x 10^8 colony-forming units per ampule, and it has an equivalence to about 50 mg of wet weight. I refer to that when I summarize this study for you.

[Slide.]

Just as an overview, with regards to the incidence

of disease, it has been estimated there is about 53,000 cases of bladder cancer in the United States per year. Ninety percent of those are transitional cell carcinoma, and if one looks at the incidence of transitional cell

carcinoma, about 32 cases per 100,000 as opposed to 3 cases of carcinoma in situ per 100,00.

[Slide.]

Again, just as overview, I would like to just mention a couple comments about tumor stage and grade. Now, moving on to a description of transitional cell carcinoma, and there has been discussion in the literature and summaries in the literature about the relationship of the stage and grade of tumor to recurrence and progression, and this certainly did bear on the primary endpoint of the study that I will just briefly overview and the discussions at ODAC.

For summary, recurrence is more likely to occur if multiple tumors are present at diagnosis versus the presentation of a single tumor. Percentages are estimated at 91 versus 51 percent.

Progression is more likely if tumor occurs at a more advanced stage, and that is, if you present with T1 rather than a Ta tumor, progression is 29 versus 9 percent.

In addition, progression is more likely if the grade of the tumor is at a higher grade, so, in other words,

Grade 3 versus Grade 1, 38 percent versus 7 percent.

Finally, mortality is more likely again is the grade of the tumor is higher, G3 versus G1, for example, 21 percent versus 6 percent.

This is the result again of a survey of a number of studies throughout the literature.

[Slide.]

The file was presented to the Oncologic Drug Advisory Committee, and the primary clinical reviewer on the file was Dr. Richard Stefan from the Office of Therapeutics. What he presented to the committee was what the company had presented to us, and basically, there were two clinical studies, two controlled studies that were submitted to the file: a study done in Europe, the Nijmegan study, which was a 3-arm study, comparing two BCG products to Mitomycin C, and a study done by the Southwest Oncology Group, which was a 2-arm study, comparing this TICE BCG to Mitomycin C.

Before getting to all of the conclusions, it was the conclusion of both the FDA and the Oncologic Drug Advisory Committee that the Nijmegan study did not support the use of BCG for this indication, and for a number of reasons that I won't get into in great detail here, a lot of that had to do with differences in the schedule, for example, in the Nijmegan study, the course of treatment was induction but not maintenance, and there were other

differences that were discussed at the committee.

Suffice as to say, the committee moved on, however, to listen to discussions about the SWOG study, which ultimately they did decide were supportive of efficacy

of this product for this indication. Again, I will detail some of the points of discussion in a moment.

[Slide.]

Again, as a quick overview, the SWOG study was a randomized intergroup comparison of BCG and Mitomycin C in superficial transitional cell carcinoma of the bladder. The study enrolled 469 patients who had been completely resected after Ta or T1 transitional cell carcinoma, and these were patients who were enrolled who were considered to be at high risk for recurrence.

The BCG used again was a formulation that I have already described, and it has been licensed previously for carcinoma in situ, which is 50 mg, and it was given at one to two weeks after resection, and then weekly for six weeks, at eight weeks, 12 weeks, and every month for a year. So, we have an induction course and a maintenance course.

Mitomycin C was given at 20 mg/20 cc or 1 mg/ml on the same schedule as BCG. The primary endpoint of this study was the time to recurrence or death.

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Again, I will just briefly summarize the final

results, but let me say that during the course of the study, an interim analysis was performed, and at the time of the interim analysis, it was actually determined that BCG had demonstrated superiority over Mitomycin C, and so when the

interim analysis was done, in fact, when one looked at the percentage of recurrence or death, at the interim analysis, it was 46 percent, and Mitomycin C was 57 percent, and the median time to recurrence has been estimated from the interim analysis to be 44 months for BCG and only 22 months for Mitomycin C.

Upon receipt of all of the results and final analysis, again, you see the numbers, 41 percent for recurrence for BCG, 52 percent for Mitomycin C, but the most important, median time to recurrence or progression, you can see median time is 22 months, but it was not reached for BCG.

[Slide.]

Briefly, just moving on to safety, although the Nijmegan study didn't support efficacy for the use of this product, it did provide additional data regarding the safety of the product, and the safety profile for adverse events in that study was very similar to what was observed in the SWOG study, but I will just be reviewing briefly the SWOG Study data.

Of the 442 patients who were evaluated in this

study for safety, you can see there are differences in the safety profile: dysuria at 52 percent versus 36; fever, higher at 17 percent versus 3.6; and malaise, 25 percent versus 14 percent.

When one looks at withdrawals, there is no significant difference in withdrawals based on toxicity between the two groups, but again, you can see there is a difference in the safety profile for BCG over Mitomycin C.

It should be noted two individuals did require orchiectomy due to BCG testicular infection, and 32 patients during the course of the study required anti-tuberculosis therapy, and in this case it was INH.

So that briefly summarizes the efficacy and safety that was presented to the Oncologic Drug Advisory Committee.

[Slide.]

We had additional concerns again about infectious complications, so Dr. Stefan went to our Spontaneous Reporting System at FDA and found approximately 500 cases of reports related to BCG infection, 77 which were serious or life-threatening, 71 included hospitalizations, 6 deaths, 2 long-term disabilities, and then, of infectious complications were also 21 distant BCG infections and 16 cases of BCG sepsis.

I should qualify this, that oftentimes this reporting didn't have a tremendous amount of detail, but we

just wanted to present some of these numbers to that committee, so that again they could get a feel for what was being reported through this system.

Interestingly enough, there have been reports of

secondary contact infections with BCG, for example, 3 infections in health care workers, 2 of those who had PPD conversions and no other symptoms, 1 of whom had a cellulitis at the site. Apparently, this was a needlestick during preparation. There have also been reports of infections in other patients, and I am sure you have probably read the report of 2 pediatric leukemia patients who contracted BCG meningitis. They were at a facility and were being treated with intrathecal methotrexate, and BCG had been prepared in the same hood as the methotrexate, and resulted in cross-contamination and infection of these patients.

[Slide.]

The sponsor also took it upon themselves to review some of the infectious disease complications, and, in fact, since their time of licensure for the indication for carcinoma in situ, they had a sponsor spontaneous reporting database, and to date, they have had approximately 1,200 adverse events in 738 patients, and that is of about 100,000 patients who have been treated.

Again, they see a number of serious and expected

AEs, 123 out of all those reported, also reports of death, and they have had, interestingly enough, 144 health care workers exposures actually reported, although I want to mention only a handful of these actually resulted in either

PPD conversion or cellulitis at the site. Interestingly enough, people who were using the product were aware that in the event of a needlestick, they should contact the company, and so on subsequent followup, even though these were not serious incidents, it was interesting that they were able to capture those data.

[Slide.]

I would like to just summarize by telling you what questions we posed to the advisory committee, and what their conclusions were at this point.

The questions posed were actually quite extensive, and what I have done here is just abbreviated the questions to what we think were the essential points. As I have already alluded to, the Nijmegen did not support the indication, and that was agreed upon by the advisory committee.

The advisory committee did feel, however, that the SWOG study did support this additional indication for transitional cell carcinoma.

The third question we had posed to the committee was really a discussion, a question about the acceptable

toxicity of BCG, and the committee opted to address this issue in the context of a risk-benefit sort of discussion when one talks about the stage and grade of tumor that one is treating.

Just in summary, let me move on then to No. 4: Do the data support safety and efficacy for stage Ta/T1 transitional cell carcinoma, and if the answer is yes, would there be recommendations for a particular subset?

The committee again agreed that safety and efficacy did support treatment of Ta/T1 tumors, however, it is difficult to do a subset analysis, and as a matter of fact, the sponsor could not do a subset analysis of the SWOG study, so there were no recommendations for subset treatment, however, there was a discussion amongst the committee that for Ta/G1, or Ta/Grade 1 tumors, upon initial presentation without recurrence, those would be tumors that people would not likely want to treat with this therapy. Rather, the recommendations of the committee were to include treatment for Ta/T1 tumors of all grades had they recurred.

So, multiple recurrences or presentation of multiple tumors would be included in that group regardless of stage or grade.

[Slide.]

Again, the last question posed to the committee dealt with actually opening discussion regarding how does

one deal with the infectious disease or the infectious complications, and how should that be dealt with in the labeling.

Just briefly, we asked the committee to comment on

whether or not labeling should specify, for example, the duration of symptoms beyond which BCG infection should be suspected. In other words, should the labeling actually indicate that if flu-like symptoms and fever are continuing beyond 48 hours, what kind of recommendations and referrals should be made.

I should mention at this point that treatment with BCG has been associated with systemic symptoms within the first 48 hours, so the discussion revolved around balancing between allowing those initial symptoms to resolve versus the chance of missing a serious infection.

The committee's recommendations were again to keep language in the labeling regarding if these symptoms proceed beyond 48 hours, to consider treatment for systemic infection.

The committee also discussed how patients should be evaluated, and there was some discussion about new culture techniques although this was not something that they felt strongly about including in the labeling.

Finally, there were some recommendations about triple antibiotic therapy, and I will talk about that in

just a moment.

Secondarily, should the label dissuade the use of prophylactic INH? The reason this was of concern was in the SWOG study, prophylactic INH, a course of four days, a short

course, had been used if certain Grade 2 or Grade 3 toxicities had been reported, and even though it is currently not in the label, there is no indication now that recommends prophylactic use of INH.

The problem is that this has become relatively common practice in the treatment of carcinoma in situ, as well as superficial bladder cancer. So, the committee felt very strong that, in fact, a short course, since there is no evidence of benefit, felt strongly about not including any mention about a short course INH, and, in fact, wanted to dissuade the use, because the balance again is whether or not one wants to subject a patient to any course of antibiotic if you are not convinced that there is infection that would require such treatment.

Finally, we asked the committee to provide us with additional recommendations and if there should be additional recommendations in the labeling to minimize the risk of nosocomial infections.

At this point, the sponsor provided us with additional information. They actually have a closed reconstitution and installation device that they are using

with their product, and that they provide to caregivers at no charge in order to minimize any cross-contamination. However, it was not in the labeling, and it was recommended by the committee that this device be mentioned and

encouraged, encourage the use of this device by practitioners.

There was additional discussion about just general safety and handling issues, but for the most part, I think it was encouraged to use this closed system.

[Slide.]

In summary, again, the recommendation of the committee was for approval of TICE BCG for treatment of recurrent superficial transitional cell carcinoma, Ta/T1.

They encouraged more detail in the label regarding treatment for BCG infection and additional comments regarding the handling of the product.

Finally, the sponsor agreed very adamantly at the meeting to work with FDA to address these infectious disease complications in the label to ensure that information is provided, and to include information even with regards to triple antibiotic therapy should it be warranted.

Thank you.

DR. FERRIERI: Thank you very much, Dr. Novak.

DR. BELSHE: Would you clarify how this drug is given or how the BCG is administered?

DR. NOVAK: It is administered intravesically. It could be either administered from an i.v. bag through a catheter is the most common method, but it is again delivered directly to the bladder.

DR. BELSHE: It in instilled into the bladder.

DR. NOVAK: Yes, it is, for two hours.

DR. BELSHE: And there is a catheter presumably, and it is clamped off for two hours?

DR. NOVAK: Correct.

DR. BELSHE: It is not injected into the bladder wall or anything like that?

DR. NOVAK: That is right.

DR. FERRIERI: Other questions from the committee for Dr. Novak? Dr. Edwards.

DR. EDWARDS: Was there a discussion about characterizing these mycobacterial strains that were isolated? Sometimes it is not so easy to know that it is a BCG strain, and, for instance, you may -- indeed, we had a child recently who had HIV and had disseminated BCG as a function of that, and with the first go-around, I think you sort of work up, well, is it MAI or is it TB, and then you say, well, it is not MAI, and then you say it is TB, and that is sort of what happens, because there is not a specific speciation.

Was there any suggestion that the isolates that

were obtained from these patients be further characterized to make sure they weren't mycobacterium tuberculosis or they were not members of the mycobacterium tuberculosis family?

DR. NOVAK: That is a good point, but, no,

actually there was no discussion in that regard.

DR. FERRIERI: I am surprised that no attempt was made of any genotyping or other characterization.

DR. NOVAK: I think, again, the discussions revolved around -- we were talking about patients who are getting multiple installations of this product, and the major concern is what is happening. Once you get beyond these initial symptoms in the first 48 hours, the real concern is then the acute treatment of what could be potentially a very severe bacterial infection.

The only discussion regarding again anything that would suggest trying to determine the organism was discussion of culture methods. I think that was more the emphasis. People were more concerned, well, can you even confirm that this is an infection rather than some sort of response to the treatment itself that is not of an infectious etiology.

That has been one of the confounding factors even in the first again 48 to 72 hours after treatment. So, that is the extent of the discussion in that regard.

DR. FERRIERI: But in the patients with the

secondary contacts, I thought that the two leukemics who developed BCG meningitis had characterization of those strains.

DR. NOVAK: Yes, I am sure they did, and offhand I

can't tell you what they were. I am not sure if anyone else can. But my recollection was they confirmed, in fact, that it was the organism that had been prepared in the hood.

DR. FERRIERI: Exactly. Other questions?

Well, if not, thanks so much, Dr. Novak.

We won't have a formal break. I think that people can get up and have cookies or something to drink, and do this while we are moving ahead.

I saw Dr. Lewis come into the room. Dr. Lewis, would you mind starting now? Dr. Andrew Lewis, who was one of the organizers of the Simian Virus-40 Workshop that was held Monday and Tuesday at NIH at the Natcher Building, is going to give us an overview of it. I had the privilege of attending this workshop and enjoyed it tremendously and wanted to extend to you, Dr. Lewis, my congratulations on your very successful outcome. I thought it was a very exciting workshop in many ways.

Update on SV40 Workshop

DR. LEWIS: Thank you very much.

Necessarily, my remarks have been prepared in somewhat of a hurry, so I apologize for any omissions or

commissions that may occur.

[Slide.]

The handout or the agenda of the workshop is listed here. The workshop was entitled SV40 as a possible

human polyoma virus, and was sponsored by five different agencies: the CBER, the NCI, the NICHD, two organizations from the CDC in the National Vaccine Program Office.

The impetus for this workshop came during the summer when a series of papers began to appear in the literature as a followup to work that was done in 1992 by Bersagel, Janet Butell, and Bob Garcia, in which they had detected SV40 DNA sequences in a series of choroid plexus tumors from young children who were born in the 1980's.

These studies were reasonably convincing or let me put it this way, these studies presented perhaps the first really convincing evidence that SV40 DNA sequences were present in human tumors.

Since the discovery of SV40 in 1960, and especially during the seventies, there have been a series of isolations of SV40 from human tissues beginning with a paper in I believe 1974, which SV40 was isolated from a human melanoma.

There were followed-up isolates of SV40 from I believe one or two cases of progressive multifocal leukoencephalopathy and the isolation of SV40 from several

other human tumors.

These isolations in reports were looked upon with some skepticism because of the stability of SV40 as an agent in the laboratory, and necessarily, people that are working

with them need to grow the virus, and this virus is remarkably stable.

So, I think that that data was out there, it was reviewed by Dr. Geissler in 1990, and retrospectively, it was quite interesting, but it didn't generate any serious interest until the Bersagel paper in 1992.

Subsequent to that paper, a paper appeared in 1994 by Michael Carbone and others from the National Institute of Child Health, in which SV40 DNA sequences were detected in about 40 to 60 percent of human mesotheliomas.

This was a startling observation because the mesothelioma of course is a tumor that is associated with exposures to asbestos, and the presence of SV40 DNA sequences there was quite unexpected.

It was prompted, however, by the ability of SV40 to induce mesotheliomas in Syrian hamsters.

Then, the most recent paper appeared on human tumors, new human tumors, appeared in July of this year, in which the Carbone group repeated their work on osteosarcomas and reported about the same incidence of SV40 in those tumors.

These particular studies began to catch everyone's attention and articles began to appear in the media beginning with an article in The New Scientist in September followed by articles in Money magazine and The New Yorker.

I think irrespective of the attention that the information was receiving in the lay press, the scientific questions that were generated by these papers prompted a need for some review on the part of the government agencies that had responsibility for worrying about these types of issues, and it is in that venue that this meeting was begun. We started putting it together, I think the middle of September, and actually it was held just a couple of days ago.

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The purpose of the workshop was basically twofold. First, to consider the possibility that SV40 is an infectious agent that is endemic in the population, and then to stimulate any efforts that were necessary to see whether SV40 is, in fact, a causative agent in human disease.

The goals were actually to summarize the current knowledge regarding the biology and the oncogenicity of SV40, that formed the basis for this type of work, to review any data related to SV40 infections in humans, and discuss the possibility of human-to-human transmission, which is the essence of issue.

The work of Bersagel and Butel indicated that if SV40 was in this choroid plexus tumors, these children were eight years old, eight and nine years old in the eighties, and therefore, they did not get SV40 from polio vaccine.

The present data, actually, to present data in addition to related to the presence of SV40 DNA sequences in tumors, and discuss the issues really related to the ability to detect this material.

Summarize the history and the presence of the removal of SV40 from viral vaccines. I actually failed to mention, of course, and I am sure most of you know the SV40 was, in fact, a contaminant of the polio vaccine from 1955 until its discovery in 1961, and its subsequent removal from the vaccine beginning in 1961.

It was also present in adenovirus vaccines that we used is military recruits during the same interval, and was removed from the adenovirus vaccines approximately the same time.

Finally, the impetus was to see what type of methods had to be developed to consider any implications of SV40 infection of humans may have for the public health.

So, with these goals in mind, we put together a workshop. There were 358 people invited. We had 286 registered participants. The organizations who were invited to attend included the WHO, the NIBSC from the U.K., the

Paul Ehrlich Institute, the Vaccine Advisory Committee, and perhaps others that I have hadn't time to detail.

In addition, we had considerable interest of the media. CBS 48 Hours was there, the Canadian Broadcasting

System was there, two NBC affiliates were there, the British Broadcasting System was there, both TV and radio. The Associated Press was there, Science magazine, Money magazine, and a British publication called Impact. So, we had quite a group.

I think that in spite of all the media attention, the meeting proceeded very, very well. There were no major disruptions, and I thought the flow of information that was exchanged was very good.

Now, we attempted to organize the meeting around three basic issues, which in essence formed the focal point for these particular goals. The first of those issues was the sensitivity and specificity of the assays that are used to detect SV40 DNA in human tissues. If you can't trust the assays, you can't trust the data, and if you can't trust the data, everything else is open to question.

The second issue was any evidence pro or con that SV40 is, in fact, a human commensal, and when you go back and look at the old literature, evidence related to that is considerable, as I will get into in a moment.

Then, finally, the issue of whether SV40 is

possibly a human pathogen. For this particular meeting, pathogenicity of SV40 related specifically to its possible association of a causative agent in human neoplastic disease. We didn't have an opportunity to get into the

possibility that other diseases might be associated with SV40 infections.

Now, to consider these three basic issues, the meeting was organized into essentially three units. What we did was because this data goes back over 40 years, it was quite a challenge to review all the data for a lot of people who were there, who were not familiar with SV40 and for those younger members who were there, who actually were studying SV40, who were not familiar with the old data, as well.

So, what we did was to set up speaker sessions to be followed by a panel discussion related to each of these issues, so we had speaker, speaker, panel; speaker, speaker, panel; speaker, speaker, panel.

I think that organization worked out quite well for the purpose at hand. The background material was covered, not in great depth, but I think adequately for people to understand what was going on, and the audience responded enthusiastically during the audience panel discussions to the issues that were on the table, and I really think a lot of useful ideas came out of the meeting.

So, to get into the basic flow of the meeting, I have to kind of go through my notes here. The first session was related to -- well, it wasn't related -- it was a review of the data that I have really already mentioned, and in

addition, additional information that had been published by other workers in the field.

Essentially, six laboratories came forward with information that was related to the detection of SV40 DNA sequences in human tumors. These tumors included choroid plexus tumors, mesotheliomas, osteosarcomas, various central nervous system tumors including glioblastomas, glioblastoma multiforme, as well as peripheral blood lymphocytes, normal fluids or normal cells from individuals including peripheral blood lymphocytes, and surprisingly, seminal fluids in one study.

As a followup to the work that was done on the choroid plexus tumors, John Lednicky and Janet Butel at Baylor had actually recovered infectious SV40 from one of the choroid plexus tumors and had done fairly extensive sequence analysis on the recovered virus to show, to be absolutely certain that what they recovered was not a contaminant of the same type of virus that they had in the laboratory.

That data was also covered in some detail, and they found, surprisingly, that the virus that they had

recovered from SV40 from the choroid plexus tumor, in fact, only had 172 enhancer element compared to the 272 base-pair enhancer elements that are of the standard configuration of the genome wild type SV40.

They also had strain-specific mutations or differences in the carboxy terminus of the protein compared with what is considered to be the wild or archetype SV40.

Now, in contrast to all these data, there were three other laboratories reported data that was completely contradictory. Using the same probes, the same technologies, the same types of PCR assays, they could not detect SV40 DNA sequences, not in the same tumors, but in different preparations of the same tumors.

So, that set the stage, I think, for the panel discussion following the first two sessions. Now, in addition to the first session, the second session was related to the presence of BK and JC viruses in the population.

Now, you probably are aware that JC and BK viruses in SV40 are related about 75 percent homology. They are even more closely related in the region of the early, early genes that produce the T antigens.

So, it was necessary for people to understand the relationships of JC and BK infections in humans to the relationship of SV40 infection in humans, and the

possibility of cross-reactions between the probes and the serological reagents that are used to detect all three of these viruses.

I should also mention that certainly JC virus, as

you know, is associated with progressive multifocal leukoencephalopathy in humans. Eighty to 90 percent of us have antibody to both these viruses by the time we are 20 years old, the antibody persists for life, and the virus persists in our tissues for life. It is variously excreted in urine and feces and sometimes by the respiratory route, as well. It has also been reported in peripheral blood lymphocytes.

So the stage is set for considerable problems in determining the specificity of the reactions that are being used to assess this material, and, in fact, some of the probes that are being used will amplify sequences from the T antigen region of all three of these viruses at the same time. That issue came across loud and clear.

To summarize the outcome of the Panel 1 audience discussion, the following points I think should be made. First, the methods that are used to prepare the DNA from human tissues can determine whether the DNA sequences that occur at low levels can be amplified by PCR.

Data from one laboratory showed that spooled DNA gave a negative reaction while the fluids from which the

spooled DNA was removed gave a positive reaction. The PCR conditions that could amplify low level DNA sequences could vary according to which set of primers were used in the reaction mixture.

Only one laboratory really attempted to assess the sensitivity of the PCR assay they were using, by using serial concentrations of cells containing a single copy of the SV40 genome per cell.

The assay used by this laboratory could detect somewhere between 10 and 100 copies of the SV40 genome per reaction mixture. The other people who were doing the assays did not report sensitivity data.

The PCR assays using primers that were supposedly specific for SV40 in the hands of one laboratory could amplify what appeared to be whole cellular DNA sequences once they were sequenced, but the interesting thing was that the fragment size of the whole cellular DNA sequences was exactly the same fragment size as would be predicted by the pair of primers that were selected.

It became obvious that verification of any virus-specific material or any material that is amplified that is presumed to be virus-specific is essential that it be carried out by DNA sequence analysis of that material.

I think that the theme of the first panel audience discussion was or the outcome of it was intense or

considerable effort should be extended to developing some type of standardized biological or PCR assay for detecting SV40 sequences, and its sensitivity and specificity are rigorously tested before we can proceed too much further

trying to assess the level at which SV40 DNA sequences may or may not be present in human tumors.

In addition, other work needs to be carried out to actually attempt to recover infectious SV40 from tissues that are supposedly SV40-positive to support the data or to refute the data that has come out of the Lednicky-Butel study.

In Session 3, there were papers related to human exposure to SV40 in the polio vaccine. One of the great features of this particular session was given by Dr. Maurice Hilleman. He began the session by describing the events that led up to the discovery of SV40 and the detection of SV40 in polio in the vaccines. He noted the contribution of one of the officials I believe of the National Zoo for suggesting the use of African green monkeys imported from Madrid as a way of obtaining relatively clean animals that had not been exposed to other primates during the holding period in which the rhesus monkeys were being put through when they were being processed for the polio vaccines.

When they got these monkeys in and tested their tissue cultures, they were relatively free of contaminating

viruses, but much to their surprise, we inoculated some fluids from rhesus cultures, they developed this peculiar vacuolation which was then shown to be specific for simian virus 40 or SV40 as we know it.

He then reviewed the data on their detection of SV40 in the polio and the adenovirus vaccines that was published in the paper that he and Dr. Sweet put out in 1960. He mentioned the manner in which they presented and discussed their findings to the Division of Biological Standards and to several of the polio committees in 1961.

I think we were very fortunate to have Dr. Hilleman there to relate this rather amazing story.

The next series of papers related to SV40, the detection of SV40 and its ability to replicate in human glial tissues, but its inability to replicate very efficiently in human renal cells, and so the question that this data raises is to how SV40 can spread around the population when it replicates so poorly in human cells.

There was a considerable amount of information related to the expression of VP1 in human tissues, but basically, the problem is that when SV40 infects human fibroblasts, viral protein 1 is overexpressed, and there seems to be some block to late gene expression.

But this is not the case with SV40 which can replicate just as efficiently as it does in African green

monkey kidney cells. So, it is still not clear how a virus that has this dichotomy in its capacity to replicate in human cells could, in fact, spread in the population.

I discussed briefly the presence of SV40 in the

adenovirus vaccines and the possibility that some type of SV40 recombinants resembling adeno-SV40 hybrids could be a source of genetic material in the environment.

This possibility had already been mentioned by Dick Frisque and Dr. Imperiale, I believe, when they were discussing BK-SV40 or BK and JC-SV40 recombinants. In fact, when you create a recombination between JC and BK, it seems to enhance the ability of the recombinant virus to replicate compared to the parental virus, so there perhaps is some selection pressure there for their growth in the environment.

During this session, Praxis-Lederle and Connaught reviewed the procedures for producing polio vaccines and screening these vaccines for SV40. David Sangher from the NIBSC discussed the use of PCR assays to screen current polio vaccines for SV40 VP1 antigen.

They experience some difficulty in their assays detecting T antigen, but when they switch to the primers for SV40 VP1, their difficulties went away, and they were pretty confident in being able to say that they were unable to detect any late SV40 sequences in any of some 90

preparations that they tested the polio vaccines between 1971 and I believe 1990.

Following those presentations, we sort of got to one of the major highlights of the meeting, which Dr.

Patrick Olein and Howard Strickler reviewed epidemiological data in which they evaluated the increases in the incidence of the tumors that we have been talking about in cohorts who would have been exposed to SV40 in the polio vaccines, and compared these incidences to cohorts who would not have been exposed to SV40 in the polio vaccines.

Their data was quite comprehensive. Dr. Strickler was using the SEER program that has been instituted in the United States now since 1973, I believe, on tumor incidences, and that have been gathered at over 14 different locations. Dr. Olein was using the data on I believe that they had from the tumor registry in Sweden, which has been underway for many, many years.

Neither of these studies could detect any increase in incidence of either choroid plexus tumors, mesotheliomas, osteosarcomas, glioblastomas, other types of central nervous system tumors, lymphomas or osteosarcomas, that could be related to the exposure to the polio vaccine that might have contained SV40.

Increases in incidences of human central nervous system tumors and mesotheliomas were noted in both

countries, but when they examined these increases in incidences and tried to correlate them with exposure to the polio vaccine, there was no association.

The numbers of individuals they examined in these

studies were quite large and perhaps the most comprehensive of any assays that have been used or epidemiological evaluations that have been used to screen for possible associations between increases in tumors and exposure to SV40 in the polio vaccine.

In addition to looking at the SEER data, Strickler confirmed that data using the tumor incidence data from the State of Connecticut, which has a tumor registry I believe that goes back to 1930, and it happens to be perhaps the most comprehensive set of information that we have available in the United States.

So, data from three different registries in two different countries was unable to detect any increase in the incidence of tumors in which SV40 DNA sequences have been reported which might implicate that exposure to SV40 secondary to polio immunization in the fifties and sixties was a possible factor in human disease.

I think we were all quite relieved to see this information. These data, of course, do not rule out the possibility that SV40 or SV40-like viruses have been endemic in humans before the introduction of polio vaccine, and this

possibility set the stage for the Panel 3 audience discussion.

Correction, that was Panel 2, whose charge was to explore the possibility that SV40 is a human commensal. The

work of Panel 2 was influenced by several factors. First, SV40 can infect humans, and this has been shown very conclusively by a study that was done by Morris in volunteers inoculated with respiratory syncytial virus in the late fifties.

This virus preparation was inadvertently contaminated with SV40 because it was grown in rhesus monkey kidney cells, and the individuals who were exposed to this virus developed neutralizing antibody, they shed virus. They did not get sick. The rate at which they shed virus and developed antibody was indicative of an active infection.

The second thing which influenced this panel's work was that 50 to 60 percent of humans who were exposed to rhesus monkeys or exposed to SV40 in the laboratory can be shown to seroconvert, indicating that people in contact with the virus can, in fact, be infected.

The third, rather weaker set of data, but still quite intriguing, is that somewhere between 5 to 20 percent of sera taken from humans before the introduction of the polio vaccine, from humans who were not immunized with the

polio vaccine, or from humans in isolated regions of the world, such as the Amazon forest or New Guinea, had antibody that appeared to be specific for SV40. So, it was not possible to explain the presence of this SV40 antibody in

these individuals.

Now, the possibility that these antibodies that they were detecting either could be cross-reactivity from JC and BK virus is a serious issue. The data that was presented related to that was the fact that the individuals who received SV40 during the respiratory syncytial virus infections, and whose sera converted SV40, did not seroconvert the BK virus, and when they looked that data pretty carefully, it looked like that and other data suggested there was possibly a 100-fold difference in the homologous reactions to SV40 neutralizing antibody and its ability to cross-react with either JC or BK.

That is still a conjecture at this point in time. I think that the data on that are really quite limited, but that is the area that will certainly need to be explored.

So, in view of these data, it is possible that SV40 was endemic in humans before the introduction of the polio vaccine in 1954-55. The question is how to develop the kind of assays that are needed to get at that problem.

The specificity of antibody responses to SV40 in paired sera is not an issue. That is reasonably clear.

However, as Jim Goedert of the Cancer Institute pointed out, it is not possible to use serologic data based on single serum specimens for epidemiological surveys because of the confusion as to what the antibody represents.

Thus, some type of assay that can be used to detect antibody that reacts specifically with SV40 needs to be developed. The possibility of using blocking antigens in assays for SV40 antibody was mentioned, and was received with some enthusiasm, but there has been no work in that direction.

My interpretation of these discussions is that some type of coordinated effort will need to be applied to the development of serological assays that are in fact specific for SV40, and I think from discussions that we have had since the meeting, that will take place in the very near future.

Now, during Session 4, the presentations in this session reviewed animal models and tissue culture models of SV40 induced neoplastic development, the ability of SV40 T proteins to bind to P53 and the RB protein and disrupt the G1 to S-phase cell cycle control. In the presence of a gene on human chromosome 6, designated Sensi 6 gene, which appears to be involved in a P53 independent growth regulatory mechanism, suggests two areas of investigation that might indicate a role that SV40 is making some

contribution to human tumors in which SV40 DNA sequences can be detected.

These observations set the stage for Panel 3 audience discussion. Data showing that SV40 T proteins were

associated with P53 and RB and cells from mesotheliomas was presented by Dr. Carbone, and was presented especially with P53 by Michale, and by Antonio Giordano in one of the earlier sessions. He showed that SV40 T proteins could, in fact, bind to RB, as well as P53.

These data prompted a fairly vigorous discussion as to how many cells in mesotheliomas and osteosarcomas that contained detectible SV40 DNA sequences contained detectable levels of T protein. The low levels of frequency of SV40 DNA sequences in the tumors, as suggested by the need to use PCR implications to detect them, suggest that very few cells actually contain SV40 DNA.

There is really no estimate at this point in time as to the average number of cells in any of these tumors that contain SV40 DNA sequences, nor is it known whether the sequences that are present in these tumors, are present either as episomal or they are integrated.

The sample size of the material that people have to work with from a choroid plexus tumor or some of the other tissues is so small that they don't have enough material to really do that type of analysis as yet.

So, the data was really not available to answer this question, and Dr. Carbone was not prepared to address the implications of what P53-SV40 T antigen interactions may have for those cells in the tumor that don't seem to be

carrying or expressing the protein.

The work on the Sensi 6 cell growth regulating gene on human adenochromosome 6 has really not proceeded to the point where data are available on human tumors that have SV40 DNA sequences. This was an observation that was made by Dr. Ozer, and it was just presented during the summertime at one of the DNA virus meetings.

So, I think the outcome of the panel discussions on SV40 as a possible human carcinogen were unresolved, but there are a number of possibilities that were discussed, and I think the protagonists and the antagonists in this area are well informed as to what kind of issues are going to have to be addressed in order to resolve these questions, and I suspect that we will see more on this in the not too distant future.

There were a couple of other themes that developed during the discussion that I think are relevant to the summary of the meeting. First, the work on the issues associated with SV40 expression in human tumors and SV40 expression in almost anything are proceeding with difficulty because of the lack of resources. A number of people

serving on the panels and in the audience made comments to that effect.

The second issue I think that needs to be brought to your attention perhaps is that representatives of

parents' groups reminded the audience on at least two occasions of the need to followup the questions that were raised by the workshop, that this was going to be an issue that was going to be important to them.

I think that sort of maybe in 2,000 poorly selected words covers what I had to say. If you have any questions, I will do my best to answer them.

DR. FERRIERI: Thank you, Dr. Lewis. That was an excellent summary.

Dr. Broome.

DR. BROOME: Could you give us any idea of the power of the Olein and Strickler studies to rule out an elevated relative risk, of what magnitude?

DR. LEWIS: Actually, I could not. I don't know that they really addressed that at the meeting. They just showed the curves, and I can't answer that question.

DR. BROOME: Does anybody know? It seems to me that is the fundamental issue.

DR. FERRIERI: It wasn't presented, Claire.

DR. MEIER: How many curves were there? There were three curves?

DR. LEWIS: Yes, there were. Each cohort represented a curve. As I recall, Strickler had I believe four different groups, a group that was born that would not have been exposed to the vaccine, the group that was born

that would have been exposed to the vaccine, and at least one group or two groups that were born during the interval when the vaccine was being used, and one group that was born after the vaccine was clear, and those curves were remarkably similar.

I think to get at the other question, this information has been put together just in the past I guess few weeks or months, and I don't know that they really had time to digest all of it yet. The only factor is that the incidence that they are comfortable with seemed to be in line.

DR. FERRIERI: Are there others in the room that were at the meeting who would like to comment further? Yes. Could you identify yourself, please.

MR. SCHIFF: Yes. Len Schiff from Microbiological Associates in Rockville.

Will the FDA and CBER be requiring cell line or continuous cell lines or diploid cells that are used for vaccine production, will they require SV40 sequences or PCR assays to be performed on these cell lines as part of their characterization or qualification?

DR. LEWIS: To my knowledge, there has been no discussion of that, of such a requirement. At this point in time, my judgment would be that it would be certainly premature until we understand more about what these primers

are amplifying to even consider any such requirement.

DR. FERRIERI: Dr. Hardegree, did you have anything that you wanted to add from your perspective of the meeting?

DR. HARDEGREE: No.

DR. FERRIERI: One of the things that I found quite interesting regarding the biology of infection in simians was that it would appear that this has been confined to old world monkeys, and not new world monkeys, and there were suggestions that further work should be done.

These studies have been done on relatively small numbers of animals, and what I thought would be interesting was to be able to look by PCR to see what is the presence of these sequences in some of the other animals who are negative. I don't think that the highly technological studies have been done on the animals from studies done a long time ago.

DR. LEWIS: That is correct.

DR. FERRIERI: Also, of interest I thought was that the rhesus macaque has relatively little illness when infected with the virus and that no tumors have been found

to be induced in these animals by SV40, so that not only do we need more epidemiological studies in humans including examination of mothers for antibodies to this virus, but also further studies in animals to better understand the

evolution and the possibility of true transmission from animals to humans.

Any other comments relative to this? I am sure we will be hearing more, and I think we should hear more about this as time goes on.

Dr. Edwards.

DR. EDWARDS: Will these proceedings be published in a book?

DR. LEWIS: Yes. I should have mentioned that. The conference was videotaped, it was audiotaped. Records, videos and audios will be available I believe as quickly as 10 days for people who want to pay up.

I think within three months I am told that it will be available by the Freedom of Information mechanism for a much more reasonable price.

All the speakers are aware that the proceedings will be published. We hope to have all the manuscripts in by the 1st of June, and the Development of Biological Standards Series will publish the paper, will publish the journal or a book on the proceedings, hopefully, it will be out by this time next year.

DR. FERRIERI: One of the interesting points from a vaccine production point of view, in my opinion, was the susceptibility to inactivation by formaldehyde, but as the virus goes from being closed, double-stranded circle, in a

supercoil formation, if you have one break, this relaxes the ring, and two breaks then give you linear, double-stranded DNA with no amino groups that can react with formaldehyde.

So the possibility exists that about 1 in 10,000 virus particles can escape the susceptibility or action of formaldehyde. Perhaps this is a possible explanation for the ability to have reactigenic, immunogenic material and exposure in the past in vaccines that theoretically should have been inactivated.

I think that closes this part. Thank you so much, Dr. Lewis. It was very challenging.

I think we could have a little shift here. Mimi, would you be prepared to discuss with us your activities as a member of the Future Vaccines Subcommittee of the National Vaccine Advisory Program or National Advisory Committee? I am not sure of the exact terminology here.

DR. GLODE: Yes. This will be a very brief report. I do actually have some very extensive notes back in my office, but I didn't know I was going to do this, but this is two meetings ago, and it will be from memory, and Dr. Eickhoff can help me a bit.

Update on Future Vaccines Subcommittee

The National Vaccine Advisory Committee actually has a number of subcommittees that we were able to remember. One of them is the Safety Subcommittee, and the other one

that is chaired by Dr. Eickhoff is the Committee on Adult Immunizations, and then there is a Future Vaccines Subcommittee. I think we are missing one or two others.

So, I have been on the Subcommittee on Future Vaccines as a liaison from this committee, and actually as a liaison recently from ASIP.

The committee has been chaired by Dr. Gordon Douglas until the past meeting, and the new chair is now Dr. Myron Levine. This subcommittee, as does NVAC, has a fairly wide representation including members from industry, Department of Defense, CDC, FDA, university, faculty, National Vaccine Program, and others, and has been at least an open meeting when I have been to it.

There are just two issues I would like to mention for your interest. One is that one of the products of this subcommittee is a paper that I believe has been -- and someone can correct me if they know differently -- submitted to JAMA, and so you should look for it, and we refer to it as the "delicate fabric" paper, but it basically talks about the interrelationships and interactions in terms of vaccine development between all the different groups that are

involved in developing new vaccine and the sort of potential tenuousness of those interrelationships.

So, that has been submitted as a product of this committee. The other issue that I would like to mention was

a meeting for members of the Future Vaccines Subcommittee, as well as some other invited participants that was held about the third week of November at Cold Spring Harbor, and this was a meeting with a somewhat unusual format, which was some case studies of vaccine development.

The idea was to look at a number of different vaccines, perhaps not all highly successful vaccines, but vaccines in development and review by having an individual who had been involved give their perspective on vaccine development, what were the obstacles, what were the supportive issues that eventually helped vaccine development.

So, there were six different vaccines discussed then over a two and a half day period of time - hemophilus influenza type B, rotavirus, the oral typhoid vaccine, TUI 21A, Varicella vaccine, cold adapted influenza vaccine, and RSV. I think those were all the ones, but someone can correct me if that is not correct.

Again, there were a number of sort of lessons learned, different lessons from each of these vaccines, but I think some of them, semi-universal lessons. One of them

was that one of the important aspects of vaccine development was, in fact, to have excellent disease surveillance and epidemiology, so that one could establish a disease burden, and that there was in some circumstances, that that came

sort of a little bit after the vaccine development and perhaps should have preceded it. It would have helped things along a little bit.

The second was that for some of the vaccines having really excellent basis science work, really helped facilitate vaccine development, really understanding the important antigens, the immune response, et cetera, was very important.

In addition, sponsor support for research and development of vaccines, which again to a certain extent was a product of the other two issues I have mentioned, how much disease burden is there, what is the perceived need and use for this vaccine, will it be universally recommended, et cetera, had to do with how involved and how supportive sometimes sponsors were for these vaccines.

Another issue was that most of the successful vaccines had a very strong champion, sort of during the lean years and during the better years of vaccine development. Sometimes that was an individual, sometimes that was an agency, sometimes that was a pharmaceutical company, but some group of people or individual people who really

believed in the vaccine and/or the need for a vaccine for that disease and really pushed it along.

As a result of that, I think there is now again a draft of a paper that describes this meeting, describes the

case studies more from the point of view of again lessons learned, and hopefully, may be helpful, not only to this committee, but to other individuals interested in vaccine development.

I would say that the Futures Vaccine Subcommittee, I think does not see themselves as being charged with prioritizing or naming new vaccines to be developed. There are other groups, such as the Institute of Medicine, that does that.

So, they are really looking at the broader picture of how are vaccines developed, what systems can be in place or modified in order to support creativity in vaccine development, you know, thinking very broadly about issues for future vaccines including international versus national issues, et cetera.

So, that is kind of what I can recall from memory. Other people could chime in who have been at a number of these meetings if they would like to.

DR. FERRIERI: Thank you, Mimi.

Is there further discussion on this or any questions for Dr. Glode?

DR. GLODE: I forgot to mention one thing, and I may have this one wrong, but it was kind of interesting. They looked at average time to sort of licensure of a vaccine for a disease, and there was a range, but I think

the average was 15 or 16 years. We convinced ourselves that that was the norm.

DR. FERRIERI: I wonder if we shouldn't go on.

Dr. Baylor, would you like to carry on here? The Regulatory Uptake will be given to us by Dr. Norman Baylor from FDA.

We are doing fine with the schedule. I don't want anyone to feel inhibited about speaking or asking questions. This was scheduled for approximately 30 minutes.

Regulatory Update

[Slide.]

DR. BAYLOR: Basically, what I wanted to do today is give you just a brief update of the regulatory accomplishments that we have had in the Office of Vaccines in CBER over the last year and part of this year.

As most of you are probably aware of, and for those of you who are not, yesterday, we approved the first acellular pertussis vaccine that came out of the NIAID trial, those recent trials, and this vaccine, as I said, was approved yesterday, and it is for the primary and booster immunization of infants and children except, as a fifth

dose, in children who have previously received four doses of acellular pertussis.

The trade name of the vaccine is Enfanrix. As I said, the manufacturer is SmithKline Beecham. It is a

shared manufacturing arrangement with Chiron Boehring from Marburg, Germany. Chiron Boehring produces the DT component of this vaccine, and SmithKline Beecham Biologicals produces the acellular component of this vaccine.

Other approvals that we had this year, I will go backwards and then work my way to 1996, we approved a hemophilus B conjugate vaccine combined with the hepatitis B vaccine. This vaccine was manufactured by Merck & Company, and this vaccine is for the active immunization of persons or individuals 6 weeks to 15 months of age, born -- I want to emphasize this -- born to hepatitis B surface antigen-negative mothers, and ideally, the immunization with this product would occur at 2 months, 4 months, 12 to 15 months of age.

The other approval we had in Fiscal Year '96 was vaccine from Merck, manufactured by Merck, and this was a hepatitis A vaccine. This vaccine was approved for the active pre-exposure prophylaxis against hepatitis A virus, and this is for persons 2 years and older. The primary immunization here should be given at least two weeks prior to the expected exposure to hepatitis A vaccine.

[Slide.]

There were several approvals of major supplements in Fiscal Year '96 also, one of those being the hepatitis A vaccine from SmithKline Beecham Biologicals, and this

approval was for a new pediatric dosage formulation of 720 ELISA units per half ml dose. Currently, there are two choices with this vaccine in the pediatric to adolescent age group, that is, 2 years to 18 years.

You can either go with the 320 ELISA units at two doses, one month apart, and then you follow that with a booster of 360 ELISA units, six to 12 months thereafter.

With the approval of this supplement, in that population 2 to 18 years of age, you can receive 720 ELISA units, and then follow that with the booster of 720 units, six to 12 months later.

The adult dosage stays the same, at 1,440 ELISA units.

We also approved a hemophilus B conjugate vaccine liquid formulation, and this was produced by Merck & Company, and this particular formulation of this vaccine has reduced the dose to 7.5 micrograms from the lyophilized formulation.

We also had an approval of an acellular pertussis vaccine from Connaught Laboratories, Inc., the Tripedia, and this was approved for the primary immunization of infants

and also it was approved, the primary immunization was approved in July of last year, and in September of last year, we also approved this vaccine to be combined with Pasteur-Merieux use, hemophilus B conjugate vaccine, and

this is for immunization only at 15 to 18-month-old children. It is not for the primary series.

As I stated, we have approved the Pasteur-Merieux hemophilus conjugate vaccine to be used in combination with the Tripedia from Connaught Laboratories, and again, this is for 15 to 18 months of age.

Lederle Laboratories, in December, the latter part of December of last year, was approved for an acellular pertussis vaccine also, and this is for a new infant indication and a modified formulation was also approved with this vaccine.

This vaccine can be used for the fourth and fifth dose in children who have received three doses of Acel-Immune or whole cell, and Acel-Immune is indicated for active immunization of children 6 weeks of age to age of 7.

These were the major approvals of product license applications and supplements that we had in FY '96 and early '97. Other regulatory accomplishments that we had over this fiscal year, in December, we produced a Points to Consider for plasma DNA vaccines, and this was presented to the advisory committee in October of last year, and this Points

to Consider was intended to provide manufacturers with preliminary guidance on manufacturing and preclinical evaluation of plasma DNA vaccines intended for clinical studies in preventive infectious diseases.

We also had a Points to Consider for combination vaccines signed out of CBER this past December. This particular Points to Consider is not available. The previous draft that we discussed in October of 1995 is still available. The December draft is not available yet. It is pending release from the Agency, but that has been signed out of CBER, and we expect that to be available soon, that particular draft.

That is all I have for you. I will take any questions if you like.

DR. FERRIERI: Thank you, Dr. Baylor.

Questions? Dr. Broome.

DR. BROOME: Are there particular issues or changes that you are able to discuss with the Points to Consider document on the combination vaccines?

DR. BAYLOR: Most of the changes, they are not significant changes, so the essence of the October 1995, it is still pertinent.

Thank you.

DR. FERRIERI: Thank you. That concludes everything except the open public hearing, and I will turn

this over now to Nancy Cherry.

Open Public Hearing

MS. CHERRY: This is the time for anyone from the public who wishes to make a statement. I was not alerted by

anyone that they wished to make a statement. We are ahead of schedule, but is there anyone in the audience who would like to make a statement?

[No response.]

MS. CHERRY: If not, then, the public hearing session is closed.

DR. FERRIERI: Thank you, Nancy.

That concludes the meeting, and we can now adjourn. I wish everyone a good trip home.

[Whereupon, at 4:00 p.m., the proceedings were adjourned.]