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UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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VACCINES AND RELATED BIOLOGICAL PRODUCTS
ADVISORY COMMITTEE

MEETING

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WEDNESDAY,
JANUARY 30, 2002

The Advisory Committee met at 9:00 a.m. in the Versailles I and II Rooms of the Holiday Inn Bethesda, 8120 Wisconsin Avenue, Bethesda, Maryland, Dr. Robert S. Daum, Chairperson, presiding.

PRESENT:
ROBERT DAUM, M.D., Chair
MICHAEL DECKER, M.D., Member (non-voting)
PAMELA DIAZ, M.D., Member
WALTER FAGGETT, M.D., Member
BARBARA LOE FISHER, Member
JUDITH GOLDBERG, Sc.D., Member
DIANE GRIFFIN, M.D., Ph.D., Member
SAMUEL KATZ, M.D., Member
KWANG SIK KIM, M.D., Member
STEVEN KOHL, M.D., Member
AUDREY MANLEY, M.D., M.P.H., Member
PETER PALESE, Ph.D. Member
GREGORY SLUSAW, PhRMA.
DIXIE SNIDER, M.D., M.P.H., Member
DAVID STEPHENS, M.D., Member
RICHARD WHITLEY, M.D., Member

ALSO PRESENT:
WILLIAM FREAS, Ph.D., Executive Secretary
NORMAN BAYLOR
DANA BRADSHAW
LINDA CANAS
ROBERT COUCH, M.D.

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ALSO PRESENT:
NANCY COX, Ph.D.
BENEDICT DINIEGA, M.D.
WALTER DOWDLE, Ph.D.
BILL EGAN
THEODORE EICKHOFF, M.D.
KEIJI FAKUDA
NEIL GOLDMAN
JESSEE GOODMAN
ALEXANDER KLIMOV
ROLAND LEVANDOWSKI
KAREN MIDTHUN
MARTIN MYERS, M.D.
GREGORY POLAND, M.D.
JODY SACHS
ZHIPING YE
RICHARD YORK
KATHRYN ZOON

I N D E X

PROCEEDINGS

9:09 a.m.

DR. DAUM: Good morning. We call the meeting to order and the first post-Nancy Cherry iteration of our Committee and having said that we are grateful to Bill Freas for being here and stepping into tall shoes.

I think we'll begin today with asking Committee Members and guests and consultants to introduce themselves to us and then we'll proceed into our business.

David, would you start off, please?

DR. STEPHENS: Yes, David Stephens, Emory University, Atlanta.

DR. KIM: Kwang Sik Kim, Johns Hopkins.

DR. KOHL: Steve Kohl, Argonne Health Science University.

DR. SNIDER: Dixie Snider, CDC.

DR. GRIFFIN: Diane Griffin, Johns Hopkins.

DR. DIAZ: Pamela Diaz, Chicago Department of Public Health.

DR. MANLEY: Audrey Manley, Spellman College, former Public Health Service.

DR. PALESE: Peter Palese, Mt. Sinai

School of Medicine in New York.

DR. WHITLEY: Rich Whitley, University of Alabama, Birmingham.

DR. FAGGETT: Walt Faggett, D.C. Department of Health, Howard University.

DR. GOLDBERG: Judy Goldberg, NYU.

DR. DAUM: And now our guests and consultant contingent.

Ted?

DR. EICKHOFF: Ted Eickhoff, University of Colorado.

DR. DOWDLE: Walter Dowdle, Task Force for Child Survival and Development, Atlanta.

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

DR. POLAND: Greg Poland, Mayo Clinic, Rochester.

DR. MYERS: Martin Myers, National Vaccine Program Office.

DR. DECKER: Michael Decker, Vanderbilt University and Independence Pasteur.

DR. DINIEGA: Ben Diniega, Department of Defense, Health Affairs.

DR. COX: Nancy Cox, CDC.

DR. LEVANDOWSKI: Roland Levandowski,

Center for Biologics, Evaluation and Research.

DR. DAUM: Thank you. Ms. Fisher has arrived. Do you want to introduce yourself, please?

MS. FISHER: Barbara Loe Fisher, National Vaccine Information Center.

DR. DAUM: And I'm Robert Daum from the University of Chicago. And we'll turn the floor over to Bill now for conflict of interest statement.

DR. FREAS: I would like to read into the public record the conflict of interest statement for this meeting.

The following announcement addresses the conflict of interest issues associated with this meeting of the Vaccines and Related Products Advisory Committee Meeting on January 30, 2002. Based on the agenda made available, it has been determined that the Committee discussions for the influenza virus vaccine formulation present no potential conflict of interest. The Director of the Center for Biologics Evaluation and Research has appointed Drs. Robert Couch, Walter Dawdle, Theodore Eickhoff, Martin Myers and Gregory Poland as temporary voting members for the discussion on the selection of the strains to be included in the influenza virus vaccine for the 2002-2003 season.

In the event that the discussions involve

specific products or firms not on the agenda 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 in the public 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 upon

Dr. Daum, I turn it over to you.

DR. DAUM: Thank you very much, Bill. One of the more remarkable aspects of this Committee is it ability to renew and refresh itself and the ability of FDA and other government agencies to find such a talented group of people who are willing to drop everything six times a year and come to Washington to discuss these issues. And with that, of course, comes a rotating nature and we have friends and colleagues who we've gotten used to having dinner with and debating issues with that take their leave from Committee service. So it's a bittersweet time and we're going to call on Dr. Kathy Zoon to mark the rotation of some of the Committee Members who have been serving faithfully these years. And we welcome,

of course, some of our new Members as well.

Dr. Zoon.

DR. ZOON: Thank you, Bob. I guess it is one of those bittersweet moments and there's an enormous amount of hesitation I have because some of the folks who are leaving today have made so many contributions that having them not be part of the Committee right now is going to be a very sad thing for this Committee. On the other hand, we have as Bob says, new people coming.

I would like to ask Bill Egan to join me up here because we would like to have some special recognition for the advisors who are rotating off the Committee.

I would just, in saying that, these Advisory Committees for us are so valuable. They provide us advice in a public forum that allows us to collect information and recommendations for many, many important public health decisions. In particular, this Committee which is faced with many difficult issues over certainly the past 3 years on important topics related to vaccine safety, vaccine approvals. This has been something that has challenged all of us in the Public Health Service, more broadly, as well as in the pharmaceutical industry and the communities

together and ultimately, I believe, that the advice we've gotten from this Committee over the years has always been balanced, reflected many points of view and we really try to collect that information in a way to help us give the best advice to medical care workers and consumers.

So in saying this today, we want to reach out and give special thanks. I would like to ask Dixie Snider, Steve Kohl and Kwang Sik Kim to please come to the podium and Bill, would you like to say a few words? Karen can't be with us right now this morning, but I'd like to ask Dr. Egan to just maybe say a few words reflecting on his own experience over the past few years.

Thank you.

DR. EGAN: I'd just like to echo Kathy's remarks and say that the sage advice and knowledge that's been imparted to us by this Committee has been extraordinarily important in helping us to reach all of the decisions, many, many difficult decisions that we've had to do. There have been some very tough issues over the past year dealing with vaccine preservatives, additives, materials in them, licensing and new products. It's always been hard and having this group here and their combined knowledge and

wisdom has been just extraordinarily helpful and it's hard to imagine how things could have been done without this group.

We and the Office and certainly CBER are truly grateful for everything that everybody here has done.

DR. ZOON: Thank you, Bill. I now would like to provide these three gentlemen plaques, but first I'd like to read a letter to all of them that was signed by Linda Sudam. Linda Sudam is the Senior Associate Commissioner for Communication and Constituent Relations and has responsibility for the bigger FDA Advisory Committees and overseeing them. And she says to the Members, "I would like to express my deepest appreciation for your efforts and guidance during the term as Member of the Vaccines and Related Biological Products Advisory Committee. The success of this Committee's work reinforces our conviction that responsible regulation of consumer products depends greatly on the participation and advice of the entire health community. In recognition of your distinguished service to the FDA, I am pleased to present you with this enclosed certificate."

So I want to just say first, Dixie, I will miss you here, but I know we're going to keep on

talking because that's that FDA and CDC does, so thank you very much for your service.

(Applause.)

(Photos taken.)

DR. ZOON: Next we have Steve Kohl. Steve, congratulations and thank you so much.

(Applause.)

(Photos taken.)

DR. ZOON: Dr. Kim, thank you so much for everything. We really appreciate it.

(Applause.)

(Photos taken.)

DR. DAUM: Thank you, Dr. Zoon. We'll now move on to the formal business at hand and begin our strain selection process for the influenza virus vaccine for next year, although some might argue that the season hasn't yet happened this year. But we'll hear more about that as the day goes on.

And we will begin, of course, by calling on Dr. Levandowski who will give an introduction to the topic.

Roland, thank you.

DR. LEVANDOWSKI: Thanks, Dr. Daum. I'd like to welcome everybody here this morning and I think you know why we're here, but I'm going to give

a little brief introduction into what we plan to do. As you probably know, we're here today to start the process of selecting the influenza virus strains that are going to be included in vaccines prepared for the 2002-2003 season in the United States. Could I have the next slide, please?

The basic question to be answered by the Committee is shown on this slide. This is a little bit abbreviated from what's actually been handed out and I'll put that one up later, but really, what we want to know is what strains should be recommended for inclusion in inactivated vaccines for next year.

Next slide, please?

In formulating an answer to that question, I think it's helpful to review some facts about the currently approved influenza virus vaccines and this is true from the beginning, probably, for inactivated vaccines. The inactivated influenza vaccines, of course, act primarily by inducing production of antibodies and the hemagglutinins and the neuraminidases of the incorporated influenza viruses in the current vaccines are concentrated and they're partially purified to remove extraneous materials that are derived from the eggs in which the vaccines are produced. Although the antibodies to both

hemagglutinins and neuraminidases are protective, the influenza vaccines that we use currently are standardized, really only for the content of the hemagglutinin and therefore we place the greatest emphasis on the viral hemagglutinin, but I would point out that the neuraminidase receives consideration and it too may have some protective effect in terms of how the vaccines function.

Since the use of the first inactivated vaccines in the 1940s, it's been very clear that one of the most important predictors of vaccine efficacy is the match between the vaccine virus and the ones that are currently causing infection. What's also been made clear with yearly epidemics and pandemics that have occurred infrequently is that influenza viruses have very great scope for antigenic diversification. The on-going random mutations of the hemagglutinin and neuraminidase we call antigenic drift and exchange of entire genes can occur with other influenza viruses and we call that antigenic shift. And both of those participate in the continuous evolution of the viruses.

Can I get the next slide, please?

It might also be helpful to consider answers to these questions. Most importantly, it's

necessary to know if the new influenza viruses that are out there, really are new and there's an extensive global network that exists to collect and analyze information throughout the year and we're going to hear shortly from our colleagues from both CDC and Department of Defense in terms of the surveillance and what viruses are being found.

When new viruses are identified, the extent of geographic distribution helps to judge the urgency that we might have in trying to change the composition of the vaccine and we've often seen in the past that there are antigenic variants that occur, but sometimes these just represent dead ends and go no further than one off.

As you've also seen in the past, however, there can be some very rapid spread of influenza viruses and that, I think, is of more concern, of increasing concern in modern times when it's possible for people to jet from one side of the globe to the other.

If those strains have, or can disseminate widely, it's useful to know whether or not the current vaccines are likely to provide some form of protection against those and if it appears that the current vaccines could be suboptimal, then it's still

necessary in a practical sense to consider whether we've got any suitable vaccine strains that would permit large-scale manufacturing within the constraints of time that exist in terms of making a new vaccine every year.

So the agenda of presentations that will follow will try to supply information to answer each of those questions.

If we can get the next slide? This slide shows the recommendations that have been made during the past year and on the left are the recommendations that were made for the United States and the Northern Hemisphere by the Public Health Service and World Health Organizations, respectively. And on the right are the most recent recommendations from the World Health Organization for the Southern Hemisphere. And you'll note that currently the recommendations for vaccines in both hemispheres are identical. This isn't always so. In fact, it's more typical for us to see that there are differences between the Northern and Southern Hemisphere vaccine recommendations and that's really related again to the continuing antigenic changes that are occurring in influenza viruses. But what I could say, part of the reason that the recommendations, the most recent

recommendations made for the Southern Hemisphere in September-October of 2001, those changes reflect the fact that there have been little in the way of changes, relatively little in the way of changes that have been identified in the new influenza viruses and that's really a very unusual sort of pause in the world of influenza.

So since the recommendations are based on information, the choice of the strains that was made in September really followed from what was available then and without giving away what's going to be presented by others, I think we're going to hear this morning that the system of making recommendations is sound, as long as the recommendations can really be well-informed by sufficient epidemiologic laboratory and manufacturing data. And I'll stop there because that's really all I have to say at this point.

DR. DAUM: Thank you very much for being succinct. Are there any comments or questions based on what we've heard so far or would we like to hear a little more first?

Thank you very much, Roland. We'll move on now to Dr. Fakuda. There he is. Good morning, Dr. Fakuda.

DR. FAKUDA: Good morning.

DR. DAUM: Dr. Fakuda will talk to us about the U.S. surveillance.

DR. FAKUDA: Good morning, everybody. What I'm going to do with this talk this morning is show a couple of slides to put the season in context and really in anticipation of questions related to how does this season compare to previous seasons.

May I have the next slide? For those of you who have studied influenza, I think you all realize what a plastic -- or how the presentations can be very plastic and vary from season to season. And in this slide here, there are two things that I wanted to point out. When you look down at those circles at the bottom, these are the proportion of viruses which have been isolated each season over the past 11 years, the first season being 1991 through 1992 and the last season being the current one. The red color are influenza A(H3N2) viruses. The green color are influenza A(H1N1) viruses. And the blue color are influenza B viruses. You can see that from season to season that there can be substantial differences between the influenza viruses which are isolated each year in terms of the proportions.

Now when you look at that sinusoidal curve up above, that represents the influenza mortality

related to pneumonia in influenza-related mortality that we see each year in the country as monitored by the 122 cities surveillance system. And again, you can see that in terms of overall mortality, in terms of mortality that it varies, it can vary substantially between years.

And in general, you can see that in influenza A(H3N2) years, we tend to see fairly severe mortality, but this is not always true and you can see that in other years in which influenza A(H3N2) viruses are common that mortality is lower. So it's not such a simple correlation. But again, you can see that the severity of seasons vary substantially and the mix of viruses can vary substantially from season to season.

Now in this slide here what I wanted to depict was that the onset in the timing and peaking of influenza seasons can also vary tremendously depending on what season we're talking about. Now these curves here represent the proportions of specimens that are testing positive for influenza viruses by each week and generally these represent when the season is peaking and you can see that in this first curve here, this blue curve which represents the 1999-2000 season, that we have a relatively sharp upswing and a fairly early peaking in influenza viruses being isolated, so

that in the 1999-2000 season, the season really peaks somewhere towards the end of the year and the beginning of the following year.

By contrast, you see this red line over here, this red graph which represents the 1987-1988 season and you can see that the up slope of the viruses being isolated is somewhat flatter. And you can see that the time of the peaking of the season is really quite different and this is about Week -- I don't know, between 14 and 16.

And when you look over the data for the past several years, there can be a separation of about 18 weeks between seasons in terms of when we see peaking. So that's quite large variability. And so this black line right here represents the current season and as I will show I think that we haven't yet peaked, so we don't really know when the peaking of the seasons is going to occur.

Now this is the last of the background slides, but here what we did, we went back over the past 25 seasons and tried to identify in which month each of those seasons peaked, again to give you a sense of how seasons progress in the country and you can see that over the past 25 years, the most common month in which the season peaked was in February, but

again, there were four seasons which peaked in December and there were a couple of seasons which really peaked pretty far out there and so again, the variability and the timing of the influenza season can be quite wide.

Next slide, please. Okay, so let's go -- this is the current season now. This is what we're seeing right now. And this graph here represents the viruses which are being isolated in the United States for this current season. The yellow bars represent influenza A viruses which have not been subtyped. The red bars represent influenza A(H3N2) viruses and then again the green bar represents B viruses and blue represents A(H1N1). And so when you look at this, it's very clear that this is an influenza A season so far in the United States. And of those influenza A viruses which have been subtyped, by far the majority are influenza A(H3N2) viruses.

Now this black line here represents the weekly percentages of respiratory specimens that are being tested and that are positive for influenza viruses and you can see that on each week the percentage of respiratory specimens being tested has increased in terms of being positive for influenza viruses. At our last point, this represents about

13.9 percent of specimens being tested are positive for influenza and to put that in perspective, again, when you look over the past several seasons, seasons usually peak out at about 24 to 33 percent of respiratory specimens being positive for influenza viruses. And so although again we don't know when the season is going to peak this year, these data suggest that we haven't yet seen the peaking of this season and so we don't know when that's going to occur again.

Next slide, please. So just to run some of the numbers by you, so far we've had about almost 26,000 specimens tested. Of these, about 5 percent or 1,299 have been positive for influenza and of those positives, 98 percent of them have been influenza A viruses; 2 percent have been B viruses. And again of those that have been subtyped or 37 percent of those viruses have been subtyped and of those which have been subtyped 98 percent are A(H3N2) viruses and 2 percent have been influenza A(H1N1) viruses. So again, an influenza A season with A(H3N2) viruses predominating.

Now by contrast, when we look at clinical activity in the country and these represent two sentinel physicians for influenza-like illness and currently this represents about 650 physicians spread

throughout the country that are reporting fairly regularly. We can see that the percentage of visits of influenza-like illness has really just been going up pretty slowly. And I think this captures pretty well the general perception that it's been a fairly low and slow season so far.

Now if you look at the national baseline for influenza-like illness visits, it's about here, about 1.9 percent is a rough national average for influenza-like visits. And again, when you look at earlier seasons you will see that this graph will peak out somewhere between 4 and 5 percent to about 7 percent when we're at the peak of a typical season. So again, this suggests that the activity is fairly low, but it is increasing and again suggests that it has not yet peaked out.

Now this map of the United States represents reports from each of the State and territorial epidemiologists and this represents the most recent reporting week, the week ending January 19th. The red States are those States which are reporting widespread influenza activity. The blue States are those representing regional activity. And then the green States are reporting sporadic activity and the yellow States are reporting no activity.

So again, you can see that the activity is somewhat scattered around the country and again if anything we would typically see more States reporting either regional or widespread activity if we were toward the peak of the season.

And then finally, this is a graph of the same data, just graphed out in terms of bars here and you can see that the aggregate number of States reporting either regional or widespread activity has been increasing, but again, it remains fairly moderate.

And this is the last graph and this represents mortality associated with pneumonia and influenza. And again, this is data reported through the 122 cities surveillance system. I think all of you remember that last year it was a pretty mild season in terms of mortality, especially, and so far this year it also remains relatively mild in terms of mortality. We haven't seen any real increase over the so-called threshold level. So I think I will stop there and see if there are any questions.

DR. DAUM: We'll take a few minutes for Committee questions and opinion.

Dixie?

DR. SNIDER: Could you tell us -- I think

some people may not be aware about the change in the coding and how that might influence the pneumonia and influenza deaths, mortality surveillance and whether you've got that worked out so that you think we're getting, are able to show data that are comparable now?

DR. FAKUDA: All right, you're talking about the ICD 9 to 10 coding?

DR. SNIDER: Right.

DR. FAKUDA: I think in terms of the graph which I just showed, that takes that into account because the reporting case definition for that sidesteps that issue of ICD9 going to ICD10 and uses the case definition which specifies what a PNI death is and doesn't rely on PNI coding. But the coding issue is a rather profound issue for people monitoring diseases. Over the past decade, WHO has been working to revise ICD9 coding to ICD10 coding. And in terms of reporting for respiratory diseases and particularly pneumonia and influenza-like diseases, the change from ICD9 to ICD10 codes has been quite profound and those changes, if they had been implemented as first written down would have decreased measured deaths by about two thirds in the country, looking at NCHS data sets.

What happened subsequently was that after

that profound change was detected, there was a working group of WHO with input with a lot of other people and they went back and looked at the coding algorithm and made some modifications so that the affect on respiratory deaths or measurements of respiratory deaths will be less profound, but I think the current estimates are that when deaths recorded by ICD10 begin to come out, that there will be about a 33 percent or one third decrease in measured deaths and those deaths which aren't being measured and categorized as respiratory deaths then go out into a number of other categories such as strokes or other particularly chronic diseases.

But at least in terms of the data here, it takes those into account and the reason why we made the reporting case definition change was because of all of those changes going on.

DR. DAUM: Dr. Diaz?

DR. DIAZ: I just wondered if you could comment, I'm always perplexed when I look at the WHO and NRVs reporting, the percentage of unknowns under the As or Bs as the case may be, and wondering if those unknowns represent isolates that have yet to be subtyped or if they're isolates that will never be subtyped and what the situation is in terms of the

time frame for those. I'm always worried about not having that information and if the tie up is at the local level, State laboratory level or what the situation is.

DR. FAKUDA: Well, Nancy can probably talk in more detail to this, but it represents a mixture of both viruses which have yet to be subtyped. We don't have the data. That curve is a little bit behind and it's always being updated and then some of those will be subtyped, but others will not be subtyped by the end of the season.

Nancy, I don't know if you want to add anything.

DR. COX: I think that this is an issue that we've been talking with the States about for some time and it really is a resource issue, generally speaking. At the State and local level there is a paucity of resources for some of the lab work that needs to happen. And particularly, within the context of influenza pandemic preparedness we'd like to try to encourage and help the States to increase their capacity to subtype.

DR. DAUM: Dr. Couch?

DR. COUCH: I'd just like to add one comment to that though, you do specify it's influenza

A or B so that that data is always known. It's B unknown or A unknown and then it's like doing a representative group. It takes so much time and effort, as Nancy says. And that representative group says that 95 percent of H3N2, why, almost certainly if you were doing all of them you'd find the same thing. So there's a high degree of confidence that we know what the unknowns are and I think people operate in their thinking that way.

But I had just some informational questions if I might, Keiji. I think it's asking you to confirm whether in looking at the weekly surveillance of what you see is true and that is there is a reporting lag here and that what you're reporting is what you have in hand for each week because as you move the week, the other weeks begin to pick up and just in trying to go through these it looks like the data that you published the front line is lagging about three weeks behind, not only in terms of specimens reported, but in terms of the typing of the specimens as well.

DR. FAKUDA: Yes, I think that the lag for the different systems vary somewhat, but for the virologic system, clearly, you know it -- information comes up and so when you look at that curve, for

example, the most recent week will have a lower bar typically and then as we get a week or two out from there as more data comes in --

DR. COUCH: And I assume this is just the reporting from the peripheral laboratories?

DR. FAKUDA: Yes.

DR. COUCH: And it's a fact of life. Now that was my other question Is that also true for physician visits?

DR. FAKUDA: No. The data for the physician visits is, you know, it comes through and you go back and if we see something which looks strange like there are a very high percentage of visits being reported, then we will go back to confirm with the State or go back to confirm with the physician. So there's always a little bit of error checking in that system also, but I think the lag is less than it is for --

DR. COUCH: For the specimens in the virus.

DR. FAKUDA: Right, and I think the data change.

DR. COUCH: The reason for that question is that in the Houston surveillance which most everybody knows was a number of years ago in which in

one place you're right on top of it from a weekly basis. That was an extremely high correlation between the physician visits for febrile respiratory disease and the specimens acquired and the number of positives, so that if you're lagging with the specimens your physician visit may be the most current data set and your epidemic is peaking now.

Now the other question I had was, was 1987-1988, do you happen to know what the virus was and the question of influenza A versus B and Walter may comment because we -- there's been the impression that influenza B was spread out -- tends to spread out over a longer period and may be the lagging virus and the March peak as opposed to the January peak which is more typical for an influenza A and of course, you're putting them all together there with the February as the mean peak. The difference was in A and B was the question.

DR. FAKUDA: Clearly, there are seasons in which when you see a bimodal peak B frequently is the latter peak. As to 1987-1988 specifically, I'll defer to Walter or Nancy or someone with a few more years.

DR. DAUM: Dr. Dowdle, do you want to comment on this issue? Okay, then could you be second in line, Dr. Goldberg was ahead of you.

DR. FAKUDA: I can find that out, but I don't know.

DR. DOWDLE: I mean I agree with what Bob has been saying. That has generally been the case.

DR. DAUM: Dr. Goldberg, please.

DR. GOLDBERG: Just to go back to the unknown subtypes. You made a comment that you're assuming that what is typed is representative and I guess one question I would have to follow that up a little bit longer, can you really subtype them all or are there really unknown subtypes and can you do some study at least on some of these samples to ensure that we do have something representative?

Is there some way to check that assumption because you really, if you look at this as the number of samples peaks, you're testing less and less relative to the number of specimens of samples that exist, so that's my question. What's your assurance that it's representative? Are we able to test that in some way?

DR. COX: I think that it's a fairly good assumption that it is representative because as we move through the seasons, the State and local labs are able to do more subtyping and generally speaking the proportions remain similar. However, there's a

caveat. And there can be a pocket of H1 activity within the country. It's not generally true, but there can be and so therefore we like to make sure that all areas are actually subtyping. So if you have one particular area that wasn't doing subtyping at all, you might get into trouble with that assumption.

Insofar as we know, there are not unsubtypeable viruses. That is to say they are H3 and H1 viruses that are circulating. In a pandemic situation, of course, you can't make that assumption and occasionally we do have exceptions to the general rule that they are human H1 and H3. That is to say we have a swine H1 infection of a human and we can pick out those viruses.

DR. DAUM: Dr. Dowdle then Dr. Eickhoff.

DR. DOWDLE: I would just like to ask a question here about the ICD coding. As you have explained it, Keiji, that is rather profound changes that we're talking about here and it's a fairly major adjustment. So are there plans to validate that adjustment? What -- how will you deal with this in the future? I know Ted, this must be something that goes way back in the past, but this has been certainly a major measurement of activity over the years and validation would seem to be quite important here.

DR. FAKUDA: NCHS in the past year, year and a half did a validation study of it and they took the current testing algorithm and applied it and they're the ones who came up with the estimate that the decrease in measured deaths would be somewhere in the 30 percent range. And so that has been done by them on a fairly large data set already.

DR. DOWDLE: Over several seasons.

DR. FAKUDA: I don't remember how many seasons they chose. I don't think it was too many. It may have been a couple of seasons. But yes, it's something that has worried me a lot because this is such an important marker of activity for us and I don't think the people when they were originally making the algorithm changes realize what an immense impact this would have on the measurement of respiratory deaths and that certainly could have a big ripple effect in terms of the perception of respiratory diseases. But what it will probably do will decrease PNI deaths from I think the current sixth position down to the seventh position as the leading cause of death, simply because of that algorithm change.

DR. DAUM: Thank you. Dr. Eickhoff and then Dr. Poland.

DR. EICKHOFF: Keiji, am I correct in assuming that the physician office visit data is reported directly from physician office to CDC and does not go through the State Health Departments?

DR. FAKUDA: It's --

DR. DAUM: Can you repeat the question? I'm not sure -- Ted, you need to speak right into the microphone for us. I'm not sure everybody heard.

DR. EICKHOFF: The question was whether physician office visit data goes through State Health Departments or is reported directly to CDC?

DR. FAKUDA: Ted, it's kind of a hybrid situation. Just to put the hybrid in context, as you know, much of surveillance which is done in the country has data go from primary reporters to the Health Department and then from the Health Department to CDC. But also, many of the surveillance systems don't need to get their data out on a weekly basis in the way we do. So what we did was come upon a compromise in which the Sentinel Physicians report data. It goes to a server which both CDC accesses and then the States can access simultaneously and so we both get the data.

If CDC in going through and looking at the data picks up anything unusual, we get back to the

States not directly with the physicians and then ask is there anything going on in the State or can they check with the physicians about any unusual reporting issues.

DR. EICKHOFF: But that should still be the most current indicator of what's actually happening, isn't it?

DR. FAKUDA: Yes.

DR. DAUM: Thank you. Dr. Poland and then Dr. Diaz.

DR. POLAND: With the numerator and denominator kind of changing based on this coding by the same relative amount, will the epidemic threshold change?

DR. FAKUDA: No, again, these data -- there are two main systems for reporting deaths from influenza in the country. The system which I'm pointing out here, using here is from the 122 cities, 122 cities which report vital statistics data on a weekly basis to CDC. And so this represents about one third of all deaths in the United States. So we asked those vital registrars offices to represent a PNI death and we define it in a certain way so it doesn't rely upon ICD coding. But you know, a couple years after season you'll see those total number of deaths

from influenza and those are estimated from a complete national data set obtained from the National Center for Health Statistics and that does rely upon ICD coding.

To make it a little more complicated, there are a couple of cities in a couple of large vital registrars' offices in the country which do track only by ICD coding, New York, for example. New York represents about 11 percent of all deaths in the system and so there are sort of complexities built in trying to get these estimates, but in general, this system is a little bit different than how we report data, the final data set a few years later.

DR. DAUM: Thank you. Dr. Diaz, please.

DR. DIAZ: Just a couple of quick comments. In terms of the prior comment that I made regarding the unknown subtypes, I was looking at that more from the standpoint of I certainly agree that in general as Dr. Cox pointed out, if each locale is doing some subtyping, most definitely or most likely what has been subtyped would be representative of what's going on in general in those areas and represent fairly generally the unknowns. However, when you look at a surveillance system from the standpoint of trying to find unknown rare events like

a shift or some unusual subtype that's emerging in an area, having those unknowns typed in a timely fashion would be -- go more towards an early warning system for those kinds and that's what I was really referring to in terms of the unknowns perplexing me or bothering me at times.

Secondly, in terms of the Sentinel Physicians Network, having actually overseen the development of that in Chicago this season, we're just beginning our first season of direct reporting from Sentinel Physicians Network. I can comment that the system that's set up in terms of direct reporting to CDC is, as you point, very important because you have to report weekly and yet on a local level we're able to access that in real time and fashion and those two elements are critical, I think, in terms of sharing information and having information that's pertinent on a local level and pertinent on a national level be available in both at the same time.

DR. FAKUDA: Just to add one thing to your first comment, I think that in terms of viruses which represent a shift which may be found in the U.S. at least, and even though a large number of viruses aren't subtyped, I think that if those viruses which are testing low with current reagents are identified,

even if they're not subtyped generally they get slagged and I think that Sasha will frequently hear about them very quickly. So there is some sort of extra safety measure in that.

DR. DAUM: As a novice to the subject, I must say I've often wondered when people who do surveillance like this and are really expert in influenza, which I'm not, would expect to see or take into account the deployment of the vaccine program in terms of influencing the surveillance that we see. And we put out -- there's a lot of doses out there each year, X number of million and I just wonder in terms of thinking of this every day like you all do, when do you expect to see some impact on surveillance based on the program that we're here to help perpetuate?

DR. FAKUDA: Right. I think that there are really two possible analyses for that, one which really hasn't been done and the other which has been done a number of times. I think the analysis which has been done over and over again is the comparison between vaccinated and unvaccinated people for a variety of outcomes, but particularly death and hospitalizations and illnesses. And again, I think any number of studies like that over a number of

decades again show the effect of vaccinating people in terms of decreasing those adverse outcomes.

The second analysis and what you're really getting at is can we look at mortality or hospitalizations in the country over all and say that current vaccination efforts have decreased things by so and so percent. I think that -- I don't think that that analysis really has been done. Certainly, it's been somewhat looked at by some people, including ourselves, but I think that analysis is yet to really be done.

DR. DAUM: Okay, I think we exhausted our input. Thank you very much for sharing those data with us. We'll call on Dr. Cox, if she's ready to talk about world surveillance and strain characterizations.

DR. COX: Well, good morning. And it's really nice to see everyone here again. There are many familiar faces, as we go through this process of selecting vaccine strains.

Today, we have just lovely weather and I can remember a number of times when the weather hasn't been nearly this good for this particular meeting, so we can just bask in the sunshine when we go out for lunch.

Now I'm going to be presenting the antigenic data which is comprised of both hemagglutinin inhibition and neuraminidase inhibition testing. And I'm also going to be summarizing the global influenza activity and I'll summarize it very briefly, to put the U.S. within a more global context.

So we'll be looking first of all for variants as Roland said. Do we see viruses which are antigenically different from the vaccine strain? And we'll pick those out using the hemagglutination inhibition tests primarily. And then we'll be looking for spread of those particular variants in conjunction with human disease. And finally, we'll be looking at whether the antibody response to the current vaccine covers those variants and whether there are reagent viruses suitable for vaccine production.

You probably have noticed in the past that we choose, often choose to go through the virus group that appears to be the clearest cut first and that's no exception today. So we'll start with the influenza H1N1 viruses. And as you'll recall we had sporadic activity -- I don't know if that can be focused any better or not.

(Pause.)

If you look on page 11, you'll have the

correct data. What you'll see is that there actually was a reasonable amount of influenza H1N1 activity in North America and in Europe last winter. And that also -- that H1N1 activity also occurred in the Southern Hemisphere with outbreak level activity in Australia and New Zealand and also in Asia during the summer and fall months.

During the current season, there really has been only sporadic influenza activity associated with H1N1 viruses in the U.S., in Canada, and in Europe. There also has been H1N1 activity that's been rather sporadic reported in Asia and in South Africa, Northern Africa and the Mediterranean.

Now I'd like to spend just a moment orienting those of you who may be new to this to the hemagglutination inhibition tables that I'll be showing.

On page 12 you'll see our first HI table for H1N1 viruses. Now I'd like to remind you that there are two antigenic and genetic groups that we have been tracking among H1N1 viruses that have circulated globally over the past few years. The first group is represented here by Johannesburg/82/96. That was a vaccine strain that was used previously. And at one time this virus represented H1N1 viruses

that were circulating globally.

At the same time that viruses like Johannesburg were circulating globally, there was a small group of H1N1 viruses evolving in Asia, particularly in China which had a very specific -- which were already evolving and were different genetically when a deletion occurred in antigenic site A. At that point these viruses became clearly distinguishable on an antigenic level from the Johannesburg/82/96-like strains. And these viruses have been circulating globally, that is to say, both groups have been circulating over the past few years. However, we found over the past year or so that the Johannesburg/96-like viruses have not been detected. So we're really going to concentrate on viruses within the Beijing/262 New Caledonia group.

Now what we've seen over the last year is that H1N1 viruses have really been very stable both antigenically and genetically, generally speaking. However, we have isolated one particular variant which is very clearly shown in this particular slide by antigens 4 and 5 represented by these two antigens and I'll call this the Hawaii/15/2001 group. You can see that these viruses, while related to New Caledonia, are antigenically distinct.

I would like to say that there's a single amino acid difference that appears to be responsible for this change, for this antigenic difference and that we have just seen a handful of viruses popping up over the past two years. You'll notice that the Hong Kong/1252 strain was isolated in the Year 2000 and that these viruses just pop up occasionally, but they don't appear to be really spreading or increasing in numbers over time.

So now let's look down at the bottom part of the table and we see that we have viruses primarily from China and isolated primarily actually from -- mainly from South China and isolated during August, then September, through the summer and into the fall months when activity in South China is really peaking. And these viruses look very similar to New Caledonia, that is to say, their titers are within twofold of the homologous New Caledonia ferret antisera titer with New Caledonia itself. We're looking for viruses that have a fourfold or greater difference in consecutive tests. There's a certain amount of variability that's inherent in the hemagglutination inhibition test and a twofold difference in titers is not considered to be significant. A fourfold difference is considered to be significant if it can be validated in separate

tests, if it's a consistent result.

Now we do see viruses from Hubei, which have a fourfold increase in titer. We've gone on to take those viruses, sequence them and also to put a representative one in the human serology tests and we found that that strain was indeed well covered by antibody to the current vaccine.

Next slide, please.

Now we have viruses from slightly more recent activity. We have two strains that were isolated in the U.S., one from Wisconsin, one from Washington in October. That was the first H1N1 virus we received and then the Wisconsin virus is more recent from December.

We also have some viruses that were isolated in Australia and New Zealand during September and October, followed by some Asian strains from Hong Kong, the Philippines and Bangkok. Again, we see that there's a remarkable amount of homogeneity among strains. There are occasional strains including the Brisbane strain here and the Bangkok/255 strain here which do have a fourfold reduction in titer, but as I'll show you in a minute, viruses like this are relatively rare.

Next slide, please.

So now we're looking at a frequency table which summarizes the antigenic analysis that we carried out at CDC on H1N1 viruses and we have the viruses divided up by region across the top and by time going in this direction. And of course, we want to designate, we want to determine what proportion of the strains that we're analyzing are low to the vaccine strain.

As you can see, we did have some Johannesburg-like strains circulating last winter. Those were, according to the human serologic testing that was done, those were also well-covered by the vaccine.

We did have a proportion, small proportion of viruses which were not as well inhibited by antibody to the vaccine strain.

During our summer months when influenza viruses were circulating the Southern Hemisphere, we also had a fairly small proportion of viruses. Now during the period from October to January, we have not had very many H1N1 viruses to characterize. And only one of those has had a lower titer to the New Caledonia Ferret Serum.

So I think in summary, we've had relatively little H1N1 activity during the past few

months. The viruses have been remarkably stable, both genetically and antigenically. I should mention, however, that we do have some additional viruses from China which we've not yet had a chance to analyze. They arrived very late at CDC.

Okay, I think we'll move on to the H3N2 viruses.

Now we have the right table up here. Last winter we had relatively little H3N2 activity in the U.S., Canada and Europe. There was a bit more in the Southern Hemisphere, particularly certain countries and South America had a significant amount of H3N2 activity. The viruses were Panama-like.

Right now I'd like to point out that in the United States, we're having reasonable amount of, an increasing amount of H3N2 activity and the same thing is occurring in Europe. If you look at the European reports, you can see that as of the end of Week 3, they are starting to see that their epidemic is really picking up.

Next slide, please.

Now I'd like to just spend a moment on this HI test for H3N2 viruses and point out a couple of what I think are fairly important observations and sort of notes of caution.

H3N2 viruses, as we all known, are associated with more severe seasons. That is to say we see more hospitalizations and deaths associated with H3N2 viruses.

H3N2 viruses have also been more antigenically variant during the past two decades than H1N1 strains. And that had been true up until about 1997 when the Sydney/97 variant emerged and spread very rapidly worldwide and in that particular year, in the 1997-1998 season, we did not have a good match between the circulating strain and the vaccine strain. The circulating strain was predominantly Sydney. The vaccine strain was Nanching.

But since Sydney emerged, we have had relative antigenic stability among H3N2 viruses. And so based on what happened in the past, we are really waiting for the next H3N2 variant because this is really uncharacteristic behavior for H3N2. So this was a major epidemic strain. We moved on to recommending a Moscow/10-like virus to be in the vaccine and Panama is actually the strain that's included in the current vaccine and has been in the vaccine for I believe three years. Yes. Two years, two years.

So the viruses have been really quite

stable, but we have seen a few viruses which are -- which vary a bit antigenically and one of them is the Fujian/140 which we can distinguish using the Moscow/10 antiserum. The Chile virus was selected because it as an egg isolate and was representative of strains circulating in the Southern Hemisphere during this past summer.

The Darwin virus was detected as a variant by the WHO lab in Melbourne. However, sequencing has shown us that this virus has some unusual changes that haven't been seen in any other strains anywhere else in the world. And we don't really think that this is a significant antigenic variant, but we've been including it in the tests simply because it's very clear that we can distinguish this virus from our reference strains and because we were looking to see whether an antiserum to this particular virus would help us in grouping the currently circulating strains.

So we're going to concentrate mainly on this column here, because this our vaccine strain and our primary reference strain. The homologous titer is 640 and as we look down we're looking for viruses that have fourfold lower titer and we've identified one strain down here, A/S. Australia/102/2001 that was isolated in October of this past year.

We have a number of strains from the U.S. that were isolated in October, November and December which appear to be very well inhibited. And a number of strains from Hong Kong as well.

Next slide, please.

Now we're moving on to more recent data. You'll notice that we even have some strains that were isolated during January included on this table, as well as some that were isolated earlier. The most recent strains are from the United States from November, December and January. And again, the U.S. strains are actually very well inhibited by the Panama Ferret Antiserum.

We have down here at the bottom of the table a strain from Bangkok which has fourfold lower titer as compared to the homologous.

Next, please.

Again, we have a number of strains from the U.S., the H3s started rolling into CDC right after Christmas, so we've had an opportunity to look at a number of strains from the U.S.

I'd like to draw your attention down here to the bottom of the table and have you note that there are three strains from Singapore that were isolated during the summer and fall time and these

three strains all have a reduction fourfold as compared, a fourfold reduction as compared to the Panama homologous titer. And those are strains that are under continuing analysis.

Now I didn't really emphasize -- this is a table which is not in your handout. It was -- we actually did the test on Monday and so it couldn't be included in the package that was sent to you. And the reason that I wanted to show this table primarily is that we have among the viruses tested a group of viruses represented by antigens 24 through 30 from recent activity in Northern China. And we have had quite a bit of contact with our colleagues in China over the past two months. They've indicated that there has been outbreak to epidemic level activity going on in Northern China and that they were detecting some antigenic variation among these recent strains.

We received very late a package from China and have tried to really focus on the H3N2 and Influenza B viruses as much as we could to prepare for our meeting today. You'll note that there's really only one of the recent strains from China which has a reduced titer in this particular test, but our analysis is on-going and we are looking very carefully

at sequence data to see if we can correlate changes in any of these strains with antigenic differences. So we're looking at the Singapore strains and at these strains from China.

So now if we summarize the virus characterization that's occurred over the past year and a bit, we can see that Panama-like viruses were circulating in Asia. There weren't very many U.S. or North American viruses that were analyzed. But overall, of the viruses that we looked at, a small proportion had a reduced titer as compared to the homologous titer against the Panama strain.

Likewise, for the Southern Hemisphere activity we saw a relatively small proportion of viruses that were reduced in titer, but we did have some from Central and South America and we have had -- I updated this table based on the HI table that I had just shown you and there were some viruses that were low from Asia and then, of course, the single virus from China and the Singapore viruses as well.

So what you can see is it's a relatively small proportion but we are really very interested in the viruses that are coming out of Asia, that are low and are very concerned about making sure that we can pick up any corresponding sequence changes and as we

look forward to what might happen next year.

Now we had a request from the Committee last year, I believe it was, in particular Ed Kilbourn was very interested in seeing some neuraminidase inhibition analysis because the N2 neuraminidases, as you will see later on in the data presented by Dr. Klimov, are evolving in several different lineages and we wanted to make sure that antibody generated to the N2 in the Panama strain would inhibit neuraminidases of recently circulating strains. And in order to do these tests properly, you need to make reassortants and put into your reassortant an irrelevant hemagglutinin so that when you're doing the testing, you don't have steric hindrance that is caused by antibodies binding to the neuraminidase. For each of these reassortants to which we make hyperimmune rabbit serum, we have an irrelevant hemagglutinin in these three cases, contributed by an equine virus.

What you can see if you concentrate on the data down here in this row is that the currently circulating strains are all -- all have neuraminidases that are well inhibited by antibody to the Panama neuraminidase and why this is important will become clear when Dr. Klimov presents his talk, but we've chosen viruses which are representative of the

different genetic groups for neuraminidase. So we feel pretty comfortable that the neuraminidase of the Panama is able to induce antibody that's cross reactive.

So now we're going to move on to the third group of viruses which has really provided the greatest challenge for us this year. And I think you'll find quite a few interesting points of discussion in this group of viruses. Now if you have been with us fora while, you'll remember that we've been tracking two separate lineages of Influenza B viruses, the so-called Panama lineage or Yamagata lineage and the so-called Victoria lineage. Now the Victoria lineage have been circulating worldwide and in the early 1990s for reasons that we don't understand, was really displaced in much of the world by viruses on the B/Yamagata lineage or the current vaccine strain on that lineage is actually the Sichuan/379/99 lineage.

The Victoria viruses continue to circulate in Asia where they've evolved and activity was -- has been detected in China, Thailand and Japan over a number of years that was caused by the Victoria strains while the Yamagata or Sichuan viruses have been circulating worldwide.

So if we look at what was occurring last year at about the same time we were having outbreak level activity in the Northern Hemisphere, in Europe, North America and certain parts of Asia associated with Influenza B/Sichuan-like viruses, but in Asia, we had also Victoria lineage viruses that we now are calling B/Hong Kong/22-like. That is one of the most recent reference strains and is fairly representative of the Victoria-like strains that are circulating at this time in various parts of the world.

During the summer months there was outbreak level activity associated with Influenza B virus isolations in Australia, New Zealand and Central and South America and then if we move on to the current influenza season in the Northern Hemisphere, we see that we've just had pretty much sporadic activity up until now.

Next, please.

Now I'm going to show you only two influenza B tables. The first one is a table which shows the antigenic relationships between viruses that are genetically and antigenically related to the current vaccine strain which is, once again, Sichuan/379/99-like. Different manufacturers have used, globally at least, three different Influenza B

strains that are antigenically equivalent to the Sichuan/379 reference strain.

What we are seeing is that we have a number of viruses which have a significant reduction in titer compared to the homologous Sichuan/379 vaccine strain. We've seen some viruses from the U.S. that have such a reduction, viruses from Europe and China and indeed from the Middle East. So we are seeing a number of strains that are not as well covered by our reference antiserum as we would like. I don't think I need to point out too many additional items. I would like to point out the fact that the antiserum to the Shizuoka/15/2001 strain does appear to cover most strains very well.

Now we're moving on to viruses that are related to the B/Victoria/87 strain, so these are all Victoria lineage viruses. In particular, I'd like you to note two reference strains, the Shangdong/797 and B/Beijing/243/97 strains. Both of these have been used in either an experimental vaccine or in commercially prepared vaccine, actually the Shangdong has been used by manufacturers to produce the vaccine that was administered in some countries in Asia and the B/Beijing/243 strain was used to make an experimental vaccine in Europe and we have -- I have

some human serology that I'd like to show you that we've done with human sera that were prepared in that particular trial.

Now I'd like to point out that the B/Hong Kong/2001 can be distinguished from these two viruses, the Shangdong/7 and Beijing/243 by using Ferret Antiserum. And we've seen that a number of viruses that are currently circulating are less well-inhibited by this Ferret Antiserum. Here we have our reference strain Hong Kong/22. This was one of the first strains that was sequenced and characterized extensively in our lab and to which we developed a Ferret Serum.

We also -- and that is actually an NDC case cell isolate. We also have two egg isolates, the Hawaii/10/2001 and the Hong Kong/330/2001 strains that have been sent out to vaccine manufacturers for further testing.

Now right here we have two recent strains from Canada which are in this Victoria Beijing/243 lineage and you can see that they are well inhibited by antiserum Hawaii/10 and Hong Kong/330 antiserum.

We have a group of viruses from Hong Kong, of course and South China. They've been seeing these viruses over the years. These Philippines strains

were actually isolated fairly recently and are similar to viruses which were causing school outbreaks in the Philippines that were widely reported in the press about the same time that the Anthrax problems were occurring in the United States.

We also have a number of viruses from India that are in the same lineage. This is the first time that we detected viruses from India that are related to Victoria. The surveillance in India has not been very extensive in recent years and these viruses actually came to us as part of a live attenuated influenza vaccine trial in Asia.

We also have viruses from Oman that came to us through the military and you can see that these are also Victoria viruses. The one thing to note is that there are -- a number of these viruses aren't well inhibited by the Shangdong and Beijing/243 serum, but there are also a number of them that aren't as well inhibited as we would like to see by the Hawaii/10 serum. The Hong Kong/330 serum seems to be a bit more broadly cross reactive, but there are strains which are clearly fourfold, eightfold and more downed compared to the homologous.

We'd like to show a map because I think this helps people visualize very clearly where the

Victoria-like viruses have been identified up to the present. We actually just got a call yesterday from the WHO collaborating center in London, and they wanted to report to us before our meeting today that they had identified four out of seven strains sent from Italy that were related to the B/Victoria reference strain. We haven't seen the HI results yet or the sequencing results, but I'm sure they'll be forthcoming within the next week or so.

We have a question mark about whether or not these viruses have been identified in Russia, simply because we haven't had a chance to analyze them, but they were reported to us by our colleagues in Moscow.

So you can see that the B/Victoria viruses have been identified in a number of countries and that the geographic distribution has clearly increased over the past six to nine months. In particular, we have isolated -- we have identified the B/Vic-like viruses in Hawaii and in Canada. There have been three isolates from Canada that have been identified as being related to the Vic reference strain and one Sichuan-like virus.

We had activity in Hawaii during the summer and early autumn, Influenza B activity and a

number of those viruses were B/Victoria-like.

So if we can summarize a fairly complex picture, we can see that we first picked up the Hong Kong/22/2002-like strains during the period from October to March. They were picked up in Hong Kong, of course, and those viruses are actually distinguishable by sequencing and Dr. Klimov will talk about the signature amino acid changes that are associated with those currently circulating B/Vic-like viruses.

We still had some viruses that we were characterizing as B/Beijing/184 which is the pre-B/Vic vaccine strain as well as B/Sichuan-like strains which were in the majority. And we had a number, but a relatively small proportion that were reduced in titer to the B/Sichuan reference strain.

As we looked at the viruses that were being isolated during the Southern Hemisphere's influenza season, we continued to get viruses from Asia that were in this group, but we also had the viruses from Hong Kong that were in this group.

We had a number of B/Sichuan strains that were low and that have continued and actually, I think, this summary table doesn't quite reflect the extent to which we see viruses that are reduced in

titer to the Sichuan vaccine strain because we haven't reported out all of the testing that we've done because we're trying to do confirmatory testing to make sure that these strains are low in successive tests.

Now I mentioned that I would be touching on some serologic information. If you turn to page 56 now, I'll only be going over one serology table and you recall that I mentioned that the B/Beijing/243/97 strain was used in an experimental vaccine in Europe and the sera were actually tested at CDC and in Europe.

What I have here on this table, remember the Beijing/243 is in the vaccine and we have three recent Victoria-like strains shown in black below the vaccine strain and then two strains that are representative of Sichuan-like viruses shown in blue. So if you look at the post-vaccine geometric mean titers, induced by the Beijing/243 vaccine strain to these recently circulating strains, you'll see there's pretty good coverage.

However, we can see that there's a reduced titer to one of the two Sichuan-like strains, the B/Anhui/2001 strain and we don't really know what that means. Actually, the Vic/504 had a reduced titer.

There's a 50 percent or greater reduction in post-vaccine geometric mean titer to both of the B/Sichuan-like strains.

Now we had done some studies earlier and we found with more limited testing that the antibody induced by the Beijing/243 vaccine strain did seem to cover earlier strains that were related to Sichuan, so the earlier iterations of viruses on the Sichuan lineage were fairly well covered by antibody to the Beijing/243, but admittedly we had more limited data. We really were only testing against one or two strains as opposed to six here.

Okay, with that, I think I'll close and entertain any questions.

DR. DAUM: Thank you very much, Dr. Cox. We'd like to welcome Dr. Katz to our proceedings and we'd like to ask people that unlike the airlines where they want devices turned off at 10 minutes prior to take off and landing, we'd like devices turned off the whole time during the meeting. And please, beepers, cell phones are really disruptive to the proceedings here. If you could turn them off or place them on vibrate or something like that so they don't disturb us. I'd be grateful.

Dr. Couch, why don't you start the

discussion, please?

DR. COUCH: I had two, Nancy. I think you answered one of them and that just to be sure though that the B/Victoria is not just a sporadic isolate that has shown up in the Northern Hemisphere and in North Africa and the Middle East. It's actually been a cause of outbreaks and even in the Northern Hemisphere, it's been a significant number of isolates, is that correct, in Canada and even here?

DR. DAUM: We are going to need the question repeated. We had events while you were asking.

DR. COUCH: The question was just trying to get at whether -- well, for those of you who haven't been on the Committee regularly, we've been looking at B/Victoria in Asia for a number of years now and I guess kind of hoping it would go away. And ignoring it with the considerations for the vaccine decision for B in this country. And it doesn't seem to be going away. But in fact, it seems to be invading our territory and the data you mailed and we had, it suggested that, but I think you verified that indeed, it does, it has been the cause of outbreaks in the Middle East and these are not just sporadic isolates, but you have a number of isolates from the

Northern Hemisphere of the B/Victoria lineage?

DR. COX: Yes. The isolates in Canada were really associated with sporadic, activity sporadic cases. The number of viruses that we received from Hawaii last summer would indicate that there was significant activity going on. The Philippines school outbreaks were caused by both B/Victoria and Sichuan lineage viruses, so it's hard to tell which were -- I mean they were both responsible.

DR. COUCH: Were the isolates in Canada from more than one location?

DR. COX: Yes.

DR. COUCH: Just a second question. I wasn't here last year, but we're glad to see neuraminidase coming of age, but I should know and I don't, I know that Ed and the group have used rabbit sera for differentiating among the neuraminidases and these would represent immunization antisera.

DR. COX: Yes.

DR. COUCH: It reminds me a little bit of the chicken for inter-immunization sera for hemagglutinins which were not so good for differentiating among the viruses whereas the ferret sera have proven to be very sensitive in that regard.

But the state of science is to use the rabbit sera, I guess is my question.

DR. COX: That's true and we also have --

DR. COUCH: So we may not be able to be quite as sensitive for those differences as we think of with the hemagglutinin in the ferret sera.

DR. COX: Right, but we did do very similar set of assays using ferret sera. Now those ferret sera were produced by infecting ferrets with the homologous virus so we didn't have an irrelevant hemagglutinin. When we use the ferret sera, the same ferret sera that we use for the HI tests and NI tests, we see exactly the same picture. We can't differentiate among the neuraminidases of the viruses that are on these different neuraminidase lineages. And they're well inhibited.

DR. COUCH: Rabbit sera tells you the same thing?

DR. COX: Yes, the ferret sera and the rabbit sera give us exactly the same picture.

DR. DAUM: Dr. Couch, could we get you to talk right into the microphone.

DR. COUCH: I was just confirming that the rabbit sera are as good as the ferret sera is what you were saying and confirming what Ed's already said, the

neuraminidase doesn't change as rapidly as the hemagglutinin.

DR. DAUM: Thank you very much. Dr. Kim?

DR. KIM: I assume that the viruses that you have used at least from this country are derived from nonvacinees, is that information available or is my assumption correct?

DR. COX: The majority of the viruses that we receive are from people who have not been vaccinated, but we do also receive occasionally, and it varies from year to year, but we receive a certain number of viruses from vacinees, but the majority are from individuals who have not been vaccinated.

DR. DAUM: Dr. Stephens and then Dr. Katz.

DR. STEPHENS: For those of us who are not as familiar with influenza as many at the table, the issue of A/Sydney in 1997, I guess, was that -- were there lessons learned by that rapid spread? Was it predictable? Can you just comment on, in retrospect, were there any lessons that we could learn from the emergence of A/Sydney as an H3N2 virus in terms of predicting for the vaccine.

DR. COX: Yes, I think that the lesson that we learned was that sometimes we're going to -- and this isn't a very helpful lesson, but sometimes

there will be viruses which will emerge and spread very rapidly and we're not really sure why. But there will be times when the vaccine does not match the circulating strain as closely as we would like.

DR. STEPHENS: So there weren't clues at that time?

DR. COX: No. Those viruses were detected, first detected as being important in August and September and so the vaccine had already been produced. So they were emerging in the Southern Hemisphere at a time when it was really too late to do anything about changing strains in our vaccine. So there will be occasions. We have been using the surveillance in Asia that goes on through the WHO global network to try to pick up new variants and we've been very successful in picking up the Beijing/353, Beijing/32, 92 and so on, and updating the vaccine almost in anticipation of what would be circulating in North America and Europe. But in that particular case, the virus emerged and spread very rapidly and was really recognized as being important at a time when it was just simply too late and that will happen on occasion.

Now we did see that in spite of the fact that there wasn't such a good match vaccine

effectiveness against hospitalization could still be measured among vaccinated individuals compared to unvaccinated individuals.

DR. STEPHENS: My second question relates to the complex B story that you've presented. It sounds like we have emergence of the Victoria lineage, but you really didn't have a solution or I didn't see a solution. The Beijing/243 strain didn't appear to be better. Can you clarify that, at least for me?

DR. COX: I think the Bs are very problematic and I don't think there is a really clear solution. We probably are going to have to grapple with a whole variety of possibilities. I think once all of this serologic data are presented and the sequence data are presented, we can really talk about those issues. But we also need to get some feedback from the manufacturers about how some of the B strains that have been distributed to them are growing. So I think hopefully some of that will emerge and become clear.

DR. DAUM: Thank you. I'm a little confused. Drs. Katz and Griffin, did you both want to speak? That's what -- I think you hand was up behind Dr. Katz and so I didn't see it. I apologize. Dr. Griffin first.

DR. GRIFFIN: I just wanted to further clarify the B story as well since I think that's going to be our problem child with this round. And one of the questions is it's clearly emerged in Asia and it's clearly spreading. I don't think there's any doubt about that, but what I didn't get is the idea of the proportions of even if you looked in the Philippines or in Southeast Asia of the two different B strains, both of which appear to be there and causing outbreaks, or is that not correct? It looks like from the chart, at least, that they're both there, they're both causing problems, but is one more abundant than the other?

DR. COX: It changes over time and so if you look at reports from Hong Kong there will be months where B/Vic-like viruses predominate and other months where the Sichuan lineage strains predominate. So it's not really clear. What we need to remember though is that because B/Victoria-like viruses have not circulated in the U.S., well, in North America, South America and Europe for a decade, we have a whole cohort of young children who are totally susceptible.

DR. GRIFFIN: Right.

DR. COX: And that's not true in Asia because they've had the two co-circulating for a long

period of time.

DR. GRIFFIN: Right, so the idea that introduction of this, successful introduction of this virus may cause us problems.

DR. DAUM: Now Dr. Katz, please.

DR. KATZ: My question is somewhat tangential, Nancy. There have been several stories in the newspaper recently about influenza-like illness with many children with encephalitis in Japan. I didn't see any isolates from Japan in any of your charts. Can you confirm that or have you received any information from WHO or is that just a newspaper story?

DR. COX: No, that is a problem, an issue that the Japanese have been grappling with for a number of years. I don't know what the situation really is this year. I don't know if you're referring to recent press reports, but Japanese colleagues have been publishing information over the past couple of years and I think that pediatricians in this country are interested in why we haven't been seeing a similar picture in the United States when the viruses circulating in Japan and the U.S. are very similar.

DR. KATZ: These are confirmed as truly influenza illnesses?

DR. COX: Influenza has been isolated from a number of these patients and maybe Keiji will want to comment further about it. He's been in touch with our Japanese colleagues. It's not always clear that there's a causal relationship between the influenza and the encephalitis. I think there are a lot of questions to be explored, but there are some very interesting observations.

DR. KATZ: Thank you.

DR. DAUM: Do you wish to comment?

DR. FAKUDA: Just to add a couple of things to what Nancy said. You know, in Japan in the last couple of years, they've identified probably a couple hundred cases per year at least and these are actually typically encephalopathy cases, not encephalitis cases and they've been quite severe, a substantial proportion of these young children die and then the vast majority of them who live have some chronic sequelae, some substantial chronic sequelae. And in the majority of the children, influenza viruses have been isolated, but typically from respiratory specimens. There have been a small handful of cases in which using PCR virus has been or antigen has been identified in the CSF, but I think that's much more controversial. And when you look at the picture

epidemiologically, there appears to be some seasonal pattern in which the increase in these cases occurs in the winter time and it appears closely superimposed on the influenza virus isolations. There is a case control study which has been either started or is being designed. I don't know where it is right now because I think some of the questions are whether this is really associated with influenza. Is this potentially associated with some medications or other factors associated with influenza or associated with winter time illnesses? I think those things are not clear right now. But there is a great deal of interest in this.

DR. COUCH: One interesting feature of that, I think the case control study is supposed to be under way right now to try and clarify that, is that the onset is almost identical with the respiratory disease as opposed to something like Roya Syndrome. Maybe the case control study will identify the relationship between virus and something else.

DR. DAUM: Thank you very much. I have Dr. Eickhoff, Ms. Fisher and Dr. Myers.

DR. EICKHOFF: A question again on Influenza B.

Nancy, are you aware of any precedent for

this kind of behavior among Influenza B viruses or even Influenza A viruses for that matter in which a lineage of B virus that was once prevalent sort of goes into eclipse and falls almost totally off the radar scope, but never totally off the radar scope and then a decade later appears to be going, undergoing a resurgence and coming back to haunt you?

DR. COX: I think that probably I don't know of any other case where we can say decisively that that has occurred with Influenza B. Part of it has to do with the fact that Influenza B, we haven't been looking at Influenza B for so many decades, but it's very clear that the circulation of Influenza B viruses is more complex than it is for each of the subtypes of Influenza A, but what we have observed with the H1N1 viruses was the separate evolution of a lineage of H1N1 strains that could not be distinguished antigenically from what was in Asia that could not be distinguished antigenically from viruses that were circulating in the rest of the world. Then an amino acid deletion occurred. We could distinguish the two groups and the Chinese virus, we could distinguish the two groups antigenically and genetically at that point and then the Chinese groups, so-called Chinese group actually spread globally and

have sort of supplanted the Johannesburg-like strains. So I think that given the epidemiology of influenza and the B/Vic-like strains or B/Vic lineage strains do pose a real challenge to us because we do have a lot of people, especially children who are fully susceptible.

DR. DAUM: Thank you very much. Ms. Fisher, please.

MS. FISHER: This returns to the question of the reports of the encephalopathy in children in Japan that appears to be flu-related. Are children in Japan routinely vaccinated with the flu vaccine, given a flu vaccine and those children, had they received flu vaccine?

DR. COX: Flu vaccine is not now recommended for pediatric use, so those children, generally speaking, were not vaccinated. I don't know -- there might have been one or two cases where they were vaccinated, but generally children in Japan now are not vaccinated.

There was a time in the past, however, when Japanese children were vaccinated, when the recommendations were, in Japan, were to focus on vaccinating school children to help limit the spread of influenza in the community, but their

recommendations have undergone an evolution so now they recommend flu vaccine for high risk groups and elderly, pretty much as we do.

DR. DAUM: Thank you. Dr. Myers and then Dr. Couch and then we're going to move on to hear from Dr. Klimov.

DR. MYERS: Nancy, within the B/Victoria isolates, there looks like there's another lineage. Are these new isolates related more like the Oman, India, Philippine isolates or are they more like the B/Victoria, the ones that you're recovering now?

DR. COX: I think that Dr. Klimov will be talking about the genetic characterization of these viruses and it's very clear that the antigenic picture that we're seeing is a bit complicated by some of the sequence changes that we see among them, in particular, we're seeing the presence or absence of a glycosylation site at a particular point and that seems to have some effect on how they appear antigenically, but genetically, they're pretty homogeneous as you'll see. Antigenically, they're a little more heterogeneous and it's not easy to peg them.

DR. DAUM: Thank you. Dr. Couch?

DR. COUCH: Just a quickie, the serology

that Nancy showed us showed that in these adult and elderly sera there were responses reasonable for one antigen and not for the other annually, but we had no children sera results here, but Roland and Nancy can confirm if my memory is correct, that children sometime in the past when we started the concern about the Victoria vaccinated with whatever the Yamagata lineage was at that time, their post-vaccination sera had extremely poor -- my recollection is almost negligible coverage against the B/Victoria virus, so in children it just exaggerates this uniqueness of the B/Victoria.

DR. DAUM: Thank you, Dr. Couch. I think we'll move on now and ask Dr. Klimov to share his comments with us and look at some of the molecular characterization of some of these strains.

DR. KLIMOV: Good morning. You know, the genetic data which we are collecting quite a lot in the influenza branch of CDC from our point of view are providing some additional information to the antigenic representation of the viruses and I will on in the same order like Nancy did, starting with H1 through H3 and we'll finish with Influenza B viruses.

So the first slide shows the evolution for the HA1 part of the hemagglutinin of recent Influenza

A H1N1 viruses and I should mention that this slide represents viruses isolated June and after June of 2001. So this the most recent Influenza H1N1 viruses.

A current vaccine strain is indicated here on the top. It's New Caledonia/20/99 and just to remind you that previous vaccine strain was Beijing/262/95 just to give you some idea about sort of genetic differences between the previous vaccine strain and the new current vaccine strain.

Also, I should mention that these vertical distances do not have any meaning, only horizontal differences can indicate relative genetic relationship between strains. For example, genetically this strain would be different from let's say this strain by somebody of this distance plus this distance. Distance from this line through this line.

Anyway, vertical distances are not essential, just horizontal lines should be taken into account.

You can see that if you look at the scale, you can see that there is no dramatic genetic involvement among recent influenza H1N1 viruses. They are different, very little from each other. They do form two genetic subgroupings and you can see that the viruses from U.S. are presented here, there are some

Hawaiian viruses in the bottom part of the three. And you can see some so-called signature amino acid differences which characterize those groups. But I should stress that there is no antigenic differences between those two genetic subgroupings.

Also, I should mention that rather few viruses which are low antigenically to the current vaccine strains. They are spread quite evenly among those two genetic groups and we see some particular groupings which would characterize low reactors.

Nancy already mentioned that we had previously viruses belonging to another genetic lineage of Influenza AH1N1 viruses which is so-called Johannesburg/82/96 lineage or sometimes we call it A/Berne lineage. And this year we didn't see -- this season we didn't see viruses from this genetic group from Influenza AH1N1 strains.

This table shows the number of amino acid differences between consensus sequence, sort of typical sequence of currently circulating viruses and egg grown viruses which we have available right now. And those tables are useful in sort of two senses. First of all, they show us to what extent circulating viruses, including, for example, vaccine strain are different from the consensus. Our experience shows

that, generally speaking, the closer the vaccine strain is to the consensus sequence, the better the vaccine is to make it -- to say it in plain words. So you can see that New Caledonia vaccines -- I'm sorry, I tried to highlight but I did a mess. It's still pretty close, just three amino acids difference from the consensus. So it's pretty close to the consensus of current influenza viruses circulating worldwide. There are some viruses which have 4, 5, 6, 7 amino acid differences and we studied those viruses in human serology tests or just in HI tests. And they behaved lower, I mean they weren't caught very well by the current vaccine strain, but all those strains have unique amino acid changes which could explain why they are antigenically rather different from the vaccine strain, but as Nancy mentioned to you, you do see very few viruses which are low to New Caledonia vaccine strains.

Now I'm going to move on. In neuraminidase N1 genes evolutionary tree and again, New Caledonia is here. This tree includes not only viruses from June 2001 through now, but more older ones as well, just because we do not have too many neuraminidase sequences right now and in particular, you can see one of the strains which is currently

1/2001 in the Johannesburg or Berne genetic lineage, but this is the end of last influenza season, so the Berne-like or Johannesburg-like virus was isolated at the end of the previous influenza season. So during this influenza season, as we mentioned, we do not see viruses from the Berne or Johannesburg/82/96 lineage. So the majority of viruses form a pretty homogeneous genetic group and you can see that once again the majority of them are still cloned genetically to New Caledonia in the neuraminidase gene sequences. There is another group of sort of genetic subgrouping of the neuraminidase genes, but importantly as you saw from Nancy's talk and you saw from the H1 tree, you do not see dramatic differences in antigenic properties of the viruses against the current influenza of vaccine strain New Caledonia.

The next table shows, demonstrates a number of differences for the neuraminidase gene from the consensus and you can see that New Caledonia is pretty close to the consensus sequence of the neuraminidase genes and as I mentioned it's a good sign for the vaccine. It's still matches pretty well the majority of separating viruses.

Next slide please.

Now we will go into H3 hemagglutinin gene

evolution and to some extent the picture here is a little bit more complicated than it was for Influenza AH1N1 viruses. In red you can see the current vaccine strain A/Panama/2000/799. That means actual vaccine strain. Moscow/10/99 WHO recommended strain is over here, and you can see that there are two genetic, major genetic subgroupings of the recent Influenza AH3 hemagglutinins. With these sort of arrows, I tried to indicate some of the low reactors, as Nancy mentioned, we did see still quite a few of low reactors. And they are spread more or less similarly on both genetic groups. But Nancy mentioned that we had one more H3 test, the day after we actually sent the package. And yesterday morning, some more sequencing data became available and those data relates to the viruses from China which we have received recently which Nancy mentioned. And I allowed myself to actually add several branches or several more strains in here to indicate that new viruses, H3 viruses from China which we received in the last package, they tend to group in this area and they have some additional signature changes which may be indicating on sort of additional evolution of recent Influenza H3 viruses in the Asia area.

I should add that several viruses from

Singapore which Nancy mentioned are also behind this actual point, so Singapore viruses and recent Chinese viruses form a sort of separate genetic group right now and we are working right now very hard to get details about the sequences.

This is a table which demonstrates amino acid differences between the consensus and available egg grown viruses and you can see that Panama/2000/799 so far is matching pretty well the consensus of circulating viruses. We have some more egg isolates, some of them like, for example, Darwin/3/2000 which Nancy mentioned which was low in both HI tests and human serology tests, but this particular virus has some unique changes which can explain those low reactivities.

Once again just to point out that unfortunately, we do not have yet data in this table about the Chinese viruses. As I mentioned, there is some evolutionary events which are definitely happening in Asia right now and we are watching this very carefully.

The neuraminidase gene evolutionary tree, once again, Panama, is in here and there are two genetic groupings within this recent Influenza H3N2 neuraminidases and as you can see by scale which is

here, the genetically evolved recent viruses are pretty much evolved from the Panama/12/799 vaccine strains. That's why actually we considered very important to have neuraminidase inhibition tests to be done and as you remember Nancy demonstrated this test and they are in the package. So far we do not see obvious antigenic differences between neuraminidases, even between Panama vaccine strain and neuraminidases of currently circulating viruses.

So I should say that the majority of those changes which we see are not in the antigenic sites of the neuraminidase model.

This table demonstrates amino acid differences between consensus and available egg isolates. You can see that Panama, in this particular case, is rather different from the consensus sequence, but once again, fortunately it doesn't seem to influence the antigenic properties of current influenza viruses which are still reasonably well covered by a Panama vaccine strain.

Now Influenza B evolutionary tree for the hemagglutinin of the B/Yamagata lineage which is different from the B/Victoria/287 lineage. The vaccine strain is Sichuan/379/99, but the recommended vaccine strain is very important and one of the real

vaccine strains Victoria/544 is next to Sichuan here.

I have to mention that the Yamagata lineage also consists of two genetic subgroupings and one of them is let's call it Sichuan subgroup and another one is -- we call it Harbin/7/94 genetic subgrouping and those of you who are involved in influenza may remember that Harbin 7/94 virus was a vaccine strain four, five or six years ago for a couple of years. But genetically, it's sort of emerged into two genetic subgroupings.

Now we start to see and for a number of years, actually, we did not see Harbin-like genetic lineage viruses in Americas, but this year we started to see them. In Argentina, there was one strain. There was on strain in Minnesota and this is also -- sort of forms the top of the study related to B/Victoria lineage. It's sort of another interesting point to mention today that this genetic subgrouping seems to be expanding as well.

So far we did not see dramatic intergenic differences between Sichuan and Harbin genetic subgroupings, but it looks like recent data shows that it could be that recent B/Harbin-like viruses are becoming antigenically more diverged from the Sichuan-

like.

Next slide. This has quite a number of egg isolates and this is the table demonstrating the differences between the Yamanashi-like -- Yamanashi is 166 right here. It's the same Sichuan-like lineage. It's the same lineage. Panama, and let's say Beijing/184, Yamanashi, Sichuan. The same lineage.

This yellow line divides viruses belonging to the Sichuan genetic subgrouping and Harbin genetic subgrouping.

You can see that both Johannesburg/5 and Victoria/544 existing vaccine strains are pretty close to the consensus, but the consensus sequence is becoming more complicated when you look at the -- when you summarize actually Sichuan lineage and Harbin lineage. The Harbin lineage has, of course, more amino acids differences from the consensus. As I mentioned so far we didn't see dramatic antigenic differences between those two groups in spite of the fact that quite a number of amino acids changes. But as I mentioned it could be that during the evolvement of this season we may see more viruses from this genetic subgrouping relating very well to the vaccine strain.

This is hemagglutinin of the B/Victoria

lineage and here is actually a clear cut -- just for reference, this is a Sichuan current vaccine strain and you can see that it's different genetically. And you can see that there is clear cut in genetic groupings between previous B/Victoria-like viruses presented, for example, by Shangdong/7/97 strain here and recent viruses from Hong Kong, Hawaii and some other areas, from Japan for example. And Nancy mentioned that there are at least three so-called signature amino acid differences which clearly distinguish this genetic group of new B/Victoria viruses from the old ones.

Next table shows the number of amino acid differences between previous B/Victoria lineage -- and you can see that there are several strains of grown viruses which are almost identical to the consensus sequence. The only point I have to make is that the only difference which isn't in position 197 or in the position 199, either of them are creating a potential glycosylation site in the HA molecule of the B/Victoria like viruses and that's why in some cases all egg grown viruses we have so far and some MBCA grown viruses can behave different from the viruses which do not have these potential antigenic site. It's related to the question which was raised earlier

today.

And a couple of words about the -- okay, this is a table, sort of frequency table but for the genetic data, not for the antigenic data and we do so-called PCR restriction analysis for rapid differentiation between different genetic lineages. We don't need to sequence all the viruses. We may use some specific restriction enzymes which would differentiate between Sichuan subgroup, Harbin subgroup and B/Victoria subgroup for example.

And you can see that if we didn't see many B/Victoria-like viruses from October to March of 2001, you started to see much more of them from during the summer time and in particular, there were 28 viruses which are mentioned here under the USA column, but actually all of them are from Hawaii. Just to repeat that we found quite a number of Victoria-like viruses in Hawaii, some belong with Sichuan-like viruses in the same region.

Also, it looks like there is a tendency in increasing of the percentage of B/Harbin/794 genetic subgroupings among recent viruses. So-so far, starting from October through January, we have approximately 50 percent of viruses tested worldwide, belonging to the B/Victoria lineage and presented

mostly, almost exclusively actually, by B/Hong Kong/22/2001. Still, there is about some subgroups belonging to the Sichuan/379 and there is some increasing -- not extremely dramatic but there is some tendency in the B/Harbin/794 genetic subgroup.

Just a couple of words about the neuraminidases evolutionary tree for the B viruses, and in this case we have both B/Victoria-like viruses in here and interestingly recent B/Victoria/487-like viruses form separate genetic group of the neuraminidase gene as well and here are the signature, I mean as it changes for each different shape, new B/Victoria neuraminidase from the previously circulating B/Victoria neuraminidase. So we have genetic changes not only in the HA but also in the neuraminidase. It's very difficult to say right now to what extent this could influence the intergenic part of this, of the intergenic neuraminidase.

The Sichuan or Yamagata lineage, Sichuan vaccine strain is over here. Both of the neuraminidases also consist of two subgroups and one of them is Sichuan and another one is Harbin/794 and agents are in parallel in this sense for B viruses and you can see that recent viruses which are here and here belong to both Sichuan genetic subgroup and

B/Harbin/794 genetic subgroup.

Okay, the amino acid difference table shows -- again, this yellow line divides the Sichuan genetic subgrouping from the Harbin genetic subgrouping and you can see that the Sichuan/379 vaccine strain matches consensus during the sequence pretty well and actually the B/Shizuoka/15 virus which was mentioned also pretty close to the consensus in the sense of the neuraminidase.

Thank you very much and I will answer your questions.

DR. DAUM: Thank you, Dr. Klimov. Committee questions or comments?

Dr. Couch?

DR. COUCH: I have one. Help me with the consensus sequence data which is based on 27 viruses isolated.

DR. DAUM: Dr. Couch --

DR. COUCH: The variety of viruses, the consensus data based on 27 viruses, it's going to depend on some extent on the 27 viruses and to what extent is the B/Victoria represented in those 27?

DR. KLIMOV: No, no. This is consensus. Are you talking about the HA?

DR. COUCH: Well, I was actually looking

at the neuraminidase at the time, but I guess the question would be for both.

DR. KLIMOV: Neuraminidase, so the neuraminidases consensus as well as HA consensus is done for just Yamagata lineage, not for B/Victoria because we did for HA, we did several consensus for the HA. We didn't do this for the neuraminidase because we have just very few sequences.

DR. DAUM: Okay. No other Committee input. Thank you very much, Dr. Klimov and that concludes this initial cluster of presentations.

What I'd like to do now is move to the Open Public Hearing which I inadvertently bypassed before. Is there anyone that wishes to address the Committee from the audience?

There being no one scheduled and no one rushing forward to the microphone I will conclude the open public hearing at this point and put the Committee briefly into recess for a break. We will break for 10 minutes and resume at 11:35.

(Off the record.)

DR. DAUM: Could we take our seats and come to order? I'd like to get everybody settled in so we can continue, please.

Ms. Canas, are you ready? We'd like next

to call on Ms. Linda Canas from the Department of Defense who always has, in my view, an additional interesting perspective on this flu surveillance business and I hope she will follow in step today.

MS. CANAS: Good morning. The Department of Defense has been following influenza for many years, especially in the Air Force as part of the health protection of the forces that are stationed around the world. And since we are around the world it has worked very well to do surveillance for influenza and it has been so successful that in 1997 when the Presidential Decision Directive was instituted for the Global Emerging Infections System that this program became tri-service.

There are two parts to this. The Navy, at the Naval Health Research Center in San Diego conducts population health surveillance where they track health viruses and diseases in the recruit population for all the services. The Air Force at Brooks Air Force Base and my laboratory in San Antonio, we're out in bases around the world doing etiology-based surveillance. We like to say we're just trolling for bugs. Whatever is there, we're looking for it. We have a case definition consistent for influenza. That's what we're interested in, but we want to know what's going

on and that's what I'm going to talk about today It does cover all of the services, but it's what we have collected in San Antonio.

And since there are new Members on the Board and certainly new people in the audience, I want to do a quick run through of just how this program works since it is a little bit unique. Every year we have a meeting, usually in the summer with the epidemiologists and laboratory people from all the services get together and we talk about what we've done and where we can go. We want to look at the sites that we have, what's going on in the world, are there areas where deployments are taking place, should we have new surveillance sites. And this input is forwarded then to the Surgeon General, the Air Force Surgeon General particularly, and he sends out a letter every year mandating that all of the active duty individuals in the Air Force will be vaccinated. Each of the services has this policy. They are required to vaccinate the active duty individuals. And in this message for the Air Force they also name the Sentinel Sites. And these Sentinel Sites then are supplied with any collection materials that they need for the collection of specimens and the public health officers at each site run this program to make sure

they're collected and then they're sent to us at Brooks. Now this is a full service reference laboratory. We have specimens coming to us for all the areas of laboratory testing from all over the world which makes this whole program possible. It also makes it cost effective because these are coming in the same FedEx boxes with other samples so they can come to us in a timely basis. This is a surveillance program, but we also treat it as a clinical program and we try and turn these samples around as quickly as possible so they can have some idea of what's going on in their facility.

We put our results back into the computer where they get patient results, they can treat them. It also goes to the epidemiologists where they will contact the public health officer at a base to tell them they have influenza on site so they can take any interactive measures that may be necessary.

And then of course we get to make all kinds of reports and send up recommendations every year which will lead to changes in the program. We also do our own subtyping analysis on site of selected samples and we send others on to CDC where they do their own analysis and then I can come here today and tell you what we have. So this is an overall view of

how the program works.

Next slide.

This is what our map looks like today. These are the Sentinel Sites. Now we do get samples from other areas because we certainly have bases from other areas, but these are our named Sentinel Sites where they're asked to send so many samples each week from symptomatic patients. We choose these sites based on location. If they're on the coast we've got people that are traveling in an out of the country where they may be bringing their own viruses. We have training sites where people may be crowding together from different places and then we've also been able to add with making this tri-service, the Army and the Navy have research labs in various areas of the world doing research on various Malaria, Dengue, other diseases and we've been able to institute protocols consistent with influenza. And these have been very successful. This is especially true in Thailand with surveillance in Nepal and it's been very extensive in South America.

We have just established a site in Uganda. This has been established. They made me go over there and set this up.

(Laughter.)

We haven't gotten any samples yet, but the infrastructure is in place and it's being set up. We've been able to hook onto an existing health protocol over there in Kaloisso, Uganda.

HIV and Malaria rule the diseases in this country and they're so overwhelming, but by their own statistics, acute respiratory illness is the third most common reason for individuals coming to the clinic there in Kaloisso. And they have no idea what really is the underlying cause. So we hope to provide them with their own information of what's going on as well as give us samples from an area that is undersurveilled right now and on this trip I was able to make some more contacts and perhaps they can encourage me to go back and set up some more sites.

If we look at what we've done so far this year, as has already been presented, it's been very light. I've had a busy year. It wasn't too bad for me to have to go along with nothing, but as far as I'm concerned flu hit last week. The season has begun and we're in it full swing. Our samples generally are about two days away from collection when we get them. This is not true, of course, from South America and Thailand. They can be up to 5 months, but the collection dates are represented here. And this is

the actual isolates that we've had and you can see that we've had a dramatic input. Everything has been -- excuse me, Influenza A, so far.

And if we look at by week the number of samples that have come in compared with the percentage of isolation, you can see it pretty much follows along with what's been on the CDC charts and this is real time so in the later months, excuse me, the later weeks, these are still works in progress. They've just come into the lab. On Monday, we have been working up 20 to 30 samples a day, consistently and on Monday we had 84 samples and 32 of those were positive. They tended to be from the same sites, but we are starting to see it traveling. And if we look at this over time because this a global picture, just numbers doesn't really tell me what it looks like. It did start out very slow in October. About the only thing we had was in Alaska and we got seven and those tended to be later in the month and they were, the ones we got to type were the H3N2. November, Alaska was there. We pretty much every day had some coming from them and a high percentage of those they sent us were positive, with just sporadic flus around. We did get some samples in from South America and the only Bs we've had this season came in. Now they were

collected in November, but we only got them a couple of weeks ago, so we haven't been able to look at them any closer than what they are.

December started getting a lot busier with -- excuse me, Alaska not quite as heavy, but picking up dramatically in Hawaii and that has continued. And of course, there's a lot of where the sites are that we have and the emphasis the public health gives and the Navy in Hawaii has been very aggressive in tracking this and I don't always know where they come from. I believe some of them are from ships, but from the island, all over the island they're responsible for getting them to us. So we've been seeing quite a bit of activity there.

And in January, as of last week, we're seeing dramatic increases in Texas, in San Antonio, actually, we're picking up quite a few more flus and I failed to mention in December the only H1 that we've seen all season was picked up in Korea. We did get some more Koreas this week, so we'll be looking at them to see if that H1 continues or they too now have the H3.

Next.

And always it comes up, if it's not flu, what is it? We can probably answer that a lot of them

may have been collected too late to actually detect a viable virus. Perhaps it's really a bacteria. We're not going to detect any of the chlamydia pneumoniaes or the strep pneumoniaes, the more common cold viruses. RSV is certainly a big player in most hospital populations, but for us, we're not looking so much at the pediatric patients and this is also not a virus that transports well. So it's not one that we pick up in our culture system.

But we do pick up a fair number of adenoviruses and I've had a note on all of these that these numbers have been adjusted to exclude adenovirus because this is a very important player in the military recruit population. It dominates in that area and our numbers are very skewed if I have them. So I've pulled those out since it is a unique military issue. But we do still get adenoviruses as background viruses in the population. It is seen quite often and a fair number of pari-influenzas and interoviruses, we're still picking up some coccaci Bs and a few others that aren't typed any further and so roughly around 25 to 30 percent of our overall viruses tend to be the flus with some more thrown in, but probably because of the case definition, we do tend to get flu the most.

And this is our own analysis of sequence analysis of adendogram of the ones that have been looked at so far and you can see it's very similar to what you've seen already. We've only done H3N2s and they've all been very tight. We have not seen in these that we've done here any of the substitutions that have been reported. These are all that we have so far.

This is our program so far this year. I do think it's going to change a lot in the coming years or excuse me, the coming weeks. Are there any questions?

DR. DAUM: Ms. Fisher, then Dr. Katz.

DR. KATZ: I understand your exclusion from the original data of adenovirus. Does your lab do the typing of adenovirus so you can tell us if these are 4 and 7 or what serotypes they are?

MS. CANAS: We try and keep up with it a little bit. Mainly that's done in San Diego and it is, it's actually 4 right now with some 7s in there. It's still staying very tight with the historic 4s and 7s. We would like to do more of this. In fact, there is some talk of picking up a site in Venezuela of military populations and looking specifically to see if they might have an adenovirus in their, recruit

population also. We haven't been able to find anyone else who actually looks in their recruits for this particular virus.

DR. DAUM: We are nothing if we're not flexible.

Ms. Fisher and then Dr. Dowdle.

MS. FISHER: I just want to be clear. You say it's 17.3 percent of all samples of suspected flu cases were positive for any respiratory virus.

MS. CANAS: That was also then including parainfluenza, interoviruses, I'm not looking at that particular chart right now.

MS. FISHER: It's only 17 percent were positive for any virus?

MS. CANAS: Right now, yes. It's been very low up to this point.

MS. FISHER: Well, then when you are categorizing flu cases and you're not actually looking at whether or not they're positive, doesn't that seem like there's an awful lot of suspected flu cases that are not actually caused by the flu?

MS. CANAS: Oh yes, that's what I was trying to say. Many of them may be bacteria. They may have been collected too late for us to actually detect them.

MS. FISHER: But what does that say in terms of vaccination though? In other words, the total number of suspected flu cases in this country, potentially only 17 percent are actually due to the flu?

MS. CANAS: But this is at a part of the season where we don't really have flu circulating yet. We're just now getting into the season when we'll actually see flu. It will go up dramatically.

DR. DAUM: Dr. Dowdle and then Dr. Goldberg.

DR. DOWDLE: I just had a question about demographics, if I may. Now on your Sentinel Sites, is this some attempt here to standardize this or do you have some sites you have military personnel, some sites you have mixture of both military and dependent personnel or how do you do this, how do you work this out?

MS. CANAS: Anyone who comes to a military treatment facility that presents with a case definition would be eligible whether they're dependent or military. We make no distinction. We do keep track of that data. The obvious question here is can we follow vaccination status. That's an attempt we're always trying to make, that data is, especially in the

Air Force, is input into a computer system where we do try to track it. We actually are trying to set up a trial in Misawa, Japan where we have a population we can study, but they haven't had flu this year yet so we haven't been able to do anything. But we don't make any requirements --

DR. DOWDLE: But is it fair to say that in each of these Sentinel Sites that you do have a military population that's under surveillance?

MS. CANAS: Yes.

DR. DOWDLE: But they may be recruits as opposed to seasoned personnel?

MS. CANAS: The recruits are at the recruit centers, so in this data only Wilfred Hall or Lacklan would be represented, just because historically they've sent to us and we've kind of handled their clinical isolates, but they also sent isolates to San Diego for recruit studies.

DR. DAUM: Dr. Goldberg and then Dr. Diaz.

DR. GOLDBERG: Just one clarification. The military are all vaccinated you say, so therefore, if I'm following correctly, I would assume that you should see less flu.

MS. CANAS: Yes.

DR. GOLDBERG: If the vaccine is against