FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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VACCINES AND RELATED BIOLOGICAL PRODUCTS

ADVISORY COMMITTEE

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MEETING

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FRIDAY

JANUARY 28, 2000

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The meeting was held at 8:00 a.m. in the Versailles I and II rooms of the Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland, Dr. Harry B. Greenberg, Chair, presiding.

MEMBERS PRESENT:

HARRY B. GREENBERG, M.D., Chair

KATHRYN M. EDWARDS, M.D., Member

MARY K. ESTES, Ph.D., Member

STEVE KOHL, M.D., Member

ROBERT S. DAUM, M.D., Member

KWANG SIK KIM, M.D., Member

OPEN

MEMBERS PRESENT (continued):

WALTER L. FAGGETT, M.D., Member

DIANE E. GRIFFIN, M.D., Ph.D., Member

BARBARA LOE FISHER, Member

NANCY CHERRY, Executive Secretary

INVITED PARTICIPANTS:

ROBERT COUCH, M.D.

NANCY COX, M.D.

THEODORE EICKHOFF, M.D.

L. PATRICIA FERRIERI, M.D.

THOMAS FLEMING, Ph.D.

CHARLES HOKE, JR., M.D.

EDWIN KILBOURNE, M.D.

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(8:02 a.m.)

CHAIRMAN GREENBERG: Good morning. Good morning, everyone. I'd like to welcome you to the second day of the VRBPAC meeting. I have no major annoucements, so, without further ado, I'm going to go to the boss here.

MS. CHERRY: Good morning and welcome. Let me repeat an announcement I made yesterday because I know that many of you in the audience are here for the first time. And that is if you are parked in the parking lot across the street, Bethesda is diligent about checking parking meters so don't get so wrapped up in what you're hearing today that you forget and let your meter go.

And I have a conflict-of-interest statement to read: "The following annoucement addresses conflict-of-interest issues associated with the sessions of the Vaccines and Related Biological Products Advisory Committee on January 28, 2000. Based on the agenda made available, it has been determined that the committee discussions for the influenza virus vaccine formulation for 2000-2001 and the briefing from the Laboratory of Pediatric and Respiratory Virus Diseases presents no potential for

a conflict of interest.

The director of the Center for Biologics Evaluation and Research has appointed Doctors Robert Breiman, Robert Couch, Theodore Eickhoff, Patricia Ferrieri, Thomas Fleming, Charles Hoke, and Edwin Kilbourne as temporary voting members for the discussion of the flu formulation. In the event that the discussions involve specific products or firms not on the agenda and for which FDA's participants have a financial interest, the participants are reminded of the need to exclude themselves from the discussions. Their recusals will be noted for the public record."

With respect to all other meeting participants, we ask, in the interest of fairness, that you state your name and affiliation and address any current or previous financial involvement with any firm whose products you wish to comment on. This includes anyone who speaks in open, public hearing.

I'll return the microphone.

Okay, is Dr. Zoon here?

CHAIRMAN GREENBERG: Ah, good. You're up.

(Laughter.)

That's an auspicious entrance. This type of thing is always fun, although sad, so I think Dr. Zoon is about to make a presentation of plaques to

retiring VRBPAC members. No problem.

DR. ZOON: Well, this truly is a special, special honor. I was coming down Rockville Pike this morning. Of course a bus was stuck blocking two lanes of traffic. So it never fails, when you're trying to be someplace on time. But I said, I will not let that thwart me. And then I go to the elevators here in the Holiday Inn and it nearly done me in.

(Laughter.)

So I think you can all relate to this.

Well, it is my very, very dear pleasure to present to Dr. Kathy Edwards a wonderful plaque. And I would just like to, one, for her service on the VRBPAC. And I'd just like to personally thank Kathy. I have thoroughly enjoyed interacting, working with you, and I want you to know you're not going to get away this easy. None of our members ever leave the committee. They merely reinvent themselves in other ways. And I think Ted is the true victim of this process.

(Laughter.)

So, with great pleasure and gratitude, Kathy. Thank you very, very much.

(Applause.)

CHAIRMAN GREENBERG: I'd just like to

second that. Actually, I don't think I was really aware that Kathy was going to leave. Are you? I don't think that's correct. She's not leaving, is she?

(Laughter.)

So, yes. So you've been a spectular member of the committee and we may lose our ability to say anything sensible if you really leave. Oh, okay. So Dr. Adimora also. That's too bad. So, will she get the plaque?

DR. EDWARDS: She's already received the plaque, yes.

CHAIRMAN GREENBERG: Okay. Okay.

I'd like, I guess, to go around the room and have people introduce themselves, starting with there with Diane, since Dixie isn't here.

DR. GRIFFIN: Diane Griffin from Johns Hopkins School of Public Health.

DR. ESTES: Mary Estes, Baylor College of Medicine.

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

DR. KIM: Kwang Sik Kim from Children's Hospital, Los Angeles.

DR. FAGGETT: Walt Faggett, Amer...

Preferred Provider, Washington, D.C.

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

DR. EDWARDS: Kathy Edwards, Vanderbilt University and, as I remineded everyone yesterday, I have the home of the Tennessee Titans.

CHAIRMAN GREENBERG: Right.

(Laughter.)

DR. DAUM: I'm Robert Daum from the University of Chicago. No commercial.

(Laughter.)

CHAIRMAN GREENBERG: Harry Greenberg, Stanford University and the Palo Alto VA Hospital.

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

DR. EICKHOFF: Ted Eickhoff, University of Colorado.

DR. FERRIERI: Pat Ferrieri, University of Minnesota Medical School, Minneapolis, and the team that didn't make it.

(Laughter.)

DR. FLEMING: Tom Fleming, University of Washington, Seattle.

DR. COX: Nancy Cox, Centers for Disease Control and Prevention.

DR. KILBOURNE: Ed Kilbourne, New York Medical College.

DR. COUCH: Bob Couch, Baylor College of Medicine, Houston, Texas, the former home of the Tennesee Titans.

(Laughter.)

CHAIRMAN GREENBERG: Okay, now. We now have an open public hearing and I'd like to ask anybody in the audience whether they have anything that they would like to say to the committee or to the public. I'm looking and not seeing any hands. Is that correct? Okay, if that's correct, the open and public hearing is closed.

Now we're going to start our session and, as you all know, it's January so it's the flu session. And Roland is now going to lead us through a discussion of what's happening in flu to help inform us to try to make some choices. Roland. And, Roland, I would simply say to try to ask your speakers to be expeditious and timely in informing us what's going on.

DR. LEVANDOWSKI: Okay. Thank you, Dr. Greenberg. Can you all hear me? Am I loud enough here? I can't tell from up here, so somebody will have to yell at me. Okay? It sounds like I'm getting

some feedback now, so it's probably okay.

Thanks again. I'd like to welcome everybody here and thank you all for coming on this kind of cold and chilly and icy day in Bethesda. As Dr. Greenberg has mentioned, we all know why we're here today. We're here to begin the process of selecting the influenza virus strains that will be included in vaccines prepared for the 2000-2001 season. As you're probably aware, the match between the antigen in the influenza vaccine and the circulating strains is probably the most important feature in the potential efficacy of inactivated vaccines for influenza.

This overhead shows the question that we would like to have answered by the committee. And the question is the same one that we ask every year, that is, what strains should be recommended for the antigenic composition of the 2000-2001 inactivated influenza virus vaccine?

In order to answer the question, information is needed and we are prepared to supply information this morning, although it may not be all of the information that we would like to have. But we will do this to assist in formulating the answer.

In the next overhead, just to remind

people who may be a little bit new to this, the data that are needed includes, most importantly, information on the appearance of new influenza viruses. When those new viruses are identified and they have shown that they have new antigenic and genetic characteristics, how widespread they become helps in judging the urgency in considering changing a component of the vaccine, because, obviously, it's something that we don't take lightly and don't want to do if we don't need to. If new strains have the capability for broad dissemination, it's important to know whether or not current vaccines are likely to provide some measure of protection.

And, finally, if it appears likely that the current vaccines could be suboptimal, then it's still necessary to have some virus strains that grow well enough to permit manufacture of vaccine within the current constraints of time.

The vaccines are actually being prepared now. They are being prepared now so that they can be available in the early fall to ensure that administration of the vaccine is done before onset of the influenza season in the following winter.

Now this slide is a little bit out of date. I somehow misplaced the most recent one. But

it's not too far off. What I would like you to get out of this slide, this shows the production of influenza vaccine for the United States over the last 10 or so years. And you can see that that vaccine production has been rising. This is what makes all of these deadlines quite important for the manufacturers. Vaccine is not produced in a single day. It takes many months to get it ready and it takes many months for it to start to get out for public use. Currently, the vaccine production is somewhere between 80 and [illegible] million doses for the United States. So that's quite a lot.

So you can turn the overheads off, please. Thank you.

Okay, so the balance between enough information to choose wisely and enough time to make the vaccine and deliver it is usually very difficult. We're at that point in the year when there is an urgent need to ensure the vaccine production goes forward.

During the past year, recommendations were made for vaccines that are currently in use and in the United States, the vaccines are trivalent and now include an A/Sydney/5/97 (H3N2) component; an A/Beijing/262/95 (H1N1) component; and

B/Yamanashi/166/98 component.

In September of 1999, that's last September, the World Health Organization made recommendations for influenza vaccines to be used in the Southern Hemisphere. Those recommendations were for vaccines incorporating an A/Moscow/10/99 (H3N2)-like strain; an A/New Caledonia/20/99 (H1N1)-like strain; and a B/Beijing/184/93-like strain which, in most cases, will be the B/Yamanashi/166/98 strain.

I should make some mention about how those recommendations have been implemented. And, actually, they've not been implemented in the case of the A/Moscow recommendation. Although much work went into developing A/Moscow-like reassortants, it was not possible to produce a virus that had both the growth properties needed and, more importantly, the correct antigenic characteristics. As a result, World Health Organization amended its recommendation to indicate that an A/Sydney/5/97-like viruses and its reassortants could still be used for the current manufacturing campaign for the Southern Hemisphere.

There may be some more information on that in some presentations to come, but, in the interests of time, I'd like to get things moving. I just would remind all of our speakers that we are on a very, very

tight schedule, as we usually are, and we'll all need to be somewhat brief and to get going.

So, initially, to give us information about U.S. surveillance, Dr. Keiji Fukuda from the Influenza Branch at CDC will begin.

DR. FUKUDA: Thanks, Roland, and good morning. Usually I try to be very brief in presenting the U.S. surveillance information. This morning, I will be a little bit more involved, because some of the features of this season which I think need some explanation.

In general, the 1999-2000 season has begun relatively early compared with the last two seasons, which were also H3N2 seasons. They have been similar to the previous two seasons in terms of the percent of respiratory specimens testing positive for influenza; in the percent of patient visits for influenza-like illness to sentinel physicians; and in the number of states reporting either widespread or regional activity.

However, pneumonia and influenza mortality levels have been unusually high this year. And there's also been an unusual amount of media interest. Last year, between October and March, CDC received a little over 400 calls from the media about influenza.

This year, between October and January 26, about 850 to 900 calls have come in from the media, and, largely, over a two to three week period.

In terms of the viruses which have been isolated in the U.S. so far, approximately 46,000; 47,000 respiratory specimens were tested for respiratory viruses. About 19 percent of these have been positive for influenza. The percentage of positive specimens peaked around week 51 and, as of week three, which is the most current reporting week, ending January 22, that percentage has fallen to 21 percent.

There have been 8,736 influenza isolates. A small number, 29, have been B viruses. The vast majority have been Influenza A viruses. And, of the 2,084 A viruses which have been subtyped, again, the vast majority have been Influenza A(H3N2) viruses. There have been very few H1N1 viruses.

In this slide here, this just graphically depicts what I just went over. Basically, you can see that the number of influenza isolates peaked somewhere around week 52.

Now in terms of the sentinel physician system, there are approximately 400 sentinel physicians who regularly report to the states and CDC

and these sentinel physicians report on the number of patients coming in for influenza-like illness. We saw that the national rates of these visits peaked at around week 52 at six percent and, as of week three, this has fallen to three percent.

In terms of regions, the region which reported the highest percentage was the West South Central Region, consisting of Arkansas, Louisiana, Oklahoma, and Texas. And that reached a peak of 14 percent. The other region which reached a high percentage was the Pacific Region at nine percent, also during week 52. And, again, this graph here shows what I just went over, showing that these sentinel physician visits peaked around week 52 and that the percentages have been coming down rapidly.

Now in terms of estimated levels of either widespread or regional activities from the state and territorial epidemiologists, this appears to have peaked at around week two with 43 states reporting either widespread or regional activity. And, again, this graph of the three clinical and virus activity markers basically show the same picture where activity appears to have peaked somewhere between the end of December and the first part of January.

However, when we look at the pneumonia and

influenza mortality data from 122 cities, you can see that the peaking of that activity has been unusually high and you can see that there is also this blip early in the season. And here are the levels. During week 51, we had eight percent and this has increased, as of week three, up to 11 percent. This is somewhat provisional, because, for the most recent week, we always have some missing data. But the percentage shouldn't change too much. To put this in perspective, in the previous three seasons, we have seen peaks of 8.8 percent, 9 percent, and 9.1 percent.

Now just to go over a couple of considerations about P&I mortality. In general, there are some main factors which influence measurements of P&I mortality. One of these are the infectious agents out there, and, in particular, the incidence and prevalence of influenza virus infections. A second thing is the virulence of influenze virus strains. And then the incidence of other pathogens.

In addition, there are a number of host protective and susceptibility factors out in the population. And these things include things such as the overall levels of protective antibody in the population, resulting both from previous natural infection as well as current levels of vac-

coverage. And then, as Roland mentioned, the vaccine match is an important factor and the effectiveness of the vaccine. We also know that changing behaviors can affect P&I mortality. And then, finally, population demographics and underlying characteristics are quite important. And then, finally, there are a number of measurement issues which are important.

Now in terms of influenza viruses, essentially, we do not measure the incidence or prevalence of these infections nationally each year. And so this is really an unmeasured factor. And this would be extremely difficult to come up with for a figure each year.

In terms of strain virulence, we can make a couple of general and specific observations. Since their appearance in 1968, in general, the H3N2 viruses have been more virulent and have led to more hospitalizations and P&I deaths than H1N1 and B viruses.

In terms of this season, specifically, because of the high P&I mortality, the New York City Department of Health pulled the death certificate records and went over them by hand to look and see whether there appeared to be any unusual diagnoses on the death certificates and did not see them. And they

also were able to break down the death certificates by age and compare some of the rates from last year to this year. And, again, we do not see an unusual distribution of deaths by age. So, as of right now, we do not have any indication that there is an unusually virulent strain out there.

Now in terms of pathogens, you know that each winter there are a number of other pathogens which circulate, and this is certainly no exception. In particular, this year, in parts of the country, the curves for RSV virus and influenza viruses have really been almost superimposable.

Now in terms of population factors, there are some things that I want to go into. In terms of overall levels of protective antibody, again, this is a factor that we do not normally measure year-to-year. Now in terms of vaccine coverage, as Roland showed, the doses which have been produced in the country have been increasing and, for the past year, as Roland mentioned, there has been approximately 80 to 90 million doses which have been distributed in the U.S. In terms of vaccine match between what's in the vaccine and what's been circulating, it's really been very good this year.

And, in terms of vaccine effectiveness, at

this point we do not have any specific data on vaccine effectiveness. These will be available from a couple of different health maintenance care organizations, but not until the end of summer.

Now one of the things I want to point out is that elderly age is a key risk factor for P&I mortality. And if we look at the data for H3N2 seasons dating from 1968 up until the middle part of the 1990s, you can see that the elderly have accounted for a high proportion of P&I deaths each year. So that, at this point, they account for well over 90 percent of the P&I deaths that we see each year. Now when you look at the numbers of people who are over the age of 65, they have increased rather dramatically from 1950 to 1996, going from about 12 million to almost 34 million people.

Again, this graph here simply shows what I just mentioned in a more graphic form. But, again, you can see that this has been a rather dramatic increase.

Now what are some of the things which tell us that age is important? Well, in this slide here, this upper part represents P&I mortality as measured from the National Center for Health Statistics databases. This is complete national data here. This

bottom graph down here represents P&I mortality as measured by the 122 cities system. This is the data that we're currently talking about.

And there are a number of similarities and differences between these two curves which I won't go into. But one thing that I want to point out is that, in both of these curves, here you see a somewhat increase in baseline and here you see a somewhat increase in baseline. And we think that this is probably related, in part, to the aging of the population.

Now this is another complicated graph, but, basically, there are two lines here. This upper line here is P&I mortality in the Western part of the United States. And this other up-and-down curve down here is P&I mortality in the Eastern part of the United States. And, in general, you can see that P&I mortality is generally higher in the West with higher peaks and a higher baseline, and somewhat lower on the East Coast.

Now when we look at the percent increase in the elderly population by region, you can see that the percentage in the 85 and year-old group has been particularly dramatic and the increase has been the highest in the Western part of the United States,

followed by the South and by the Northeast and by the Midwest. But the relationship between age and P&I mortality is not so straightforward and simple. When you look at the absolute numbers of elderly people, you can see that the largest number of elderly people reside in the South, whereas the lowest number reside in the West. So, again, there's the relationship between age and P&I mortality, but it is not so straightforward.

The other major issue I want to mention for this season are some important measurement issues. Now, in general, we look at two main data sources for P&I mortality. The first one is the so-called 122 cities mortality reporting system. And this system reflects about one-third of all U.S. mortality. It's a rapid death monitoring system and the results are always considered preliminary. Again, these are the results that I showed you when I showed you that big peak for the season.

About two or three years later, we look at the data from the National Center for Health Statistics. This is complete national data, but, unfortunately, they usually are not available for another two or three years after a calendar year.

Now this year for the 122 cities system,

the P&I death case definition was changed. The old case definition said that a P&I death consisted of influenza anywhere on the death certificate or pneumonia on part one. For this season, the new case definition is influenza anywhere on the death certificate or pneumonia anywhere on the death certificate. So you can see that it's a somewhat broader case definition. And so the expected effect of this would be to increase the number of P&I deaths.

Here's the reason why that case definition change was made. Now over the past decade, WHO has been working on revising ICD-9 coding to ICD-10 coding. In January of 1999, ICD-10 coding was implemented in the United States. The effect of this on P&I deaths and pneumonia death recording has been profound. Based on both NCHS projections and then confirmed by us, by looking at some data from cities, this ICD-10 coding change decreased P&I mortality and pneumonia mortality by over 60 percent in the United States.

This is a really dramatic change. And because of the drasticness of it, WHO may end up modifying this ICD-10 pneumonia coding. This is a process in discussion which is going on right now.

But, in the meantime, what we did for the

122 cities case definition, was basically change the old case definition to something which would be called a multiple-cause-of-death case definition. And the importance of this is that the numerator data that we're looking at this year is based on this new case definition. That sinusoidal baseline which you look at is based on the old case definition. That's based on the previous five-year's worth of data. So we have a difficulty there.

So does the case definition change account for this entire increase in P&I mortality? Well, the answer is probably not. Here, again, you see two different curves. Now it turns out that in the 122 cities system, there are 29 cities that always were reporting a so-called multiple-cause-of-death case definition. And so this change to the new case definition really represents no change for those. Those cities are represented by this solid curve here, and you can see that, in cities in which no case definition change was made, we still see an increase in P&I mortality.

Now this dotted line down here actually represents the bulk of the data that we normally look at. And in these I guess 93 cities down here which did make a change in their case definition, we see

see that mortality has increased for this season.

So, in conclusion, in this somewhat confusing picture, I think that we can say that three out of the four surveillance systems have indicated that activity levels have been similar to the previous two Influenza A(H3N2) Sydney seasons. P&I mortality measurements definitely have been high and the full explanation for this is uncertain at this point.

We think that increasing aging of the population is certainly an important factor and will continue to be an important factor in the future. We know that there was an important change in the case definition, which we think increased the deaths that were recorded. But we also think that there are other factors and some relationships between these factors which, at this point, we don't fully understand.

So, at this point, there are a number of action steps which will be taken to understand this phenomenon a little bit better. During this season, there will be continued analysis of these P&I data and they will continue to be broken down in several different ways. As I mentioned, vaccine effective estimates will be available at the end of the summer and we'll try to factor that in. Normally we do not analyze the NCHS data until about two or three years

later, but I think, because of this season, what we'll do is go ahead and obtain a subset of the data and try to do an analysis and compare the results between NCHS and 122 cities data more quickly.

And then, finally, as usual, there will be ongoing analysis of these viruses, trying to look and see whether there's anything unusual about these viruses, compared to the other Sydney viruses.

So that was rather a hurried explanation of all of this, but I'll take any questions if there are any.

DR. LEVANDOWSKI: Okay. Thank you, Keiji. Dr. Greenberg, do you or the committee have any questions or comments?

CHAIRMAN GREENBERG: Yes. We have time for a few questions. Ms. Fisher.

MS. FISHER: Has there been any analysis of the data with regard to how many of the individuals who died had been vaccinated either this year or in previous years?

DR. FUKUDA: No. Every year we receive anecdotal stories or reports of people who have been vaccinated and who have developed influenza or who have died. And we also, every year, get viruses from those groups of people and look and see whether

there's anything unusual about those viruses versus viruses being isolated from other people. But right now we do not have specific data.

MS. FISHER: That's very important I would think, to find out, you know, the vaccination status of these people, both this year and in previous years.

DR. FUKUDA: Yes, that's one of the things, when we do our vaccination effectiveness estimates, that's one of the things that we've looked out and in those calculations.

CHAIRMAN GREENBERG: Dr. Edwards and then Dr. Daum.

DR. EDWARDS: Keiji, do you think that the greater availability of the rapid diagnostic tests in any way might increase the diagnosis and appreciation that influenza is playing a role in some of the deaths? Or do you think that that's not likely a role?

DR. FUKUDA: I think that, you know, with the advent of the new rapid detection tests and the approval of the new anti-viral drugs, I mean certainly there has been a really greatly increased awareness of influenza. You know, in looking over some of the data, from some places it appeared to us that perhaps influenza as a diagnosis was being coded a little bit

more often than in other years, suggesting that people may be thinking more about influenza. But, again, you know, we don't have that quantified and we don't have it compared with other years right now.

CHAIRMAN GREENBERG: Dr. Daum and then Dr. Ferrieri.

DR. DAUM: I wonder if you could comment for me, as a non-influenza person, I was struck by the vaccine uptake curve that you showed at the beginning of your presentation with its dramatic rise in the number of doses. And, yet, looking at the data on occurrence or mobidity or mortality, there doesn't seem to be any kind of corresponding effect of that dramatic uptake. You'd expect to see maybe some kind of downturn in some parameter you showed.

DR. FUKUDA: Sure.

DR. DAUM: And I wonder, are we measuring the right things? Are we looking at the right things? Or is this just not working?

DR. FUKUDA: Sure. This is something which comes up commonly. Basically when we look at the data and we look at the increase in the elderly population versus the mortality rates, it appears that the mortality is decreasing in proportion to the increasing -- or the P&I mortality is not keeping up

with the increase in the elderly population. But when you look at these curves there, you don't really see that effect because those curves are not adjusted for the increasing elderly population.

But this is a question which comes up a lot. And the basic answer is, in fact, we do think that we are seeing some effect from vaccination coverage.

CHAIRMAN GREENBERG: Dr. Ferrieri, Dr. Kohl, and then Dr. Couch.

DR. FERRIERI: May I add to your anecdotes? I direct a large microbiology laboratory and, although it doesn't include the virology lab, I get all of the feedback from that lab, as well as other information in our institution from infection control.

And this year I feel there's been a lot more background noise in Influenza A-proven illness in a population highly immunized. And I have a colleague in another institution, I don't have permission to use his name at this point, but he has at least patients, normal people more like us, not the elderly with proven virus, Influenza A isolates who had documented to have immunization this year. And I hear more and more community physicians saying

same.

And so I'm having a hard time convincing everyone who works for me and other people in the hospital who say, well, I got immunized and I still got sick. And my rejoinder always is, well, you might have died, so that's the good news, that you did not, you know.

(Laughter.)

But what's your reaction? And are you getting a lot of that type of information that is informal, if you will?

DR. FUKUDA: Sure. You know, every year we get a lot of informal information and a lot of calls. And we get frequent calls every year about people who have been immunized and who have developed either confirmed influenza or influenza-like illnesses.

But we also get calls on things like outbreaks. You know, we get lots of calls on that. And I think that we have gotten a lot of calls about immunized people who have developed influenza-like illness or confirmed influenza. By contrast, we haven't gotten that many calls about outbreaks occuring in the country. And so that's something which has been noticeable to our group.

I can't really quantify those calls for you, but that was one of the reasons why we asked New York City to take a look at the distribution of deaths by age group, because, in talking with Marcy Leighton, she said, in going out to the community and giving talks, she had heard lots of comments from primary care physicians saying we're seeing a lot of young people coming in with this. But, again, when we look at the actual data and the breakdown, we don't see an unusual hump of deaths in young people. So I think, you know, that's where it stands right now.

CHAIRMAN GREENBERG: Dr. Kohl.

DR. KOHL: Some of us elderly, although they still consider us normal --

(Laughter.)

-- every year we ask about this year's vaccine effectiveness. And, of course, we can't tell that. So I'd like to ask you, in retrospect, do we have any data on last year's vaccine efficacy rates, since the viruses look like they are pretty much the same?

DR. FUKUDA: Yes. We got vaccine estimates last year from a couple of different sources. The first estimate that we got was from outbreak out in California in an institution and, if

I recall correctly, the vaccine effectiveness estimate from an outbreak was somewhere around 50 percent or so. And this was, I think, in an elderly population.

However, when we looked at the data that was made available from the HMOs, from the health maintenance care organizations at the end of the summer, as far as I can recall, I think that that was lower, around 40 percent or so. I'd have to go back and see what the actual figure was, but I think somewhere around there.

CHAIRMAN GREENBERG: Dr. Couch.

DR. COUCH: Keiji, I don't want to claim credit for this comment. It came to me from Mark LeForest. But I thought it was interesting. I'd ask you to consider that he was suggesting this trend of increase in pneumonia that had gone over in the past few years and your suggestion of pneumonia/influenza mortality increasing progressively is partly reflective of cost-reimbursement procedures requiring, over the course of years, a considerable improvement in the quality of the coding of discharged diagnosis and of death diagnosis than was true earlier. So it's not a change in disease, but a change in the notification of disease.

DR. FUKUDA: Yes. I mean, I think that,

you know, when we analyzed P&I hospitalization data, that was clearly an issue. I think that hospitalization coding has really been affected a lot by reimbursement practices.

I'm less aware and less sure of whether there has been that much of an effect on death coding because of reimbursement practices. My sense is that if there is an effect it's less, but I'm not sure.

DR. COUCH: In both cases, the physician is doing the coding, with the help of administrative officials in the hospital. But for the deaths, as well.

CHAIRMAN GREENBERG: Dr. Kilbourne.

DR. KILBOURNE: I just wonder. When we're talking about levels of projection of 40 to 50 percent are those actually proven cases of influenza?

DR. FUKUDA: No. These are clinically defined cases of influenza.

DR. KILBOURNE: Okay. Because that's what you have to really look at, ultimately.

CHAIRMAN GREENBERG: Dr. Cox.

DR. COX: Yes. I'd just like to comment that those were effectiveness estimates against hospitalization in the elderly.

CHAIRMAN GREENBERG: Dr. Kim and then Dr.

Faggett and Estes and then we're done.

DR. KIM: Since you have viruses available, do you have any information on in vitro activity of your standard serum against those viruses? Whether, you know, they are still active or, you know, activity differs.

DR. FUKUDA: Well, I think that would be some of the data that would be gone over subsequently. So I think I'll just hold on that. You're going to get more than enough.

CHAIRMAN GREENBERG: Dr. Faggett.

DR. FAGGETT: A little clarification. Were you saying that about one-third of the cases that look like flu are really RSV?

DR. FUKUDA: No, no. What I was saying was that deaths for pneumonia and influenza reflect a number of different factors and a number of different agents out there. We know that influenza viruses are one of the main factors which affect it, but we also know that people can die from other viral agents.

And this year, for example, in some parts of the country, when you look at surveillance data for viruses such as respiratory syncytial virus, you know the rise in those viruses has really been almost exactly the same as the rise in influenza viruses

And so, again, we can't say what proportion of those P&I deaths are due to RSV or mycoplasma or adenoviruses. But we know that they're out there and that they play some role.

DR. FAGGETT: Before we went to that, this year, was your impression that the RSV was affecting more adults in a more virulent fashion, this year?

DR. FUKUDA: No. I don't have any information or any impression that the impact of RSV has been different than in other years. But I think that, you know, traditionally we think of RSV as impacting very young kids but I think it's clear that they have some impact on the elderly also.

CHAIRMAN GREENBERG: Dr. Estes.

DR. ESTES: I'm a little concerned at the answers about vaccine effectiveness. So every year we ask what was the vaccine effectiveness? And you say that next year by the end of the summer we'll hear what the data were for this year. And yet, for last year, we don't seem to have good numbers for flu-proven cases. Are studies ongoing now that we really will get good data on vaccine effectiveness?

DR. FUKUDA: No. There is no ongoing program of vaccine effectiveness studies, looking at laboratory-confirmed cases. I mean, these kind of

prospective studies, again, would be very expensive, especially to have a laboratory component and we certainly don't have any funding for those kinds of studies.

DR. ESTES: Well, I would strongly recommend that somebody reconsider this because at some point we really need to know what the real vaccine effectiveness is.

CHAIRMAN GREENBERG: Dr. Cox.

DR. COX: Yes. We've had similar discussions for the last 10 years at least and probably over the last 20 years. And we would be delighted to have the funding to do such studies. If it were made available, we would be happy to organize those studies. But the vaccines have been in use for such a long period of time that, at the current time and the current funding base that we have, the best that can be done is to do a retrospective look back at the decrease in hospitalizations among vaccinated individuals, using large databases and that type of study. Because adding a laboratory component is very expensive.

Now in the future, there may be a couple of -- and maybe Kathryn would like to talk about this -- there may be a couple of studies which will be done

to look more generally at respiratory illnesses and to integrate a laboratory component which could help us understand the contributions of the different respiratory agents during specific years. But, again, you would want to have this as an ongoing study for a number of years to really understand what's going on.

CHAIRMAN GREENBERG: Dr. Couch and then Dr. --

DR. COUCH: Well, I just wanted to assure Mary that we wouldn't want to trivialize that comment, but it has been raised year after year after year.

DR. ESTES: But I think that's even worse that's it has been raised for 10 years and --

DR. COUCH: But still nothing has been done or has been put in force. I find Nancy's comments to be very encouraging that maybe there is a possibility that some studies will be set up.

CHAIRMAN GREENBERG: Dr. Daum and then Ms. Fisher and that will be the end of the comments.

DR. DAUM: Yes, I just want to strongly reinforce Dr. Estes' comments. I'm a relative newcomer to this process and this committee and already have heard several cries and outpourings for more information about this. I'd be very happy to be informed by Dr. Cox or anyone else as to what we can

do to help. To whom can we send the message? But we're doing an intervention to 70 or 80 million people a year in this country and what we know about how it's working is almost pitiful. I mean, we just don't know enough about its performance.

I would like to have a lot more information and would like to encourage anybody who is in a position to help to signal the urgency of this crucial health problem and do something about it quickly.

CHAIRMAN GREENBERG: Ms. Fisher.

MS. FISHER: This has to be done immediately because there is a push to use flu vaccine in children going on right now and it is not right that we go forward with this kind of a recommendation for children when we don't understand what's happening in the general population.

DR. FUKUDA: Actually, let me put the vaccine effectiveness question in somewhat of a different perspective. There are many, many, many studies looking at vaccine effectiveness in small populations. What we do not have -- and these are laboratory-based studies looking at laboratory confirmed information. I think the issue of whether a vaccine is effective or not is not really an issue.

I mean, there are just very large numbers of studies addressing that question.

What is not addressed is the national vaccine effectiveness. I mean, if you look at all people in the United States and all of this vaccine, what's the effect on this very large group of people? And so that's the data which we do not have because it's so expensive to collect. But that's a different issue, there.

CHAIRMAN GREENBERG: We're going to move on, Dr. Couch. I'm going to take the last word myself and simply say that I think what you've heard here is that -- and virtually everybody in this panel knows that there is a huge history of documentation of vaccine effectiveness at points in time in small studies. But since flu is a moving target and things change, it would seem appropriate that there is a prospective, ongoing evaluation because there is the potential that effectiveness may be changing as flu changes. And some handle on that would probably be very useful.

Dr. Cox, your turn.

DR. LEVANDOWSKI: All right. Dr. Nancy Cox is the chief of the Influenza Branch at CDC and she's going to tell us about surveillance and

antigenic characterizations.

DR. COX: Thanks very much, Roland. I'll try to move through the presentation very quickly. There is rather a lot of information to cover and I would suggest that anyone who is sitting too far in the back to see move forward so that you can see. There are a lot of slides that are fairly complex and may be difficult to see.

We're going to move from a U.S. picture of influenza to the global picture of influenza. And we're going to start with the viruses that we have the best handle on at the moment. So we're going to move through the different groups of viruses in the order of complexity and the number of questions that we have about them.

We're going to start this year with Influenza A(H1N1) strains. This overhead simply indicates by the number of pluses that you have associated with a particular month in a particular area of the world the estimated extent of activity attributed to H1N1 viruses.

If we look at the activity that occurred between April 1999 and September 1999, which is mainly activity in the Southern Hemisphere, you'll see that there was only sporadic H1N1 activity. We had only

sporadic isolates from various parts of the world. That is also true for the period October 1999 to January 2000, with the exception of Asia, where we know that during December and January, particularly in Japan and you'll hear more about this later, there was significant activity caused by Influenza A(H1N1) viruses.

Now if we look at the viruses themselves, for those of you who have been here for the past two years or past few years, you'll recall that we have two antigenically and gentically distinct groups of H1N1 viruses which are circulating. The first group is represented here by A/Beijing/262/95 and A/New Caledonia/20/99 which you'll be hearing quite a bit about today.

These two viruses belong to one genetic and antigenic group. You can see that here we have the reference "antigen" and we have the post-infection ferret antisera titers. The homologous titers are shown diagonally here in red and they're underlined. And we consider a fourfold difference in titer to be significant if it's reproducible from test to test.

Here you can see, first of all, that when we look at the relationship between the Beijing/262 and New Caledonia strains, we see an asymmetric

difference, that is, we see a fourfold reduction in titer between the New Caledonia strain against the Beijing/262 antiserum, but we don't see the reciprocal difference. Nevertheless, when we look at a series of viruses, we can clearly see that the Beijing/262 serum does not cover this set of viruses down here as well as the New Caledonia serum does. So we have seen antigenic movement of the what were formerly Beijing/262-like viruses so that they're looking more like the New Caledonia antigenic variant.

Now, of course, circulating in some parts of the world, close circulating in some parts of the world and circulating separately in some parts of the world, we have this older lineage of influenza viruses which are related to the Texas strain that was in the U.S. vaccine for a number of years. That group of viruses is represented by Johannesburg/96 and Moscow/13 in this particular slide. And you can see that these viruses are very clearly differentiable by hemagglutination inhibition testing from the New Caledonia and Beijing/262-like strains.

There was sporadic H1N1 activity in South America during their winter months, our summer months. These viruses were isolated during May and July of '99. And these strains from South America were

clearly related to the older Johannesburg and Moscow and the Bayern/07 reference strain, which you will remember.

Next slide, please.

Here we have a slide showing some more recent viruses. And, in particular, I'd like to point out some strains that were received from Dr. Nerome in Japan where they're having a significant H1N1 outbreak. We have the Kobe strain here and Sendai strain here. And these viruses were isolated in November and December of '99. Once again, we see that the viruses down here, and we have actually three viruses from North America, one from Wisconsin and two from Canada, which are more poorly inhibited by antiserum to the Beijing/262, but well inhibited by antiserum to the New Caledonia strain.

On this particular slide, we have the most recent Johannesburg/82-like strain that we've received listed at the bottom, antigen number 18. This is a virus from China and it just looks like a typical Johannesburg strain.

We're going to concentrate mainly on the bottom part of this slide here. And just to demonstrate, I have actually the page number up on the top, page number 11 in your packet. We had only 40

H1N1 strains that were isolated between April '99 and September '99 to analyze in our laboratory. And only a total of 11 strains that were isolated between October and January. Of the most recent strains, the majority are in the Beijing/New Caledonia group and the majority are New Caledonia-like.

When we do the genetic analysis, we see that here's the Beijing/262/95 strain and, of course, these viruses do not remain very stable genetically; even if they appear similar antigenically, they are marching along and evolving with time. So here's our vaccine strain and there are a number of conserved amino acid changes between the Beijing strain and the currently circulating strains on the same lineage.

Here's our New Caledonia strain. And I've put red dots by a number of the viruses that you had seen on the HI table shown previously and these are strains that are well covered by the New Caledonia antiserum. Down here shown in blue, we have the Bayern/Johannesburg lineage and you can see these viruses are also evolving, although, antigenically, they look very homogeneous.

We like to look at our sequence data in ways that are fairly simple to present. What we've determined in the past that, oftentimes, strains which

have a sequence that is close to the consensus sequence of the viruses circulating actually produce a ferret serum with antibodies that are quite cross-reactive. And so we like to look at the egg isolates that we have because those are the strains that are actually considered to be vaccine candidates because we must have strains that have been cast only in eggs in order to go into the vaccine. So we restrict our analysis here to looking at strains that have a pure egg-passage history.

And when we compare the New Caledonia strain to the consensus sequence for the Beijing/262 lineage of virus, we see that it has an identical sequence to the consensus sequence. So perhaps this is one of the reasons the antiserum is covering the currently circulating strains on that lineage so well.

Next slide, please.

We also look at the neuraminidase -- not antigenically, perhaps we'll be doing that in the future -- but we do look at the neuraminidases of these viruses genetically. And, once again, we see our vaccine strain is here and the neuraminidase of the New Caledonia and one of its corresponding high growth reassortants is up here, so the neuraminidase is also evolved.

Next slide, please.

When there are two lineages of viruses within a given type or subtype, we like to keep track of exactly what the geographic distribution is of the viruses that have been identified. And here we have the geographic distribution of the Beijing/262-like lineage viruses that have circulated between October '98 and January 2000. And you can see that they're pretty well distributed in all continents where surveillance occurs.

I'm going to just show one overhead with the post-vaccination human serologies. Roland is going to be presenting a lot more data later, but this data did not get to Roland in time for him to incorporate it into his analysis. So I would just like to show you that if we concentrate just on this column for the time being and look at the post-vaccination geometric mean titers against the vaccine strain Beijing/262 and against New Caledonia; a representative Japanese strain from the current outbreak in Japan; and a virus from North America, the Canada virus, we see that we have a greater than 50 percent reduction in post-vaccination geometric mean titer for these representative strains.

Next overhead, please.

Again, if we look at an elderly population. I neglected to mention that we were looking at healthy adults in the previous slide. If we look at the elderly population, once again, if we look simply at the post-vaccination geometric mean titers, we see at least a 50 percent reduction for these strains, as compared to the homologous titer that we observed for the vaccine strain itself.

We'll move very quickly onto the Influenza B viruses. The picture is a bit more complex for Influenza B, but similar to the situation for Influenza (H1N1) viruses. We really have not had a great deal of Influenza B activity when we look globally, neither for the Southern Hemisphere winter nor for the Northern Hemisphere winter that's occurring now.

Next overhead, please.

Once again, we have two lineages of viruses circulating. We have the so-called Yamagata lineage, which is represented here by Yamanashi, Beijing/184, and Harbin/07. And then we have what we traditionally have called the Victoria lineage, which is represented here by Shangdong/07/97. And it's very easy to see that these viruses are distinguishable, easily distinguishable, using hemagglutination

inhibition tests with post-infection ferret sera.

This was a test that was performed in early November and we had some isolates from Tennessee that had been collected in early October. And the vaccine strain that we are currently using as our B component is Yamanashi/166. We see that, for these viruses, we had good inhibition for the Tennessee strains and a strain from Brazil that was also isolated in October. This virus from Ohio had a fourfold reduction in titer compared with the vaccine strain, but was only twofold reduced when compared to the Beijing/184 prototype.

This test was done in early January of 2000. And as we continued to do more testing with the Bs, we started seeing a slightly different picture emerge. If we concentrate here on the titers that we're seeing against the B/Yamanashi ferret serum, we see that we have the Zagreb and New Caledonia strains, which are well-inhibited, and a number of strains that are just two fold down.

But then we have antigens 17 through 21 here, which had been received recently. They've been isolated in August and September of '99, but we've received them rather recently. We had three viruses from Vietnam and two from Southern China. And very

clearly, these viruses were not well-inhibited by antiserum to the Yamanashi. They were still reasonably well-inhibited by antiserum to the Beijing/184 and they were clearly on the Yamanashi lineage, as confirmed by sequence analysis and so on.

We were very interested in looking at these viruses in more detail. We did multiple tests with these to be sure that the HI values were reproducible. And we chose one particular strain, that is this Shenzhen/654 strain; put it into ferrets; and got a ferret antiserum, which shows us quite clearly that we have a new Influenza B variant. That is, we have a greater than fourfold reduction in titer when we're looking at the ability of the Yamanashi ferret antiserum to inhibit this strain and we have a reciprocal difference when we look at the ability of the Shenzhen antiserum to inhibit the Yamanashi virus.

Now as you can see, this test was just completed last Monday, right after the ferret was bled. And so we haven't had a chance to do a large retrospective analysis to actually see how this Shenzhen antiserum would perform against, for example, the Tennesee strain and some of the other strains that you've seen in previous tests. So this is one of the next steps that we'll be performing. But you can see

that this antiserum clearly inhibits these viruses much better than the Yamanashi serum does.

The other thing I should point out is that the B/Johannesburg strain was also well-inhibited. In our hands, it's well-inhibited both by the Yamanashi antiserum and by the Shenzhen/654 antiserum.

Next slide, please.

We'll concentrate mainly on the bottom part of this table, the frequency table. If we look at the period between April '99 and September '99, we have analyzed a total of 97 strains. Only 10 of those, or approximately 10 percent, have been Victoria-like and those are from Asia. The majority of the strains are Beijing/Yamanashi-like or low to Yamanashi. And you'll see a number of strains here, 16 in fact, all from Asia, which were low to Yamanashi. And that includes the Shenzhen and some of the Vietnam strains.

If we look at the recent period, we've had relatively few Influenza B viruses to analyze. Only a total of 14. And we have one strain from Asia which is low to Yamanashi. We have two from the U.S. which are low to Yamanashi.

Okay. This shows the molecular analysis of the hemagglutinin genes of these strains. As

mentioned, we can clearly distinguish these viruses genetically. This is the so-called Victoria lineage. This is the so-called Yamagata lineage. Here's our vaccine strain here, Yamanashi/16/98. And it's more or less in the middle of the majority of strains that we have analyzed.

The new variant that I mentioned is located up here and it's actually shown right here. There are a number of specific amino acid changes between these strains and these strains that could account for the differences in antigenicity. And you'll note that this new group of viruses up here is more closely related to the previous vaccine strain Harbin/07/94 than it is to the Yamanashi/16/98.

Next slide, please.

We looked at the extent of amino acid difference between the egg isolates that we have for Influenza B/Beijing-like strains and the consensus sequence. And you'll see that the Yamanashi vaccine strain is actually very close to the consensus sequence. And this has been the sublineage that has predominated in most of the world in recent years. But, again, it should be noted that we have a relatively small number of strains.

Next slide, please.

And here we're looking at the separate sublineage of Harbin-like strains. And here we see that the Shenzhen/654 has five amino acid differences, compared to the consensus sequence for the sublineage. Now part of the problem here is that we have relatively few viruses that are in this lineage. We don't do know the significance of this new antigenic variant. We only have a handful of viruses that are like this. We have just received a package of strains from the National Influenza Center in Beijing and all of the strains in that package are Influenza B strains, so we're very keen to look at those in detail and see if we can find similar viruses from other locations in China.

Next overhead, please.

If we look at the neuraminidase genes's evolutionary relationships about the B Influenza, neuraminidase genes, once again, we see the Yamanashi strain, here sort of smack in the middle of the most prevalent influenza virus strains that are circulating. We'll need to sequence some additional neuraminidase genes from these recent strains. We haven't been able to complete those studies yet. Well, Shenzhen is actually done here, but we want to look at the neuraminidases of some of the viruses from

Vietnam and the other Shenzhen strain to see if they cluster together.

Now just to remind you, we've been talking about this for a number of years, but we need to keep in mind that we do have these two separate lineages. The vaccine for Europe and North America has contained viruses from the Yamagata lineage, but the Victoria-like viruses have continued to circulate in Asia. And the red dots here on the map just show the locations of B/Victoria-like strains isolated between October '98 and January 2000. And we really haven't seen these viruses spread outside of Asia, which is quite surprising.

I have just one post-vaccine serology exhibit to show you today. And, again, I'd like you to concentrate simply on this column, which shows the post-vaccination geometric mean titer against the vaccine strain Yamanashi and some other representative strains. And I'd just like you to note that the titers are markedly reduced for the B/Shenzhen/654 variant in all of these different panels.

Next overhead, please.

And I said we were going to move through the virus groups in order of increasing complexity and now we're talking about H3N2 strains. When we look at

the influenza activity that has occurred worldwide, and this is just an estimate of the extent of activity, but it certainly contrasts markedly to the picture that we saw for the B viruses and the H1N1 strains, you can see that there was really significant activity due to H3N2 viruses in the Southern Hemisphere in South Africa, Australia, and New Zealand and also on Central and South America during their winter season.

You can also see that there is significant influenza activity due to H3N2 viruses in the U.S., Canada, and Europe. And there's also activity occurring in Asia, but it's not quite at the same intensity, at least insofar as we understand it.

Now looking at the HI reactions for the H3N2 strains has been extremely interesting. All of us who have been watching the evolution of H3N2 viruses over the past few years would have predicted that Sydney-like strains would not circulate for three years in a row. That has not happened for H3N2 strains for a number of years.

We have looked in great detail and with great care at whether or not the currently circulating strains are indeed Sydney-like. Here I'm showing you one particular batch of post-infection ferret serum.

We have checked three different batches made with serum from five different ferrets. And we see the same picture with all three batches of ferret serum to the Sydney strain.

This is a test that was performed in mid-December and it is very representative of what we had been seeing during November and the first part of December, and that is to say that, regardless of whether we were looking at viruses from the United States, which are shown here and with test antigens 7 through 12, or whether we were looking at viruses from Asia, shown here with test antigens 13 through 18, we were seeing a very good inhibition of these viruses with antiserum to the Sydney vaccine strain.

We were also seeing a great deal of homogeneity, regardless of what serum we were looking at. Here we have the Moscow/10 strain that Roland mentioned earlier. We were seeing very good inhibition with this particular antiserum. Here's another virus that you'll hear about quite a bit. This is the Panama/2007/99 strain and its antiserum was inhibiting all of these strains very well.

We have two high-growth reassortants that were made against the Panama antiserum. The reason we did that is that we saw that the Panama virus itself

had a fourfold in many tests, sometimes a twofold, reduction in titer when compared to the homologous Sydney titer. So that's the reason that we went ahead and made a ferret antiserum to this virus and then high-growth reassortants were made. And the antisera to these two high-growth reassorts, NIB-41 and 42, inhibited the viruses that we were seeing early on quite well.

Here we have another virus which is fourfold reduced, very reproducibly fourfold reduced in titer as compared to the Sydney homologous titer. And antiserum to that strain also inhibits these strains quite well.

Here we have viruses that were isolated during October and November from the U.S. and these strains were isolated a bit earlier, between April and September of '99.

Next overhead, please.

You notice that this test was done a month later in mid-January. And this table is organized in very much the same way. It's fairly complex. I'll try to walk you through it.

What we were seeing -- by this time, we had identified another strain that was fourfold reduced in titer to the Sydney antiserum that's shown

here in reference antigen number 6 Alaska/37/99. And, of course, we made a ferret antiserum to that strain, so that's the new antigen that's been introduced here.

But if we concentrate first on this column here, which shows the inhibition of viruses by the Sydney antiserum, we see that, if we look at viruses from North America, we have a number of viruses with a fourfold or greater reduction in titer against the Sydney strain. And if we look across here and look at how these viruses are inhibited by other antisera, what we tend to see is the viruses which are more poorly inhibited by the Sydney antiserum also tend to be more poorly inhibited by the other antiserum.

Now if we look at the viruses that we've received from other countries, we have a similar pattern. There are a number of strains which are very well-inhibited within twofold versus the Sydney antiserum. But we also have a viruses from Hong Kong and one from Korea which are reduced in titer.

I think I will go on to the next overhead, rather than spend too much time there on that particular one. This is the latest test that we performed this week and in this test we have one additional antigen and ferret antiserum, the Shenzhen/510/99 strain. And this was the most recent

egg isolate that we had or one of the most recent egg isolates that we had from Asia and so we thought it would be a good idea, even though it wasn't reproducibly reduced in titer with the Sydnedy antiserum, we thought it would be a good idea to see what kind of a profile we observed with antiserum produced against this virus.

Once again, if we concentrate on column A, we'll see that there are strains from North America, which are very well-inhibited. These are strains isolated in primarily in December and January of this season. And we also have some strains that are fourfold reduced in titer, compared to the Sydney antiserum. Again, these strains were isolated in October. If we look at viruses from abroad, we see a similar pattern. We could find viruses which are reduced in titer.

We had been looking quite closely at the Panama antiserum and in many tests the Panama antiserum performs as well if not better than the Sydney strain in covering the currently circulating viruses. In this test, it's not readily apparent.

We haven't tested the Shenzhen antiserum a great number of times. I think we've only had it in two large tests, but we do see that this Shenzhen

antiserum tends to cover almost all of the strains. We only have one strain here, the Philippines/26/99 strain, which may be mentioned by others later, which is reduced fourfold or greater in titer.

So what I would like to just pause here and mention is that we have a picture for the H3N2 viruses that's a little bit complex. We're really looking for a distinct new variant and we haven't seen one. We're looking for a variant where we have a fourfold reduction in titer that's symmetrical, that's going both ways. And if you look at this table carefully, you'll see that there are no strains here which give symmetrical, fourfold reductions in titer.

The viruses are reasonably homogeneous and when they are less well inhibited by the Sydney, they tend to be less well inhibited by the other antisera. The only antisera that we have at the moment, and we have much less experience with it, but the only one that we have that tends to give a significantly broader pattern is this Shenzhen/510 antiserum.

So in the past what we've always tried to do is to find the new variant and really move to the new variant. But you could think about a variety of strategies for updating vaccine components.

You could think about, of course, you have

one strategy where you stay with the component that you have in. You could have one where you moved to a strain that is somewhat different, for example the Shanghai/42 even though it isn't very representative of what's circulating genetically. Or you could try to just follow and move where the viruses seem to be going genetically and move to the Panama strain. Or you could try to surround the strains by moving to a strain that really you have a limited rationale for changing to, but the antiserum actually seems to cover better. So these are some of the ideas that we're exploring.

Next overhead, please.

Now I've shown you tables that have been selected to make certain points. This shows the composite data for H3N2 viruses. If we look at the viruses that were isolated between April '99 and September '99, we have a total of 346 strains that we've looked at and of those just about 11 and one-half percent were fourfold or greater reduced in titer to the Sydney strain. If you look back at what was happening last year, we also had about 10 percent of strains which were reduced in titer to Sydney. So it's really not a very different picture from what we were seeing last year or what we saw during the summer

months.

And the same thing is true of the period October '99 to January 2000. Again, it's about 11 percent of the strains which are reduced in titer.

The molecular picture is fairly complex. I've put red dots by some of the viruses that you've seen on your HI table. Here's the Alaska/37, the Panama/2007. Sydney vaccine strain, of course, is down here and the viruses have been evolving with time as we always expect at a molecular level. And here's the Moscow strain here up in this sublineage. And the Shenzhen/510 is here.

Now what I've done also here is to put a small green L by the strains which are low reactor in HI tests. And what you'll see is that those so-called low reactors, the viruses that are fourfold or greater down in titer as compared to the homologous titer with ferret serum, are scattered throughout the dendrogram. They don't cluster together. So what we have is a picture where we don't have a clearly emerging variant of H3N2. We have low reactors which are in each of these different clades.

Next overhead, please.

If we look at the sequences of our egg isolates or our possible vaccine candidate strains, as

compared to the consensus sequence that we've obtained for strains circulating, we see that the Sydney vaccine strain now has nine amino acid differences compared to the consensus sequence. Panama/2007 has three. Shenzhen/510 has five. Another strain that's been mentioned quite a bit or will be mentioned more in the future is Moscow/10, which has five.

The relationships between the neuraminidases of these strains at a molecular level are also complex. We have different subgroups of neuramidases that are circulating. And we see that the Panama neuraminidase is here in this clade while the Moscow and Shenzhen neuraminidases are up here in this clade. Sydney neuraminidase is down here and there are a number of amino acid changes that have occurred in the neuraminidase.

Next overhead, please.

Now I'm going to finish up my talk with a bit of an aside, but I know that the committee has had a number of questions over the summer months about what was going on in China with regard to Influenza A(H9N2) infection that had been reported from Hong Kong and then also from Guangdong Province in Southern China.

The story that you're probably

familiar with is that that emerged from Hong Kong in March of 1999 -- I apologize for the typo -- when H9N2 viruses were isolated from two hospitalized children ages 4 years and 13 months. These children had underlying health conditions that may have predisposed them to more serious disease, nevertheless they were hospitalized. Both of them recovered uneventfully and no further cases have been reported from Hong Kong.

The viruses were analyzed in detail and contain all avian genes, that is to say there was no reassortment between human strains that were close circulating at the time and these H9N2 viruses. Quite a lot of work occurred in Hong Kong to determine the source of the infection and it was already known that some of the poultry were shedding H9N2 viruses, that had antibody to H9N2 viruses. And it was reported by the Department of Health in Hong Kong that about 70 percent of the batches of poultry that they tested were positive for antibody for H9 virus.

After an investigation in which CDC participated extensively but which was led by the Department of Health in Hong Kong, it was determined that poultry are the likely source of infection and serologic studies indicate that human to human transmission is rare and inefficient, similar to the

picture that was seen for the H5N1 viruses.

Isolation of H9N2 viruses was also reported by Dr. Guo Yuanji at an international meeting in March of 1999. He reported that five H9N2 viruses had been obtained from individuals who had accute respiratory disease in Guangdong Province. And the individuals were ill, actually, in December of 1998.

Subsequently, this work was published in the Chinese Journal of Experimental Clinical Virology and the title of the paper is "Discovery of Humans Infected by Avian Influenza A(H9N2) Viruses." The age of the patients ranged from 1 year to 75 years of age. And the severity of infection varied somewhat and there wasn't a great deal of clinical information in the paper that was published.

The H9N2 viruses that were reported by Dr. Guo are antigenically different from the ones that were isolated in Hong Kong. And I'll show you the relationships between these viruses on this slide. We haven't actually received any of the viruses isolated by Dr. Guo so we haven't been able to confirm his analysis, but the viruses from Hong Kong are listed here, antigens 3 through 6. And we just have MDCK and egg isolate pairs shown here.

And you can see that these viruses that

were isolated from humans, whether in MDCK cells or chick cells, are closely related to a reference avian virus A/Quail/G1. And we'll just call it G1 for the sake of convenience. So these viruses are closely related to this virus, which was isolated from the live bird market in Hong Kong during December of 1997 right before the slaughter of the chickens that was undertaken to eradicate H5 viruses.

The viruses that Dr. Guo has reported apparently are related to a reference avian strain Chicken/G9 which is shown here. So it appears that there are two antigentically and, I'll show you in a minute, genetically distinct groups of H9N2 viruses that are circulating in poultry in Asia and both lineages have shown the ability to jump from birds to humans. Here I've just pointed out with red arrows the G9 reference strain and it's genetically and antigenically from the G1 group that's shown here.

I think that's my last overhead.

CHAIRMAN GREENBERG: Nancy, thank you very much for a very complete talk. Now that talk took a little more time than the schedule Dr. Levandowski had planned, but I think it was very complete and very helpful. What I would please ask is for the next speakers, who I am sure have wonderful data to tell

us, that when it overlaps with what you've just heard, you don't have to tell us again. And, in order to try to keep this on track, I would hope that, again, the next speakers really present the committee with the data that is important to make the decision for next year's vaccine.

I have time for one or two questions for Nancy. Dr. Kim.

DR. KIM: So it appears that, based on your H3N2 data, that it seems unclear why there seems to be an increase in influenza activity this year compared to let's say last year.

DR. COX: Yes, the viruses that are circulating this year appear very similar to the strains that have circulated during the previous two winters. So it is unclear, first of all, why, based on past observations, we haven't seen a new variant emerge. And, secondly, why we would have an epidemic caused by H3N2 rather than H1N1 or B when we would expect the antibody levels to be lower to those two strains.

CHAIRMAN GREENBERG: Dr. Edwards.

DR. EDWARDS: I have a quick question. When you're looking at hemogglutination inhibition with the A/Alaska strain, making the antisera in

ferrets, it appeared that the neutralization of that homologous strain was quite low whereas neutralization of other viruses with that strain was higher. Does that happen frequently?

DR. COX: That happens with viruses which we typically call "low avid." They just don't appear to bind antibody as efficiently as some other strains. So occasionally, when we put one of those strains into ferrets, we find a ferret antiserum that inhibits the homologous virus less well than it does the other viruses, which bind antibody better.

DR. EDWARDS: Would they be not very good ones to select as vaccine strains? Or are ferrets and humans not alike?

DR. COX: We tend to try to stay away from those strains if possible.

CHAIRMAN GREENBERG: Two more questions. That's it. Dr. Faggett and then Dr. Couch.

DR. FAGGETT: With the H9N2 virus, was that a mutation in terms of the one reported first in Dr. Guo's? And was there an implication that there person-to-person capacity for Dr. Guo's virus?

DR. COX: I'm sorry. I'm not sure I understand your question.

DR. FAGGETT: For H9N2.

DR. COX: Right. The H9N2 viruses that are circulating in the poultry in Asia --

DR. FAGGETT: Right.

DR. COX: There are two distinct lineages.

DR. FAGGETT: Okay so no mutation there, just very distinct to start with.

DR. COX: That's right.

DR. FAGGETT: Okay.

DR. COX: Distinct to start with.

DR. FAGETT: Right. But did Dr. Guo's reported virus have any potential for person-to-person transmission?

DR. COX: We really don't know very much about those viruses and epidemiologic studies comparable to those done in Hong Kong haven't been done yet, although Dr. Guo has done some serum surveys.

CHAIRMAN GREENBERG: Last question, Dr. Couch.

DR. COUCH: Just a couple quickly, Nancy. One is a lot of, including Dr. Kilbourne, are pleased to see the emphasis coming on on neuraminidase and looking forward to antigenicity data that you said you're working on for the future.

But the puzzle is on everybody's part, as

you've indicated, is why three years in a row of A/Sydney? And one suggestion that you've made that may have contributed is perhaps the neuraminidase are different and that, in the presence of a high population immunity and the absence of neuraminidase in it, perhaps this antibody and this virus has a little better ability to survive. So I think that will be interesting.

You've emphasized the low reactor frequencies and I can't remember from past years that -- see you said it was 10 percent all the way across the years period. It that about the usual? Or is there a higher frequency this year?

And my last question relates to Influenza B. Any outbreak or epidemiologic data to go with the Shenzhen strains?

DR. COX: I'm not sure what you're -- your first question was more of a comment than a question, I think. Yes, why three years?

DR. COUCH: Well, I just wanted you to speculate a little bit. You didn't mention the neuraminidase as a possibility.

DR. COX: Right. Right. We're going to -- yes. Neuraminidase is a possibility. We're going to be looking at that in much greater detail, trying

to sequence more neuraminidase genes and eventually trying to set up some antibody neuraminidase inhibition tests. And we're also going to be looking at internal genes as well, just in case.

DR. COUCH: Have previous low reactor frequencies been low, 1 or 2 percent, versus 10 or 11 now?

DR. COX: It depends on the year, but 10 percent is not unusual because there's just a degree of hetereogeneity among viruses circulating that causes us to see this kind of picture. What we expect to see when a new variant is really emerging is an increase over time. So 5 percent, 10 percent, 30 percent, and so on and then predominance of that new antigenic subtype.

And the third question was?

CHAIRMAN GREENBERG: The last question was on B.

DR. COX: On B we don't really have very good epidemiologic information about the significance of the strains that have come to us from China, but we'll be following up on that and trying to get as much information as possible.

CHAIRMAN GREENBERG: I'd like to move on now and we have a series of speakers. Dr. Canas. And

what'd I like to say is for each of you, you've got a maximum of 10 minutes and then a hook is coming out.

DR. LEVANDOWSKI: I need to reinforce what Dr. Greenburg said. We're severely behind schedule by about 45 minutes so all the speakers need to be very succinct.

Linda Canas is the chief of diagnostic and pyrology at Brooks Air Force Base. She's with the Department of Defense and she has information that overlaps with the surveillance data that's been presented by CDC.

CHAIRMAN GREENBERG: And when you have overlapping data, just say you've learned this already. You don't have to present it again.

DR. LEVANDOWSKI: Okay, I meant "supplements."

(Laughter.)

DR. CANAS: Good morning. DOD is very interested in maintaining the health of the men and women in the armed forces and respiratory disease, of course, rates very high on this. For over 20 years now, the Air Force has conducted influenza surveillance.

It's been a successful program and it's now operated through the Global Emerging Infectious

Disease Office out of Washington and is tri-service. Each of the services has their own portion. The Air Force still continues mainly in the overseas and stateside surveillance by sentinel base.

Now last year I went through a detailed process of how this works and let's just through it very briefly so you know what we do. We do have sentinel sites that are set up around the world. Throat cultures are collected from the physicians of anyone presenting with a case definition meeting respiratory illness. These are sent to us generally by FedEx to our laboratory in San Antonio where we do traditional laboratory methods and isolate whatever virus we get.

We are looking for influenza, but it's a clinical test in our labs so we report whatever we get and get this information back to the public health officers at the bases. We then go on to do any molecular tests and hemagglutination inhibition subtypings in our lab and also send on to Dr. Cox's lab at CDC.

And just to give you an idea of where all of these different sites are, we do have them set up around the world. We have two that are proposed. Agreements have been signed and we should, hopefully,

start getting some specimins from Uganda pretty soon. Bolivia is also supposed to come on line. The stateside bases, our military bases, have been chosen -- training sites where people are coming together, points of entry into the country, and our overseas sites. My handout didn't get here, so it lists all of these and their countries and states to give you an idea that we do have a pretty broad range.

One of the most exciting additions has been in collaboration with Army and Navy research labs in overseas areas where we've been able to get specimens from Nepal and Thailand for several years now. This summer we ran into practical problems getting specimens into the country, but I think that's finally all worked out. We are expecting another shipment shortly from them. They say they are having some significant outbreaks.

South America has been particularly prolific in sending specimens. They've been very excited about the program. I understand now that the National Police is going to be involved in getting supplies out and getting them back to us. And, as I mentioned, Bolivia in South America and Uganda will be coming on line very shortly.

Our graphs of what's been going. You will

notice that we have a signficant respiratory increase this season and that is very true in the military population. But it's unique. We're getting a lot of background parainfluenza. Our program is not designed for RSV, but we have a uniquely military consideration with adenoviruses in our recruit population. So the majority of those isolates have been adenovirus as opposed to influenza.

There's been very little influenza isolated in the recruit population. And this is true for all services. And those that have been influenza cases have been in the new recruits who really haven't had time to develop an immunity yet. So we're not seeing influenza in the recruit population.

In the active duty population as a whole, we do see it. We're trying to do some vaccine efficacy studies. We know we have a unique population here. They are required, the active duty are required, to be vaccinated. We can track their records; we can track their travel; we can track their medical history, but it takes money. So we're trying to do the retrospective studies of matching up vaccination and travel histories with the laboratory case definitions and this is an ongoing process. It is one of our priorities to try to get true vaccine

efficacy studies down the line.

In Asia, we are just now beginning to see a real increase in samples coming out of Asia. We've had one H1 out of Hawaii and that has been a New Caledonia. We had one H1 just last week out of New Jersey. And we've had two Bs in the Pacific and just last week we got a B out of Oklahoma. Everything else we've seen has been H3N2.

One of the things in the Pacific that we're trying to get off the ground is surveillance on board aircraft carriers in the Navy. And we can have more access to places like Singapore and those places, but that, again, is still in development.

Most of the European surveillance is done through the Army at Landstuhl and there were some technical difficulties and I wasn't able to get that information. Everything we've seen, which has been -- we've had several from Turkey lately; a few from England and Germany. They've all been H3.

And just a summary of our numbers are very similar to what you've already seen. We're seeing a big increase. It has been an early season, but it hasn't been anything particularly unusual in our experience and H3 is predominate across-the-board. We are expecting shipments from South America and Nepal

shortly, but we have nothing to contribute on that at this point.

We're just getting all our molecular work on line. We've got some nice new equipment and we expect to be able to start contributing more information and being able to compare that to the libraries that are set up with CDC and other places and contribute to that knowledge. But this is our program as we have it right now.

CHAIRMAN GREENBERG: Thank you and thank you for finishing quickly. Roland.

DR. LEVANDOWSKI: Actually, I have a question about the B strains. Are any of the strains that have been isolated by the military B/Victoria-like, particularly from the Pacific Rim or from Thailand?

DR. CANAS: Well, we've had very few and even those we had last year have all been very nice 184s, the Beijing.

CHAIRMAN GREENBERG: Dr. Kilbourne.

DR. KILBOURNE: What is the current vaccine coverage in the military? It used to be very complete.

DR. CANAS: It's considered to be 90 percent by all studies.

DR. KILBOURNE: So, in essence, when you're seeing the adenoviruses emerging, you've just subtracted flu, do you think?

DR. CANAS: Well, adeno -- of course, you know, we had an adeno vaccine that's no longer available, so that has just increased a lot but we are looking for both. But not too much in the recruits, we're not getting much flu. But in the population -- and the adeno is in the recruit population as opposed to the population at large and it hasn't translated into the civilian communities around them either.

CHAIRMAN GREENBERG: Okay. Any other questions? Okay, well let's move on to Dr. Hampson. And, Dr. Hampson, the same admonition.

DR. LEVANDOWSKI: Right. Alan Hampson is one of the directors of the WHO Influenza Center in Melbourne and he has some information about what's happening recently in the Pacific and the Southern Hemisphere.

DR. HAMPSON: Okay. Just very quickly to outline the collection of strains that we've had in the last 12 months or 13 months and just showing you our collection network, which is mainly Australia, New Zealand, and into Thailand and some lesser percentage of viruses from some of the Asian countries.

And just to show you quickly that in Australia and New Zealand, we have the typical temperate climate distribution of viruses. This one's in weeks. One in months. And during the course of this season, we've had Influenza A and Influenza B scattered throughout the season. Maybe a slightly increasing tendency towards Influenza B towards the end there.

Whereas in New Caledonia and Thailand, these are more typical of the tropical distribution where we see virus throughout the year. In the case of New Caledonia, we tend to see outbreaks occurring at sporadic intervals. Interesting this year, we've had two outbreaks of Influenza A. The first purely H3 and the second purely H1. And here's the New Caledonia strain Nancy was talking about and some later Influenza B.

And if we quickly have a look at the distribution of the Influenza As, the greater percentage have been H3N2 with a very small percentage of H1N1, again just paralleling what Nancy has told you. Then showing you that all of the H1N1 viruses that we have seen for the year fall into this Beijing lineage and are very well-inhibited by the antiserum against this new virus isolate that we achieved

earlier in the year, the New Caledonia strain.

And just to show you a difference table from minoesets from the Beijing virus showing this characteristic distribution of a number of minoeset differences. And these are persisting in very recent isolates, including some which we've just received in the last week from the Philippines.

With the Influenza Bs, the greatest majority of our strains have been the B/Beijing lineage. A very small number of B/Shangdong viruses.

Next.

And the important thing to note is that the only place that we had this B/Shangdong or the B/Victoria lineage of viruses from was Thailand. We didn't see it anywhere else in Asia. We had expected this year that we might. And, then again, it only occurred in the first part of the year and you will have noticed in that earlier graph that we've had quite a reasonable amount of Influenza B activity later in the year in Thailand and these were all B/Beijing/184 lineage. So this change to the B/Victoria strain has changed back again to 184-type of strains in Thailand.

Now our results with the Type B, the recent Type B/Beijing/184 lineage viruses has been

maybe just a little different from Nancy's in that the viruses that we're seeing are better neutralized overall -- some of the viruses are around fourfold down against the B/Beijing/184 virus antiserum. Certainly many of them are twofold down. A number of them are fourfold down against -- two-to-fourfold down against the Yamanashi antiserum. And in all cases these viruses are much better neutralized by two recent isolates, the South Australia/05 and Johannesburg/05.

And I've just put in the dendrogram to show all the ones marked in blue are our recent 1999 isolates and they are fairly closely grouped. The current vaccine strain, Yamanashi here, the previous vaccine strain, B/Harbin there, and the typical isolates that we're seeing now neutralized by these two antisera against B/South Australia and B/Johannesburg. So there is drift going on with those viruses.

And we've had a look at some post-vaccination seriological responses and we are seeing a significant reduction against viruses of this type in vaccines containing the Yamanashi virus. So we've got reduction in B/Johannesburg. These are younger and older adults here. And in the youngest here, but

not in the oldest here from Australia for some reason at this stage, we've seen a significant reduction against the new strain, the B/Shenzhen strain that Nancy referred to in her talk.

We are seeing an intriguingly different picture with the H3N2 viruses. I've divided them up here into low reactors. These are strains that are -- I'm sorry. That should say "low reactor" on this group here. These are strains that are fourfold down in reaction with Sydney antiserum. These are the standard Sydney-type strains which Nancy's already shown you. And we've selected some out which appear to be more strongly reactive with Moscow antiserum and with a particular monoclonal antibody that we use which differentiates the Moscow virus. So we have a much wider split of these viruses than Nancy showed you in her results.

And just to show you some selected results. These are not by distribution in terms of numbers, but just some selected results to show you the type of range of reactivity we get from strains that react strongly with all of our antisera. Just occasional strains which react extremely poorly, very low titers, with all of our antisera.

Now just to stress that most surveillance

is done with cell-grown viruses these days rather than egg-isolated viruses, we went back and took a number of the clinical samples for which we had these low-reacting strains and reisolated the viruses directly in eggs and made the comparison. And what you can see here is the cell-egg pair, or the egg-cell pair. We've shown it for both the type strain, the reference strain A/Sydney.

And you can see there is a difference there in reaction with antiserum. And, in fact, all the way down this column where the virus has been significantly low in its reaction as a cell-grown isolate with the Sydney antiserum, when we've grown it in eggs, the reaction is increased quite significantly. Many of these viruses are more reactive, as you will see, with the A/Moscow antiserum. So there seems to be some degree of influence here on the cell culture system having been used to isolate these viruses.

And I just put in one dendrogram here to show you with the A/Sydney virus at this point, virtually all of our recent isolates have fallen in this part of the dendrogram, close to the A/Panama strain which Nancy has mentioned and fairly well away from the Moscow/10 strain, which has also been

mentioned as a potential vaccine strain.

Now I don't expect you to be able to read this in terms of the difference table for the amino acids in these viruses, but what we did was to take a number of viruses. The ones marked in yellow are the ones that are normal reactors in our HI test. The ones marked in pink are the ones that are low reactors. And I've marked here three in red at the top which are extremely low reactors with A/Sydney antisera and our other antisera.

And just looking across at where we've colored the amino acid differences. And these are all common amino acid differences across these groups. There is absolutely nothing emerges, as Nancy said previously, to show a genetic difference that relates to this low reactivity. There is some intriguing difference here that's not explained by the hemagglutinin sequence.

But one thing we did do was to have a look at a number of these viruses and I apologize for the poor scan here of this electromicrograph. But it does show fairly dramatically what we did see. In a small number of viruses that we looked at where we took the very low-reacting strains, put them under the EEM. Took normal strains. And the thing that was

outstanding, we saw these huge aggregates of virus in the viruses that were low reactors. And I'm sure that Dr. Kilbourne will probably tell us that there's someting defective about the neuraminidase in these viruses which is giving us this reaction. We haven't been able to investigate that yet.

A quick look at the H3N2 strains. You will have seen at the bottom of one of Nancy's HI tables a virus known as the Philippines/26 strain which is reacting very, very poorly with the antisera raised against A/Sydney virus. These are just normalized to 100 percent in all cases. But some lowering with this Shanghai/42 strain which you mentioned. No lowering with the Moscow/10, in our hands. And lowering with a number of other recent isolates.

Now there has been mention made of the A/Moscow strain that was selected for vaccine production in the Souther Hemisphere. And it became a real rod for our backs when we tried to work on this strain because when we took the earliest reassortant that we had which was one made in Australia, this IVR-112, we found to our surprise that it had a dilution mutation and the adjacent amino acid change because of the triplet that are being cut out here in

antigenic site, in antigenic site B.

And just to go on with a number of reassortants that were made in the efforts to produce a suitable vaccine strain, as I'll show you in a moment, this correlated with antigenic differences. Essentially everything that we have seen from that virus in terms of reassortants has had genetic differences and fairly significant genetic differences from the wild-type virus.

We also did fine with the virus that we were working with. In fact, had changes from the original sequence that had been distributed by CDC. And, clearly, when we looked at our original sequences, we found evidence that these viruses were mixed. So this was a mixed population of viruses obviously throwing off mutants as it went.

And here's an example of two of these reassortants showing some difference in the reaction of their antisera that were produced against them, against the A/Sydney virus and clearly losing the advantage that had been seen here with the Moscow and quite dramatically seeing the change with a number of our recent low-reacting strains.

This Victoria/390 and Brisbane/156 are strains which we've used as markers when we found that

we had this genetic change in the virus to have a look and see whether it was having a significant effect. And it certainly was. It was certainly causing a significant reduction in the potence of the antiserum losing any advantage from putting that strain in the vaccine.

Next slide.

And, again, when we went on further and had a look at one further reassortment listed here to sera against that reassortant, seeing exactly the same sort of thing. Even though this virus did not have a dilution in it, it had other mutational changes. And so we did not come up with a virus that produced any sort of advantage seen with the original Moscow antiserum and maybe in part the breadth of reactivity of the Moscow antiserum may have due, and this is my speculation, to that being a mixed virus infection at the outset.

CHAIRMAN GREENBERG: Thank you very much. Roland.

DR. LEVANDOWSKI: I've got another question, if I can ask it. The experience with the Moscow strain, does that have any significance for what's being seen with low-reacting strains generally amongst the H3N2s? Is that sort of one example of

what may be going on elsewhere?

DR. HAMPSON: We haven't seen any evidence that they mixed in terms of their genetics. We have found a couple of strains which clearly are, one Philippino strain which had a very low reactivity which clearly had quasi-species in it. But the others we haven't and, now that you mention it, maybe we should go back and have a look a little more closely at some of those.

DR. LEVANDOWSKI: Well, I'm just wondering if that's state-of-the-art for H2N3 viruses today.

DR. HAMPSON: Possible.

CHAIRMAN GREENBERG: Diane.

DR. GRIFFIN: I was intrigued with the differences you saw between the cell-grown and the egg-grown viruses. And the vaccine is grown in eggs and those are egg-grown viruses. I assume most isolates are probably made in cells. And are most of the viruses used for testing in these wide variety of tests we're seeing grown in human, I assume these are human, cells?

DR. HAMPSON: No. They're MDCK cells for a canine kidney cell line that we grow the viruses in.

DR. GRIFFIN: They're MDC -- oh, I see.

DR. HAMPSON: The interesting thing is

that we retain our reference panels and this is uniform across the WHO system. Our reference panels are in-grown viruses with antisera prepared against those in-grown viruses because we are using these are the basis for looking for vaccine strains.

Unfortunately, the isolates that come to us are cell-grown viruses and sometimes when we go back and reisolate these viruses in eggs because they've looked interesting and looked like a vaccine candidate, we finish up with a virus which is different. The receptors on the cells, the MDCK cells, and the receptors on the egg embryo cells are different and there is a receptor-driven selection of influenza viruses. This may, in part, explain some of this low avidity reaction that we've seen, that Nancy described.

DR. GRIFFIN: I guess what I am really most interested in is what the virus is like that's actually from the person before it's isolated. You know, just because if there was any possibility that that was somehow different than the vaccine, that that might help explain some of the things we're seeing. Has anybody done direct sequencing prior to isolation?

DR. HAMPSON: Yes, they have. And the answer is that, generally, what we see in direct

sequencing is viruses that have the same sequence as the cell-grown viruses rather than the egg-grown viruses. And there was a proposal a number of years ago that, in fact, we should be looking at cell-isolated viruses as the starting strains for vaccine. And, in fact, there have been a number of meetings on that. It poses a number of regulatory issues which haven't been solved as yet.

CHAIRMAN GREENBERG: Nancy, you want to answer this specific issue, correct?

DR. COX: Yes.

CHAIRMAN GREENBERG: Nancy Cox.

DR. COX: We have been looking at sequences specifically for host-mediated changes since the late '80s when a lot of the data first came out where isolates were sequenced directly so a clinical specimen was obtained and the HA sequence that was sequenced -- was obtained directly from that rather than after isolation.

And so when we look at strains that are candidate strains, we're always keeping in mind what we know about host-mediated selection. And when we see that a virus that comes out of eggs that has a particular amino acid difference from the majority of strains that are circulating, we want to be sure that

we don't have an antigenic difference that's conferred by that change. This is always taken into account as much as possible.

CHAIRMAN GREENBERG: Dr. Kilbourne, is this directly on point?

DR. KILBOURNE: It's directly on the point.

CHAIRMAN GREENBERG: Okay.

DR. KILBOURNE: Because I think a very important consideration comes up here and that is that it is very arbitrary what we define as Moscow/10 or anything else. Will the real virus stand up? Because we're dealing in each instance with a heterogeneous quasi-species mixture and, out of our reassortment procedures, we will fish different variants. And I think it's hard to say whether those variants which seem to be artificants of reassortment are the true representative or not.

We go back to wild-type a lot. What is wild type? It's a mixture anyway. So I think it's, well not to overemphasize these differences unless we really show they're antigenically significantly different.

CHAIRMAN GREENBERG: Okay, last question is Dr. Couch.

DR. COUCH: Alan, that was a great deal of data in a big hurry. And between last night at 11:00 getting this and what you said, it's a little trouble here. Will you tell me, remind me, if Australia has had H3N2, or the Southern Hemisphere, H3N2 epidemics three years in a row as we did? And what your thoughts are about A/Moscow, low-reactivity strains and low aggregation as being a reasonable explanation for our third year in a row.

DR. HAMPSON: Yes, we've had A/Sydney for three years in a row. The outbreak this year was not quite so significant as the previous years. Last year was a very serious outbreak. This year was a moderate outbreak. And the preceding year we did have A/Sydney in the population. It was mixed at that stage with the previous strain A/Nanchang.

I'm perplexed by why we've had this virus repeatedly in the population. I don't understand it and we're still trying to come to terms with our findings here with these low-reactive strains and exactly what is contributing to this. It's far more dramatic than we have seen in the past, but it's more dramatic than what Nancy is seeing and so there's clearly some difference in our surveillance or our test system which is throwing this up a little more

than she is seeing at CDC.

CHAIRMAN GREENBERG: Okay. I'd like to move on to Dr. Zambon. And, Dr. Zambon, again, as expeditious as you can be.

DR. LEVANDOWSKI: Dr. Maria Zambon is from the Public Health Laboratory Service in London. And I think you probably have seen in the news that London, and England in particular, have been having a fairly severe influenza season. And we would be most interested to know about what's happening there.

DR. ZAMBON: Thank you very much. Just like in the United States, in the United Kingdom, we have a number of different measures of influenza activity. The one that we pay most attention to is based on sentinel physician recording from a sentinel physician network, which is based on monitoring some 800,000 to 1 million people in the United Kingdom and new episodes of influenza-like illness are recorded.

This is described as the RSGP, standing for the Royal College of General Practitioners, weekly consultation rates for influenza and influenza-like illness. Shown here is the last 10 years index and you will see that, in the United Kingdom, the way in which we describe our influenza activity could be described as arbitrary in some ways, but I hope you

will see what I mean when I describe a little bit further.

We know that our baseline for influenza runs to round about 50. And we describe anything in the consultation index below 50 per 100,000 as baseline activity. Anywhere between 50 and 200 we describe as normal seasonal activity in that we recognize influenza circulates every year. Somewhere between 200 and 400 we describe as higher-than-expected seasonal activity. And anywhere that's greater than 400 we describe as epidemic activity in order to reflect a severe year's worth of influenza.

The last time that we had a very serious influenza epidemic in the United Kingdom was the season for 1989-1990, which is also recognized worldwide as being a very severe influenza season. This year, 1999-2000, we would describe what we saw as higher-than-expected seasonal activity. And this peak here, which is now on the downturn, is probably a slight underestimate in that some of the figures obtained were obtained over the Christmas period.

Next slide, please.

The GP practices involved in influenza community surveillance, some of those GP practices which do the influenza monitoring clinically also

submit swabs to us and they are a very valuable source of isolates.

Next slide, please.

The distribution of those GPs reflects the major urban areas and the population density. The thing that we can say for this year, which is a reflection of some of the press activity that you may have heard about, is that the major consultation index, major consultations took place or the peak of consultations took place in the elderly, which is a reflection, therefore, probably, of impact on the health care system and hospital bed utilization.

Importantly, when we look at the isolates, our isolates are derived either from community sources or from hospital sources, about half and half, and we see different distributions. The hospital isolates come primarily from the elderly or young children, whereas the community isolates come from the bulk of the population, that is the young and middle-aged.

Next slide, please.

Our death data -- this is as up-to-date as we have -- suggests that we have, so far, a very similar season to last year, which was reasonably severe in death terms. We estimate in the United Kingdom that there are some 10,000 to 12,000 ex-

deaths associated with an H3N2 season every year. And last year, as you know, was an H3N2 season. This year, so far in the United Kingdom, it has been exclusively H3N2 and our death data look very similar to last year.

Next slide.

Now I won't spend too much time on this because many of the points have already been made. We see our viruses really, the majority of them, react reasonably well with Sydney/5, although we do have some low reactors. In general terms, where we have used Moscow/10 antiserum, we see slightly better reactivity with the Moscow antiserum, but maybe not enough to make a substantial amount of.

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The proportion of isolates with decreased reactivity, those fourfold or less to Sydney, has stayed relatively constant, I think, over the portion of the season that we've analyzed so far, and is rather similar to the proportion that we saw last year.

Next slide, please.

And, in sequence terms, the only reason for my showing you this is to perhaps point out, we've had a bit of discussion from the panel, the question

of vaccinated individuals who subsequently go on to develop influenza. I'd just like to draw your attention here to this strain, England/650/99, which has come from a vaccinated individual.

The only point that I would note here is that we do have an additional creation of a potential glycosulation which makes that virus slightly different to the others that we've looked at this season. But we have actually seen that virus strain circulating from individuals who have not been vaccinated. We saw that at the end of last season. So it makes the point very nicely that the viruses that you recover from vaccinated individuals, at least as far as their HA1 is concerned, may not be any different to what's seen circulating in the population.

Next slide.

And, indeed, when we look at our viruses, they are clustered very closely together and closely with other viruses that we saw towards the back end of last season.

Next slide.

We've had three Influenza B strains so far, all of which have come in late December or early January. And the HI data are, therefore, not what I'd

describe as robust in the sense that there's only been one HI test. We see, in general, that the viruses are Beijing-like, although this most recent virus in this single HI test shows a slightly reduced reactivity to the Beijing/184 and the B/Yamagata serum.

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Although when we actually look at the sequence analysis, we can see no reason why that should be particularly.

Next slide, please.

So, in summary, for the United Kingdom influenza surveillance, we've had widespread influenza activity over this last season. We've had predominately H3N2 strains circulating. Our clinical activity is all related to H3N2.

We've had one imported case of H1N1, which came from a lady who'd returned from a cruise in the Caribbean. And we would actually describe this as a New Caledonia-like strain, although we cannot get at it genetically for various technical reasons.

The majority of our strains are Sydney/5-like and we see a small percentage with reduced reactivity to A/Sydney/5 with a fixation of some mutation as compared to our '98 and '99 viruses. And we clearly do not have any molecular correlate for the

low-reacting strains that we see. We've had the recent onset of Influenza B circulation and a relatively small number of Influenza B viruses have actually been assessed. And I'll leave it at that.

CHAIRMAN GREENBERG: Thank you very much. Roland. Dr. Faggett.

DR. FAGGETT: Yes. In your data, your 1998 experience appeared to be below normal. How do you account for that dip in your numbers? Was it increased immunizations or --

DR. ZAMBON: Sorry, I'm not sure I understood the question. 1998 and 1999.

DR. FAGGETT: Your chart shows a below normal incidence of influenza. Did I read that correctly?

DR. ZAMBON: No, that's not -- you mean for the '98-'99 season?

DR. FAGGETT: Right.

DR. ZAMBON: No, that's not correct.

DR. FAGGETT: That dip in '98.

DR. ZAMBON: That's the '97-'98 season.

DR. FAGGETT: Right, okay.

DR. ZAMBON: So this is the '98 [illegible] season.

DR. FAGGETT: Right. Okay. Right. That

dip. How do you account for that? That's a very significant dip.

DR. ZAMBON: We had very little influenza circulating in that year. And, if I recall correctly, that was predominately an Influenza B season.

DR. FAGGETT: So there was no increased immunization or anything like that?

DR. ZAMBON: No. Rather like the United States, we've seen a progressive increase in the amount of vaccine put out, but what is clear in the United Kingdom is that we do not necessarily have data about how well vaccine is targeted to the at-risk populations. And where that has been looked at, we have some very disappointing figures to suggest that the at-risk population only 40 to 50 percent of those are actually receiving vaccines. So even though a lot of vaccine is going out, it's not necessarily getting to those that most need it.

DR. FAGGETT: Yes. We have that same experience.

CHAIRMAN GREENBERG: Okay. If there's no other questions, we'll move on to the last speaker before the break and that's Dr. Nerome.

Dr. Nerome, Roland will introduce you in a second, but, again, 10 minutes.