UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

VACCINES AND RELATED BIOLOGICAL PRODUCTS

ADVISORY COMMITTEE

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MEETING

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TUESDAY,

JANUARY 30, 2001

The meeting was held at 9:00 a.m. in the Versailles Rooms I, II, and III of the Bethesda Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland, DR. ROBERT DAUM, Acting Chair, presiding.

PRESENT:

MARY K. ESTES Ph.D.
STEVE KOHL, M.D.
KWANG SIK KIM, M.D.
ALICE S. HUANG, Ph.D.
ROBERT S. DAUM, M.D.
DIXIE E. SNIDER JR., MDD., M.P.H.
SAMUEL L. KATZ, M.D.
DAVID STEPHENS, M.D.
DIANE E. GRIFFIN, M.D., Ph.D.
AUDREY F. MANLEY, M.D., M.P.H.
PAMELA DIAZ, M.D.
BARBARA LOE FISHER
JUDITH D. GOLDBERG, D., S.c.D
WALTER L. FAGGET, M.D.

PRESENT: (cont.)

NANCY CHERRY
Executive Secretary

DENISE ROYSTER
Committee Management Specialist

CONSULTANTS PRESENT (voting):

PATRICIA FERRIERI, M.D.
EDWIN KILBOURNE, M.D.
MARTIN MYERS, M.D.

GUESTS PRESENT:

NANCY COX, Ph.D.
COLONEL BENEDICT DINIEGA, M.D.
MICHAEL DECKER, M.D., M.P.H
DR. LANCE RODEWALD, CDC
DR. WENDY KEITEL
DR. KEIJI FUKUDA, CDC
DR. ALEXANDER KLIMOV, CDC
MS. LINDA CANAS, DOD
MR. ALAN HAMPSON
DR. JOANNA ELLIS

FDA REPRESENTATIVES PRESENT:

DR. KATHRYN ZOON
DR. KAREN MIDTHUN
MR. ZHIPING YE
DR. ROLAND LEVANDOWSKI

MANUFACTURER REPRESENTATIVES:

DR. GREG SLUSAW, PhRMA
MR. JOHN O'BRYAN, EVANS VACCINE
MR. RICHARD HJORTH, WYETH

I-N-D-E-X

P-R-O-C-E-E-D-I-N-G-S

(9:05 a.m.)

CHAIR DAUM: Good morning, the meeting is officially in session. For people that don't like surprises, Dr. Zoon will not come at 8:15 to give plaques to retiring VRBPAC members, but will rather come about 9 o'clock.

So we will proceed with the Agenda and begin hearing about influenza issues, and then take a break before Dr. Zoon's presentation, and a photo-op, if you will, of the VRBPAC committee at the same time.

We will begin with the usual introductions of the committee. And, Dr. Snider, I can barely see you out there. Maybe it is my glasses, but we will maybe ask you to start, and we will go around the table and introduce ourselves.

DR. SNIDER: Dixie Snider, Associate Director for Science, Centers for Disease Control and Prevention.

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

DR. KIM: Kwang Sik Kim, Johns Hopkins.

DR. GRIFFIN: Diane Griffin, Johns Hopkins.

DR. HUANG: Alice Huang, California

Institute of Technology.

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

DR. MANLEY: Audrey Manley, Spellman College.

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

MS. FISHER: Barbara Loe Fisher, National Vaccine information center.

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

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

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

DR. GOLDBERG: Judith Goldberg, NYU School of Medicine.

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

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

DR. COX: Nancy Cox, CDC Atlanta.

DR. DECKER: Michael Decker, Aventis Pasteur in Vanderbilt University.

DR. LEVANDOWSKI: Roland Levandowski,

Center for Biologics.

CHAIR DAUM: And I'm Robert Daum from the University of Chicago. Thank you.

We will now move on to Nancy Cherry, who will advise us of conflicts of interest.

MS. CHERRY: Well, first of all I will comment that we are happy to have Dr. Daum as Acting Chair today. Also, you may or may not know that FDA is in the process of appointing industry representatives to each of the committees.

And, today, we have Dr. Decker acting as a guest, but in that capacity for our Committee.

My final announcement is for any of you that are parked at the public parking lots across the street where you feed the meters with many quarters, please be vigilant, because the Montgomery County's finest are also vigilant.

The following announcement addresses conflict of interest issues associated with the meeting of the Vaccines and Related Biological Products Advisory Committee of January 30th, 2001.

Based on the agenda made available, it has been determined that the committee discussions for the influenza virus vaccine formulation present no potential for a conflict of interest.

The Director of the Center for Biologics Evaluation and Research has appointed Drs. Theodore Eickhoff, Patricia Ferrieri, Edwin Kilbourne and Martin Myers, as temporary voting members for the discussion on the selection of strains to be included in the influenza virus vaccine for the 2001-2002 season.

And I would add that we are sorry that Dr. Eickhoff could not be with us today.

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 any current or previous financial involvement with any firm whose products you wish to comment on.

And I will now turn it back to Dr. Daum.

CHAIR DAUM: Thank you, Nancy. I think we will move, without further ado, right into the topic of the day, the strain selection for influenza virus vaccine.

And we will begin with a trilogy of presentations that may be broken, as I mentioned by plaque presentations and photo ops. And we will call on Dr. Levandowski of the FDA to introduce us to the topic, and present us some information about what has happened since last year.

DR. LEVANDOWSKI: Thank you, Dr. Daum. I would like to welcome everybody here to this meeting. And, as usual, there is lots of excitement, not the least of which is getting all of this together.

We are trying to present, or use, some new technology here, and hope that this is going to work. However, if our power point doesn't work I think everybody is prepared with either slides or overheads to back this up, so we will just dive in and get started.

As everybody knows we are here today to begin the process of selecting the influenza virus strains that are going to be included in the vaccines prepared for 2001-2002 in the United States.

The question to be answered by the committee is shown on this slide, and it is the same one we ask every year, and that is, what strain should be recommended for inclusion in the inactivated vaccine for the coming year.

In formulating an answer to that question I think it is helpful to review a few facts about the currently approved inactivated influenza virus vaccines. Inactivated influenza vaccines act primarily to induce the production of antibodies.

The hemagglutinins and the neuraminidases of the incorporated influenza virus in current vaccines are concentrated, and partially purified, to remove extraneous material derived from the eggs in which the vaccines are produced.

Although antibodies to both the hemagglutinin and the neuraminidases may be protective, influenza virus vaccines are standardized currently only for the content of hemagglutinin.

And, therefore, the greatest emphasis is placed on the viral hemagglutinin and in the selection. However, the neuraminidase receives consideration since it, too, may add to the protective efficacy of vaccines.

Since the use of the first inactivated vaccines in the 1940s, it has been very clear that one of the most important predictors of vaccine efficacy is the match of the vaccine virus with the influenza viruses that are causing infections.

What has also been made clear, with yearly

epidemics and pandemics, is that influenza virus have great scope for antigenic diversification.

Ongoing random mutations of the hemagglutinin and the neuraminidase, which we refer to as antigenic drift, and exchange of entire genes with other influenza viruses that we refer to as antigenic shift, both participate in influenza virus evolution.

It may also be helpful to the committee's deliberations to consider answers to the questions shown on this slide. Most importantly it is necessary to know if new influenza virus is revolving in nature.

An extensive global network exists to collect and analyze information, throughout the year, as we are going to hear shortly, from colleagues at CDC and other national and international institutions, this morning.

When new viruses are identified, and they almost always are, the extent of geographic distribution helps to judge the urgency in changing the composition of the vaccine. Often antigenic variants appear, but sometimes they are dead end branches on the evolutionary tree.

As we've seen in the case of some influenza B viruses in Asia, in the recent past, they may even be spread in a geographic location without

subsequent globalization of those strains.

Of course we have seen, also, just the opposite with influenza A viruses transported freely and rapidly across hemispheres by modern travel habits.

If new strains can disseminate widely it is useful to know whether current vaccines are likely to produce some measure of protection. If it appears that current vaccines could be suboptimal, then it is still necessary to consider whether there is a strain that is suitable to permit large scale manufacture of vaccine within the perennial constraints of time.

We are prepared to assist, this morning, by supplying information in each of these areas. Customarily there is a brief review of the previous year's experience.

However, this year we are going to expand on the review of the production year just past. As everyone is, undoubtedly, aware there was a serious and unprecedented delay in distribution of influenza virus vaccines in the United States during the production season that is just ending.

It is now possible to state with certainty that the amount of vaccine produced for distribution in the United States during 2000 was similar to the

amount produced and distributed in 1999.

However, by all reports the disruption to the accustomed schedule for use of influenza virus vaccines in the fall months has been severe. Even though there appears to be sufficient vaccine to supply the existing demand, the lack of vaccine at the time it was expected for use, in effect, was perceived as a shortage.

And just as it takes months of planning and effort to make the vaccine, it also takes a huge effort, and many weeks, to administer more than 70 million doses of vaccine in this country.

This slide helps to demonstrate the magnitude of the delay. And to give some perspective, here, the data are included for 1998 and 1999 when similar total amounts of vaccine were produced.

The data are presented here as the cumulative percent of the total amount of influenza virus vaccine that was submitted to the Center for Biologics Evaluation and Research for testing and release.

The green bars here are information for 1998. The blue bars are information for 1999, and the red ones are the information for 2000.

What you can see is that in all three

years, in June there was some vaccine that was produced for release, or it was prepared for release by that time.

However, more than 50 percent of the vaccine was prepared by August in both 1998 and 1999. While the 50 percent point was not reached until October in the year 2000.

You will note that October is also the month when nearly one hundred percent of the vaccine had been prepared in 1998 and 1999. That one hundred percent point was not reached until the end of November, to the beginning of December in this year, in the 2000 season.

In effect it took about six to eight weeks longer to prepare vaccine. And nearly 50 percent of the vaccine was ready for market only after October and November when most practitioners and recipients are now very well accustomed to using vaccine in accordance with recommendations from the Advisory Committee for Immunization Practices at CDC.

The causes of the delay have been reported previously, and I've listed them here. Although there have been several other instances in which one or another vaccine manufacturer experienced an event that delayed manufacturing, there has never been an

occurrence when three of the four licensed manufacturers were delayed at the same time.

I think that is the real answer to what happened during this past year.

At two of the manufacturers, Parkdale Pharmaceuticals and Wyeth deviations from good manufacturing practices were discovered during FDA inspections of facilities.

One of those manufacturers, Wyeth, was able to make corrections in time to permit production of vaccine. Although the vaccine distribution began late in 2000.

The other manufacturer, Parkdale, was not able to complete their corrections in a timely manner, and they withdrew from further production.

Another manufacturer, Aventis Pasteur, experienced early difficulties with one of the two new viruses included in the vaccine. And I want to emphasize that there were two new strains that were recommended for the past year.

I think that sometimes has been missed in some of the reports, or some of the conversations.

Although the A/Panama/2007/99 strain grew quite well in eggs, the early yield through the process, as is often true for new strains, was low.

However, as is usually true for all manufacturers of influenza vaccines adjustments were made in handling the virus, and eventually satisfactory yields were obtained.

Unfortunately manufacturing is not only labor, but it is also time intensive. And time lost is just simply not regained. During the months that followed the recognition of the situation, FDA, CDC, NIH, and the manufacturers all worked together to develop strategies to minimize the impact of the delay, and to maximize the production and use of vaccine.

In order to give a further explanation of the public health service activities that went on, I'm first going to present some additional data on production.

Following that, Dr. Lance Rodewald, from the National Immunization Program, will discuss some of the CDC activities related to vaccine supply and distribution during 2000.

And, finally, Dr. Wendy Keitel of Baylor College of Medicine in Houston will discuss clinical studies that were sponsored by the National Institutes of Allergy and Infectious Diseases during the past year, to re-evaluate dose response of inactivated

influenza virus vaccines.

This slide shows an abbreviated version of the influenza vaccine production cycle. And here I've placed the vaccine use at the top of this little pyramid, since that is what most people see from the production effort.

What is not always obvious for everybody is that there is a continuous effort and a lot of work that goes on to support the preparation and use of the vaccine. And that is what is shown in blue and in black at the bottom of the slide, here.

Working down from the top, the vaccine can't be distributed until it is produced, obviously. Trivalent vaccine is formulated, however, from monovalent components that are produced individually from virus strains having different optimal conditions for growth and purification.

The amount of trivalent vaccine is limited by the poorest yielding strain, as is often pointed out to us by manufacturers. So a great deal of their effort goes into development of seed viruses.

The seed viruses are proprietary for each manufacturer, and they are produced by carefully controlled consecutive passage and eggs. Although each seed virus is unique, all seed viruses are

antigenically identical to the referenced strains from which they are derived.

Those referenced strains are recommended by the actions we are undertaking here today. And although the recommendations occur somewhat point events, they really are supported by all that shown below on the slide, here, underneath the recommendations occur at specific time intervals.

But the activities to support that are going on, basically, continuously.

Manufacturers use only strains consistent with the recommendations. But it is sometimes possible to have more than one choice, either from different appropriate wild type viruses, or from multiple high-growth reassortent viruses that are produced specifically to support manufacturing of vaccine at large scale.

The global activities needed to prepare for the recommendations in northern hemisphere countries in January through March, and in the souther hemisphere countries in September through November, help to focus attention and to smooth out the vaccine preparation in many ways, mainly by forcing us to get busy.

Well before the recommendations are made,

however, surveillance by CDC and other WHO laboratories identify potential new reference influenza viruses, and it is possible to explore the potential of those new strains for use in producing vaccines well before any of the committee meetings occur.

This slide shows the most recent recommendations. The recommendations on the left are the ones that were made by this committee for the 2000 production year. And the recommendations on the right are those that were made by the World Health Organization for the 2001 production year in the southern hemisphere.

Please note that the recommendations for the H3N2 strain, and the H1N1 strain, which were new for the 2000 vaccine in the United States, are the same as those recommended for 2001 in the southern hemisphere.

In fact the WHO recommendations for the southern hemisphere in 1999 that preceded our 2000 recommendations also included an A/Moscow-like and an A/New Caledonia-like strain.

The current effective recommendations differ only in the B strain, which has been updated in the southern hemisphere to include a newer strain, the

B/Sichuan/3799 strain, and the actual strains that are being used for manufacturing right now are the B/Johannesburg 599, and the B/Victoria 504/2000 strain.

This slide shows the timing by month of the year of distribution of strains for the last five new strains that were recommended by this committee since 1998.

The blue filled squares denote reference viruses that were distributed to manufacturers, and the red filled squares denote potency reagents that were distributed for vaccine manufacturing.

The little yellow bars in between indicate the months during which strain recommendations are mad in the United States, just for reference.

What you can see from this slide by Gestalt is that for the two new strains that are recommended for 2000, distribution of the referenced viruses and the potency reagents was as early, or earlier than for previous new strains.

For the A/Panama/2007/99 recommendation four newly prepared high growth reassortants with hemagglutinin and neuraminidase from the A/Panama/2000/799 virus were distributed to manufacturers by the end of January.

The reassortant viruses that were named NIB41, NIB42, Resvir 16 and Resvir 17, were examined carefully by manufacturers, and the strains selected for use, which is called Resvir 17, was chosen by manufacturers in the United States and Europe as the best one of the four available for manufacturing on the basis of the growth and the yield in small scale purification.

However, it should be noted that manufacturers can get an accurate forecast of yield only when the specific potency reagents are made available. And in the case of the A/Panama/2007/99 strains, the reagents were not available until May of 2000.

This slide shows some of the intensity of the work in developing new seed viruses for current vaccine strains during the first year the strains were included in the vaccine.

So for the A/Panama, and A/New Caledonia strain, those were first used in the year 2000, and the B/Yamanashi strain was first used in 1999.

What I'm showing is an overlap of those years just for comparison as to what happened during the actual calendar years.

The red bars here indicate when the

A/Panama/2007/99 seed viruses were submitted to the Center for Biologics for release. And what can be seen is that work to develop the A/Panama seed viruses was completed earlier, and over a shorter time interval as compared to the either the A/New Caledonia, or the B/Yamanashi strains.

What this suggests is that overall optimization of the A/Panama seed virus was not unusual difficult over all, it just takes time, as it always does for these things.

And I think it is important for people to recognize that this also doesn't happen just at one time point, it occurs over a period of time that there is work going on to make improvements continuously.

This slide provides information on the production of monovalent vaccine components during 1998, 1999, and 2000. The results are presented as a percent. Each monovalent type represented out of the total number of monovalent lots that were submitted for the particular calendar year to the Center for Biologics.

The results that are shown in light blue, you probably can't see it at the back, indicate the strains that were new within the given calendar year.

So in 1998 A/Beijing and A/Sydney were

new, and in 1999 B/Yamanashi was new, and in 2000 A/New Caledonia and A/Panama are new strains.

Although there might have been some early difficulty with the A/Panama strain, the data overall did not suggest an unusual difficulty with this A/Panama strain, as compared to other strains, either within the same year, or compared to the previous two years experiences with another H3N2 strain, the A/Sydney/597 strain.

In fact, if you look a it, in all three years more effort, that is, more total lots of vaccine manufactured ultimately went into producing either the H1N1 influenza strain, or the influenza B strain that was needed for producing the influenza H3N2 strain.

This isn't to minimize that there are difficulties with all these things, but it does show that some of the time, here, was not really -- it was not universal for all of the manufacturers.

This slide shows the number of trivalent lots that were submitted for release to the Center for Biologics over the past decade. And what is obvious is that vaccine production has been increasing by approximately two-fold over the decade.

In 1990 it was probably equivalent to approximately 40 million doses. And more recently

that equates to about 80 million doses per year that have been manufactured.

More directly relevant for today's discussion, now that manufacturing has been completed for the 2000 year, the number of lots of vaccine produced for 2000 compares very favorably with the total produced for the year before.

So, in summary, I think what we can say from this experience is that we can expect that there are going to be delays of shortages of production, delays occur at multiple manufacturers at one time.

And this really points out the need for having multiple parallel streams of product. The constraints of time and the need for all events to fall into place make production of influenza virus vaccine a delicately balanced system that requires great collaboration between the government and industry.

Temporary problems with the new vaccine strain and time needed to implement good manufacturing practices both contributed to the delay and distribution of vaccine in 2000.

And significantly these events have led to one of the affected manufacturers to withdraw from producing influenza vaccine.

In most other ways, however, the experience in 2000 was really pretty typical of influenza manufacturing, generally, with all of the usual kinds of stresses.

And I will stop there and ask if you have any questions or comments.

CHAIR DAUM: We have something unusual, on my experience on this committee, is we have the luxury of some time.

Would anybody like to ask some questions of Dr. Levandowski before we go on? Dr. Kohl?

DR. KOHL: Could you specify what you mean by problems with good manufacturing practices?

DR. LEVANDOWSKI: Well, there are procedures and processes that are put into place that are, if they are used, will guarantee that there will be consistency in manufacturing, and that the product that is manufactured is wholesome and meets all the requirements of a product under licensing requirements in the United States.

DR. KOHL: That is not quite the answer I was looking for.

This is a process of producing influenza vaccine, is not a new process, it is something that has been going on for many years. And I presume it is

roughly the same process every year.

What was special about this year that two companies had problems that were severe enough to stop their production?

DR. LEVANDOWSKI: Well, what I can say is what I had stated before, I think. That there are -- there were deviations from procedures that are put into place to ensure that the product is made in a consistent manner, and that it does meet all the standards for purity, potency, and so on.

I am afraid that is probably all I can say.

CHAIR DAUM: Dr. Katz, welcome Dr. Katz, you didn't get to introduce yourself earlier.

DR. KATZ: Well, I was at the meeting yesterday, and I mistook the beginning of time this morning.

I wondered what efforts or progress have been made in getting away from production in ovo, and getting into an in vitro system for production of virus and vaccine?

DR. LEVANDOWSKI: Globally there has been quite a lot of interest in production of vaccines and tissue cultures, and also by methods that would avoid, or would be more similar to making a purified protein.

Those are in development. When those might become realities is unclear. There are a whole set of issues that are related to cell substrates, issues that are related to safety parameters, and issues that are related to having a setup that will, in terms of the viruses that are required to make the vaccine, they still need to have seed viruses.

For example, the tissue culture system for making vaccine, all of those things need to be put into place and worked out.

And there is, I guess what I can say in the general sense, is that there is an awful lot of work going on looking at that, to see whether that has any advantages, either in terms of efficacy of vaccine, or in smoothing out production of vaccine. And it is going on around the world.

CHAIR DAUM: Dr. Snider?

DR. SNIDER: Yes. Roland, could you tell us if Parkedale has made public their intentions with regard to producing influenza vaccine in the coming year, and the amount of doses that they normally produce?

Or if you can't, is there a company representative who could tell us that?

DR. LEVANDOWSKI: I don't know if there

are any company representatives in the audience this morning. But what I can say is that Parkedale has made press releases that indicate their intention is not to produce influenza virus vaccine.

And I believe I've also seen press releases discussing what actions they would take to discontinue all of their activities in that regard.

CHAIR DAUM: I guess the follow-up question that is sort of implicit in what Dr. Kohl and Snider are hinting at, is how do you see what the occurrences this year as impacting long term issues of vaccine supply, and having enough manufacturers to ensure an adequate flow of product in a timely way?

DR. LEVANDOWSKI: Well, I think that it points out what we already knew about the system. And we use the term fragile, it really is a very fragile system.

We ask these manufacturers to do what is really a very difficult task. They basically have to make a new vaccine every year. And this product has become very widely available, and really very relatively inexpensive.

Quite honestly it doesn't make a lot of money for manufacturers. And in that sort of situation I think what we've seen for pharmaceutical

products, generally, is that if they are not profitable, the companies really have other incentives to move on to something else.

I think that is the concern. And this is not new in terms of companies making decisions to remove themselves from manufacturing inactivated influenza vaccines.

The technology is old, but it still is a fairly expensive activity, or venture to get into the market, and to have to start up and meet all of the requirements that we expect for modern vaccines.

And just because of all those difficulties, the relatively low profitability, as compared to other things, other exhibits of companies that left influenza vaccine production are really numerous.

There are probably more manufacturers that have quit making influenza virus vaccines than are still making those vaccines. And I can name some other companies like Merck, Letterly, Lilly, and there are probably a few more. Merrill National was a company that eventually became a company that is still in existence, but this is really quite an important issue that needs to be addressed.

And I hope that we can address it fully

here this morning, to tell you the truth.

CHAIR DAUM: Other questions?

DR. KILBOURNE: Could I make a comment? Maybe it is appropriate for later rather than now. But I think we may be becoming a little obsessive about how good an antigenic match we have to have.

After all we are talking about drift. And if we look at some of the data I have seen in this material furnished, if you compare the AN1 strains, the New Caledonia, and the Beijing 262, which was used for about four years, the coverage as reflected by vaccine response is not all that different.

I wonder whether one of the things we should consider is whether in a year where it is obvious, early on, that there are production difficulties, we might relax a little bit on the strictness of the antigenic demands here.

CHAIR DAUM: Do you want to comment on that?

DR. LEVANDOWSKI: Well, I think I would just restate what I stated to begin with, and I think Dr. Kilbourne was maybe involved with the FM1 strain was the strain that led to initiating all of these activities, recognizing that antigenic drift could make vaccines relatively ineffective.

DR. KILBOURNE: Well, that is a unique situation, as far as I've been able to tell, and I'm putting together a paper on that right now, in that the magnitude of change in four years, there was something greater than we've see since.

Whether Nancy would argue with that or not I don't know.

CHAIR DAUM: Thank you, Dr. Kilbourne, thank you Dr. Levandowski. I think we will move on at this point, and hear from Dr. Lance Rodewald, Director of the Immunization Services Division, the National Immunization Program at CDC. Welcome.

DR. RODEWALD: Thank you, and thank you for the invitation to come and speak about some of the programmatic responses that we had towards the flu supply problems this year.

I'm in the Immunization Services Division at the National Immunization Program at CDC, and we are the main programmatic arm of the Immunization Program. And so we do the lion's share of our work is with routine childhood vaccination, so this is a little bit different.

The scope of my talk will be to talk a little bit about what we were worried about, what was done by Public Health Service and CDC, and others, and

then what has happened so far, from our perspective, and some of the programmatic lessons that we've learned, and continue to learn.

The basic chronology we had is that if you look at the one year time line from January 1st through December 31st of this year, is the notification in mid-March of CDC possible enforcement actions, leading to the recognition that there may very well be not only a delay, but also a severe shortfall in the number of doses that will be produced.

There was an MMR, MMWR, announcing the delay with the possible sever shortage of vaccine production. And then there was the ACIP recommendations for the delay scenario.

So it was recognized that there would not be a major shortfall between the middle MMWR and the ACIP recommendations, but that the delay would definitely occur.

What we were mainly worried about, of course, are death and disease, and hospitalizations from influenza. For each million doses that were not given to elderly patients, this would translate into 900 deaths and 1,300 hospitalizations.

The estimates of supply from the FDA were

not reassuring, as I mentioned earlier, and as Roland had mentioned. And we are also worried that the vaccine supply is a bit dependent on the manufacturer, because they had different timings of when they came to market.

And so if I was in a nursing home, for example, depending on which manufacturer, I may have my vaccine earlier or later in the season. And, of course, the other thing is that this is primarily, and almost entirely, a private sector distribution, manufacturing and distribution system.

The other thing that we are worried about is how do we target vaccine in case there is a shortage, how do we really make sure that vaccine is given to those at highest risk of death and hospitalization.

I would like to talk a little bit about what was done, and I would like to go over six points. Number one is after, and basically remember that there is not a large adult vaccination infrastructure, public health infrastructure, it is largely a private system.

One of the things that we did is to communicate with our partners, the federal agencies, of course, and Dr. Levandowski had weekly conference

calls with the CDC where he indicated what the most recent and current information was about the vaccine supply.

We had conference calls with public health and private provider organizations. For example, the Association of State and Territorial Health Offices, the American College of Physicians, and other provider organizations.

We purchased a guarantee of a production of more vaccine, and I will get into that in a moment. This is the nine million doses of vaccine that we guaranteed production of.

We developed a website, I will get into that in a little bit, for exchange of information, and possible exchange, facilitating exchange of vaccine. We had some new knowledge generation to help with this season.

We created, based on the new knowledge, some good practices material, and we conducted a media campaign.

The federal contract for influenza vaccine production, I will talk a little bit about the time line for that, we contracted for the production of nine million doses of influenza vaccine, and these were doses that would not have been made available

without the contract.

This was, in other words, doses of vaccine that were produced in excess of what was planned by the companies.

The availability, we could not get vaccine that would be available prior to mid-December in 2000, so this is really late season vaccine, and safety net vaccine in case there was a sever shortage.

The prices turned out to be, through the contract, three dollars for public sector, five dollars for private sector. And, significantly, there was a public health priority on the purchase of this vaccine.

The purpose of the public health priority was to implement the AICP's targeting policy, and the purchase was done by application only. The applications were reviewed, ranked and prioritized by an algorithm that basically discussed, of this purchase, what percentage do you think will go to high risk patients, those at greatest risk of death, and hospitalization. The applications were made to Aventis.

The chronology here, if you take a look at the basic chronology that is on the bottom, and then the yellow bars here indicate where the funds were

certified to procure the production of the nine million doses.

And between that and the red bar, later on in the season, the red arrow later on in the season, at the time the funds were certified, there was still the distinct possibility that there could be a serious shortfall in the number of doses of vaccine.

And this prompted the purchase, and really sort of forced the purchase of the safety net vaccine, in case there was a serious shortage.

Between that yellow bar and the next red arrow, it turned out that there would not be a serious shortfall if you add in the addition of the nine million doses.

The website started taking orders, where you see the middle yellow bar, and vaccine began shipping on time in mid-December.

The website that we developed really indicated several things. One of them was -- the purpose was to indicate vaccine availability as the season progressed. The intent was to link providers with vaccine, to those without vaccine, knowing that there was going to be an unevenness in distribution.

The website was for information only, because this was not a site where we would sell

vaccine. Vaccine was available from either manufacturers, or wholesalers. This vaccine was put on the website.

There were also links to states that were willing to redistribute vaccine within their state. And we were pleased that all states agreed to provide contacts for redistribution of vaccine, in case that became necessary.

Initially when the site went up there was no vaccine on the website, and then later on the vaccine from the nine million doses went up there. We had anticipated that the website would become more valuable as the season would progress.

The second component of the website was information, links to the ACIP, and MMWR statements, links to news, surveillance information, and other things.

And then the third part was to provide helpful material for providers. For example, brochures to discuss flu vaccination with their Petitioners, which I will get into in a moment.

There were two pieces of new knowledge that we worked on generating this year. There were provider based studies conducted by Gary Freed and his colleagues at the University of Michigan, that

included focus groups of family physicians, and internists.

And this was followed by the focus group driven quantitative survey of the same two groups. We wanted to find out what it was that providers could look to CDC for during this flu season, and also to look a little bit at their capacity for targeting vaccination.

One of the things that we found out, from many of the providers that this survey was conducted, right around October 1st was the midpoint of the quantitative survey.

And what we found out is that many of the providers who had gotten limited shipments of their vaccine, had implemented a targeting policy, although this was challenging.

Also we found out that only one-fourth of the physicians, with no difference between family physicians and internist, really had ability to target vaccination through reminder and recall systems.

We also did studies, these are focus group studies, targeted at the general public. And the intent on this was to understand some of the barriers to vaccination, and some of the motivating factors for vaccination.

And one of the things we found out, we found out several things, that in the public's eye there is a very discreet vaccination season, and if that is missed, that is going to be problematic.

There was a real non-perception of self-identification of high risk. A 70 year old would say, that vaccine can't be for me, I'm healthy, it is really for the frail elderly, and I think there is a lot of merit to that, to feeling healthy, and not feeling like I'm a frail person.

There was a real willingness for all patients, adults, young adults and elderly adults, to protect others through vaccination of themselves. So if they said, well I'm not really particularly at high risk, because I'm healthy, but I'm willing to be vaccinated in order to prevent me from catching the disease and transmitting it to somebody who is at high risk.

We developed several one page brochures for physician use. These fliers, as Gary Freed told us, were very desirable, according to the physicians in the focus group in the surveys.

The messages for these were developed through the public focus groups about barriers to get vaccinated, how to overcome them, what were some of

the motivating factors.

Three brochures were finalized and distributed it. And they identified, number one, how can we identify, am I at high risk and do I need to be vaccinated, either for medical reasons, or for age related reasons.

The second brochure was a reminder not to delay getting vaccinated if a patient is at high risk. And the third was to reinforce the idea that one individual's vaccination protects not only him or herself, but also protects others who need to be protected.

The brochures were made widely available through HCFA's peer review organizations, provider organizations, and internet distribution.

The media campaign was conducted by Harrison, Maldonado and Associates. The target audiences are listed here, African-American individuals, Hispanic-American individuals, and the general population.

The outlets were through TV, radio, and transit ads. The materials that were developed were made available to partner groups through the same channels that we had the brochures made available, and there was a two phase campaign that was conducted.

In mid-November the message was to help identify those that were at risk of serious disease, to self-identify, and to make sure that they seek vaccination.

And the second part, that was conducted in December, was a remainder that it is not too late to be vaccinated, keeping in mind that there will be a distribution of vaccine, and that the delay doesn't mean that you don't want to have vaccination conducted later into the season.

I would like to go into a little bit of what happened so far. Of course, as the FDA predicted, and with -- I think their timing was practically down to the nanosecond, the delay was very much as they predicted.

The media campaigns were conducted, and they were conducted on time. As Roland had mentioned, the total vaccine supply was similar to last year. This time related shortage really occurred, and time related shortage really occurred.

And time related shortage is, if I need the vaccine today, and I don't have it, a delay is a very uncomfortable feeling, it is really a shortage in time.

The variation on timing and order

fulfillment was very problematic this year. One of the common complaints that we had heard is that there is a grocery store, or a drugstore that is conducting a campaign over here, yet I'm a pulmonologist, and I can't get influenza vaccine for my patients.

This was brought home several times, and in several different ways to us, this variation in timing of order fulfillment was very problematic, and this led to many upset immunization providers.

Many vaccination campaigns, as Roland had mentioned, were delayed and some were canceled. And the spot vaccine prices rose and fell. Third party redistributors of vaccine charged higher prices in the midseason, and then these prices fell, again, as vaccine became available when the delay was being resolved.

The vaccine that we procured production of, with Aventis, was available on schedule, but it did not sell well. And I would like to indicate this a little bit here. One of the things between the extremes of the yellow arrows here, is an indication of the inelasticity of the pipeline, where it takes a certain amount of time that really can't be shortened, between procurement of production, and actual shipping of vaccine.

And so even though this was safety net vaccine, it would have been more valuable had it been available early in the season, but that is really not biologically possible.

Again, the CDC procured vaccine was safety net vaccine. There were many orders of intent to purchase when the website went up. These, of course, were prioritized by the algorithm, and the peak ordering was 4.5 million doses of an intent to purchase.

But those who purchased were allowed to not follow through on the order if, for example, we had discouraged people from double ordering vaccine, or ordering sort of a security or safety net vaccine, in case their order didn't come through from the delay.

But we think that really happened a fair amount this year, because most of the 4.5 million doses that were ordered were canceled. Purchasers could withdraw intent. The total that we have sold and distributed so far is 1.5 million doses, or 16 percent of the nine million doses.

There are a large number of programmatic lessons that we have learned, and are learning, and I'm sure that we are going to continue to learn, and

I suspect I'm going to learn a fair amount today, also.

Number one, this is something that you all know, and know very well, and we are learning not only for this vaccine, but perhaps for other vaccines, is how fragile the vaccine supply really is.

The second lesson is that vaccine must be available on time in the public's eye, and the tremendous amount of time it takes to plan campaigns, and plan immunization events of delayed vaccine is very problematic to deal with.

The third major lesson is just how completely private the system really is. I mean, if you take a look in contrast with, for example, CDC's childhood immunization program, where approximately 50 or so percent of the vaccine goes to federal contracts, a very small amount of the vaccine for influenza probably one or two percent goes through federal contracts.

The distribution itself is also private. Third party distributors are very prominent in there, and they develop clientele lists, and usual customers, for who gets their vaccine.

Many of the distributors, and some providers, have early contracts, contracts may be

being made this month, next month, and into March. These early contracts sometimes have penalty clauses for failure to deliver the vaccine on time.

And if the -- for example, if the vaccine is going to be delayed, if it is not going to be delayed, usually the penalty clause is not going to be an issue.

But in a delay it makes it very difficult to consider trying to redistribute vaccine to those in greatest need.

Physician ordering behavior is probably going to be difficult to change. Again, there is sort of a routine ordering, going back to the same distributor, and it may be difficult to really change habits to order earlier, or to have more influenza immunization providers. I think there is going to be a lot of challenges there.

We had very limited ability to influence a private market. And we think that one of the other lessons is that we need to engage private sector much earlier, and as early as possible, as we can do that.

Vaccine demand, of course, is time sensitive, and that is sort of the theme of this talk. And I think in Roland's talk, also.

Matching supply and demand is very

difficult. For example, right now, there is a surplus of vaccine.

Another lesson that we are learning is that targeting vaccine is difficult, and requires change in behavior on provider parts. It is also going to, probably, require state and local public health infrastructure to help target vaccination efforts to steer vaccine to get more involved in immunization programs, and to help create the demand in the right time, for the season.

Private sector capabilities that are currently not available will also be required. With only 15 percent of physicians being able to implement, identify patients at high risk of, and recommended for vaccination, that leaves 75 percent of the providers without that capability.

And, of course, that is very problematic for targeting efforts. And a major lesson that is learned, and I think was not a surprise lesson, is that effective communications are critical.

I would like to leave you with one last set of thoughts. And we were fortunate, this year, for several reasons. Number one is that we did not have an early influenza season.

Of the last 18 seasons four of them peaked

in December. And so we are lucky that that didn't happen this year. The time sensitive shortage, if there was an early season, would have had much more impact on hospitalizations and death.

The total supply this year, we are fortunate because the total supply this year was similar to last year. Had we had a severe shortage there would have been much, much more difficulty.

And, of course, we are fortunate because this was not a pandemic year. I think you can imagine what would have happened if this was a pandemic year.

And with that I would like to stop and I would be happy to try and answer questions, if possible.

CHAIR DAUM: Thank you very much, Dr. Rodewald, for an informative presentation. We will take a few questions. Dr. Fagget, welcome. You didn't get to introduce yourself.

DR. FAGGET: Walter Fagget, private practice here in Washington.

Lance, really an outstanding report. And I just want to say, from the private practice sector, that we really appreciated the outstanding job that CDC did.

And I think it points out, as you say, how

important effective communication is in a timely fashion. Your information did help us get the word out to colleagues and patients very well.

My question, you mentioned the private -- the public health and infrastructure, state infrastructure. How responsive were they in terms of, and how helpful were they in getting the information out, and how much was available to you nationally?

DR. RODEWALD: That is a very good question. One of the -- if you take a look at, for example, our 317 grants program to states, a very small percentage, it is by and large a childhood program. Very small percentage of that goes for adult vaccination program.

The state immunization programs try to help, as much as possible, and do as much as they could do with the limited resources that they had. For example, all states really provided a contact information, and telephone coverage for redistribution of vaccine, should that become necessary.

But the real work of communicating with providers, making lists of all the nursing homes, calling all the nursing homes, did you get your vaccine, is it on time, which manufacturer did you, or not which manufacturer, but in case there was a

manufacturer that dropped out, for example, did you order from that manufacturer.

Doing all of that legwork, that capacity really wasn't there. I think communicating with providers, individual providers, and state level provider organizations is something that we would like to see happen if the capacity was there at the state and local level.

It is not so much the actual delivery of the vaccines. For example, the childhood vaccination program is largely private, also, in terms of the delivery side of it.

The public health department delivery is only about 15 to 20 percent. However, it is the assurance role that public health has to make sure that vaccine goes to those individuals in greatest need.

That is, I think, the part that needs to happen. And I think people did as well as they could, but the resources were limited.

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

DR. STEPHENS: Some of this sounds like the California power shortage.

Do you have any data on who got the vaccine first, and in what order groups received it?

DR. RODEWALD: We don't, yet. That is a good question. We don't yet, but the National Vaccine Program Office funded an evaluation so that we can take a look.

There was an agreement with the manufacturer to try to help us trace down who got the doses of vaccine and the nine million doses, so that we can try to understand that better.

Now, one of the questions is, is how -- that information is going to be very helpful in the future, and it may help us target vaccination efforts, or help to understand distribution efforts in the future.

But because the -- I think the results would probably be very different if there was a serious shortage. All nine million doses got snapped up right away, because there wasn't enough vaccine.

So I think one of the things we need to learn, and one of the things we realize, is that we have to understand sort of the epidemiology of the influenza vaccine distribution system much better than we do.

So I think your question is good. We are fortunate that we have some studies that will try to look at that. And, of course, it is too early now,

because the vaccine is still for sale.

In fact, it stops being for sale tomorrow, and the evaluation will be for this spring.

CHAIR DAUM: Dr. Kohl, and then Dr. Diaz.

DR. KOHL: I find myself in a high risk group, because I have grey hair. And I went to my private practitioner and he said, sorry, we don't have any, go to the shopping center, which is where I was immunized, and my wife.

And I guess my question is, yes, we dodged the big bullet this year, and it was kind of scary. If this had been a bad flu year we wouldn't be discussing this as impassionately as we are, and I suspect there would be blood on the floor.

Taking advantage of that, what is going to change so that a profit motivated distribution system can respond to serious shortfalls, which sounds like they will occur predictively in the future as well.

DR. RODEWALD: Obviously that is a very good and key question. One of the things that is interesting is that sort of these non-traditional sites have really become quite prominent in the vaccination system for adults.

And when we talk to the -- to companies that put on large vaccination efforts, they say that

they really do try very hard to target vaccination to the high risk patients, and give figures up in the 60 percent.

I see you shaking your head, and I think that your skepticism is appropriate, because we don't really know how well you can target this.

One example, this gets back to communicating early, and trying to understand the distribution system a little bit better. The American Medical Association has proposed to bring the manufacturers and distributors together in a conference to take a very hard look at this season, how we can improve things next season.

There are a number of ideas that will be developed. I think that these early contracts with penalty clauses are kind of challenging, because that really locks in a system that if one manufacturer drops out, or can't produce, or has a very delayed production, it is very difficult to re-steer vaccine.

And so whether or not we could develop example contract specifications that might provide a way out of a penalty clause, or something like that, I don't know.

I think that a variety of ideas need to be explored. And so we are looking to, looking forward

to the American Medical Association taking some of that on in terms of bringing the private sector together.

There are a number of discussions on what is the proper role of public health, how much of an infrastructure really is needed. I think your question also gets to Dr. Fagget's question, in terms of, you know, what is it that the public health would do, are there authorities that exist that would need to be used, or not used in these situations?

And these discussions are happening and ongoing. And I think that this season, I like how you put it, we dodged a bullet, or perhaps the bullet was mis-aimed, and we are lucky that we didn't have to dodge too much, because we are not that nimble, I guess, over here.

And we are very worried about this happening again in the future.

CHAIR DAUM: Pam?

DR. DIAZ: Lance, I wanted to make a couple of comments. One, in particular, you mentioned the effect of communications. And I really wanted to comment that I thought the CDC did a superb job this year of communicating, as has already been mentioned.

What was going on with flu season, and

what kinds of things should be done, we were able to take that and then relay that forward. So I applaud you for that, for those efforts.

Likewise my comments have been -- regarding distribution I think have already been heralded by other members. But certainly some kind of a targeted distribution versus a redistribution seems inherently more stable in the sense that there is not a third party involved in the redistribution.

There will always be some redistribution, I'm sure, of vaccine based on need, selective targeted need in various areas. But, nonetheless, I think some of the problems we experienced were very much associated with difficulties in getting the vaccine once it was available, from the manufacturer, actually into our hands.

And, finally, I was curious about your comments about contracts with clauses in them. Because I'm aware of quite the opposite situation, such as that of ordering and being bound to a contract that has no clause, and henceforth really unable to take advantage of the nine million doses, or a parcel of that, due to being bound to paying for vaccine that was already ordered.

DR. RODEWALD: That is interesting, that

is a helpful comment, because we hadn't really, you know, I don't think we've really discussed it from sort of that end of the beneficial side of the lock-in, in there. That is interesting.

DR. DIAZ: And it was limited funds, and only a certain amount of funds, once one gets locked into a contract, regardless of the delay, and perhaps availability elsewhere.

About the only thing that can be done in that sense is swap, give me some now, as soon as we get ours we will give it back, which is exactly what we put in place.

DR. RODEWALD: Right. And swapping is problematic because you have to be able to pay attention to the cold chain, and all of the --

DR. DIAZ: Exactly.

CHAIR DAUM: Take a comment from Dr. Estes, Dr. Decker, and then we have to move on.

DR. ESTES: My comment was triggered by Dr. Kilbourne's earlier statement, and I have a question about what is the shelf life of these vaccines, and since we now are in a situation where we have surplus, has anyone been discussing the possibility that should we face a situation like this again, even though it may not be the best match, that

perhaps we could have vaccine set aside from the previous year, that it could at least begin to be used for the highest risked population?

DR. RODEWALD: Yes, the latter part, these discussions are going on. And what I would like to turn it to, your first question, to somebody that has more of the technical knowledge of what the shelf life of the vaccine would be, and looking to Nancy, Keiji, or Roland.

CHAIR DAUM: Anybody sitting at the table want to comment on that?

DR. LEVANDOWSKI: I will take a stab at it. Influenza vaccines have an expiration date on them that is artificial, right now. I think everybody knows that. The date that is put on vaccines for expiration for non-military use is June 30th.

And the reason for that is to try to avoid confusion when new vaccines become available. We could debate whether the changes are always necessary, as Dr. Kilbourne was raising earlier.

But if there is a change that is a significant one in the vaccine, I think we would prefer to see the most current antigens being used.

And so that is, I believe, the rationale, the best rationale for the expiration date of June

30th. But we do know, and manufacturers can provide information on that, probably that the vaccines have stability for quite a bit longer time.

It is not a perfect vaccine, it is not stable forever, by any means. But during the period of time that the vaccine is in use, by and large, it is stable.

And probably for at least six months or maybe even longer afterward, according to the way the vaccines are produced now. I would be quick to point out that there have been some unexpected difficulties with specific vaccines, and you may recall that we had a product recall of the Parke Davis vaccine in 1996.

And that was because of a stability problem that was recognized, very early, with one of the components. But that is being monitored continuously, so it would be possible to have information that could be useful in trying to support any kind of policy that might be developed for use of a vaccine longer than the current expiration date.

CHAIR DAUM: Dr. Decker, and then I think we are going to move on.

DR. KILBOURNE: I just want to comment that even if there is no vaccine left, you still have the seed which you know is operative under production

conditions.

So that even if it is necessary to start over again, and rush in 94 strain, or something like that, it is still a potential advantage.

I wouldn't minimize the importance of the antigenic match, I don't mean to do that. But I think we may have reached a time in an emergency situation in which we have to make that kind of a trade off.

And I think the shelf life is probably far longer than is allowable. We've extracted antigens, potent antigens, from leftover bulk stocks of vaccine manufacturers, years afterwards, five years later to get antigens for biochemical studies.

CHAIR DAUM: Dr. Decker, please.

DR. DECKER: I would like to just follow up on a couple of comments with respect to the most recent issue, another alternative that can be considered, that I haven't heard mention is CDC could elect to release the unused portion of the CDC's component for use elsewhere in the world.

In the southern hemisphere, for example, where we don't run into issues of it being expired, and where the investment can be recouped, and the vaccine can do some good.

Coming back now to the issues Steve

raised, because they are obviously pressing on everybody's mind, although this was an unprecedented situation, and the particular constellation of circumstances one hopes won't arise again, companies falling out at the same time there is a difficult to grow strain.

Still, it could happen, we want to be prepared. In that regard a couple of things that I wanted to take note of.

The first is I had a clear sense, as the flu season evolved, that the system was adapting. Just as the manufacturers were learning how to make the vaccine, the distribution system, and private practitioners were learning how to deal with this delayed arrival of vaccine.

And I noticed it seemed to be much more common in the latter months, than in the earlier months, that those third party distributors, who did have supplies of vaccine because of their locked-in contracts, and so on, were shifting their distribution, and in many cases handing vaccine over to the public system, or to nearby hospitals for distribution, rather than through the systems they originally planned.

So one thing I think that we should not

lose sight of is that there are multiple elements of our current distribution system, that have been learning how to handle this, and we need to keep working on that, and training them how to deal with this. I think that will improve things.

Another thing that I know that Aventis is doing, in order to dramatically reduce the likelihood of vaccine not being able to get the high risk persons, is that henceforth there will be a new distribution system in which everyone who seeks vaccine will get only part of their order in the first part of the season, which is specifically flagged as being for use for high risk persons.

And then as the pipeline fills with available product everybody's orders will be filled. So we won't have the situation that happened this year, where those who happened to have the earliest orders got everything, and then those who got in line late got nothing until supply caught up.

That was, I think, one of the major problems. And it happened that way because no one had ever faced this situation before, and we didn't know it was going to happen.

But I think this is a major step towards avoiding this type of situation in the future.

CHAIR DAUM: Thank you, Michael. I would like to move on at this point and introduce Dr. Wendy Keitel, Associate Professor of molecular virology and microbiology, at Baylor, who will share some new, interesting information with us.

DR. KEITEL: Good morning, excuse me for must a moment while I get this straightened out.

Thank you very much for giving me this opportunity to present the results of a clinical trial that we conducted this summer in response to the delay and potential shortage of influenza vaccine.

I think Drs. Levandowski and Rodewald have painted a picture of the environment in which plans for this study were made.

The title is shown here, Evaluation of Immunogenicity of a Half Dose of Trivalent Inactivated Influenza Virus Vaccine in Healthy Adults. And I will refer to this as the half dose study.

By way of introduction, we stand on some very broad shoulders with regard to the evaluation of dose response to influenza virus vaccines. And going back 40 or 50 years it is very clear that increasing the dose of vaccine will increase the immune response to influenza virus vaccine.

Some of the earlier studies are more

difficult to evaluate because of the method for determining the antigenic content. But since SRID, or radio immunodiffusion was introduced for assessing antigenic content, studies that evaluate a broad enough range of dose have clearly shown that increasing the dose of vaccine will increase the immune response.

So over the last 30 years, or so, a number of studies have done evaluating doses between two and a half micrograms of influenza virus hemagglutinin, up to 405 micrograms of hemagglutinin.

There has been some discussions that doses differing as little as two-fold do not result in enhanced immunogenicity, but I think the bottom line is that with a large enough sample size, with two to three fold increase dose you would be able to show a difference in immune response.

But the question then becomes, would the reduction in immunogenicity be significant, and could one actually user a lower dose of influenza virus vaccines in a circumstance where there is a clear shortage of vaccine.

Before I proceed I would like to acknowledge the participants in the study. As you can see, a large number of people, as well as agencies,

made contributions to this effort. The six vaccine and treatment evaluation units, and the respiratory pathogens research unit of the Baylor College of Medicine, sponsored by the NIH enrolled the clinical subjects.

Evans provided the Medeva vaccine, and statistical support was provided by EMMES, the FDA, CDC also made valuable contributions to the design and analysis of the trial.

Notably lacking on this slide is the project officer who oversaw this entire effort, Lind Lambert, and I would like to make a special acknowledgement of her contribution, as well as that of John Trainer, who was the principal investigator for the trial, but unfortunately was unable to present the results of the trial today.

We enrolled subjects between the ages of 18 and 49 who had no medical indication to receive an influenza vaccine. For this reason pregnant women, now recommended to receive vaccine, were excluded from participation.

The upper age limit for inclusion in the trial was set at 49 because of the recent decision to target individuals between the ages of 50 and 64.

The vaccine was commercial subvirion

trivalent inactivated vaccine containing this year's antigens, and each one half mil dose, or full dose, standard dose of vaccine contained approximately 15 micrograms of hemagglutinin of each of the three strains contained in the vaccine.

The study was a multicenter, open label, blinded clinical trial. That is, the subjects were not informed of the magnitude of the dose they were receiving, but the vaccine administrator and investigators were aware of half and full dose administration.

Participants were stratified according to their receipt of trivalent vaccine within the preceding three years. And the reason for this was because it is very clear that immune responses to influenza vaccine will differ depending on receipt of recent vaccine.

After stratification they were randomized to receive a single full dose containing the 15 microgram per dose, or half dose, containing approximately seven and a half micrograms of each strain per dose, into the deltoid muscle.

Although primary end point of the trial was not to asses differences in reactogenicity between a full dose and a half dose, we did have an interest

in collecting some type of information about how well the vaccine was tolerated.

So subjects were asked to complete a diary card asking them about questions in the injection site, and overall systemic reactions.

Blood samples were collected immediately prior to immunization, and three weeks after immunization, for determination of HAI antibody levels, and these assays were conducted in both the CDC and the FDA labs on the samples.

For the rest of the presentation I will use the CDC data to display the results. However, I would like to emphasize that, as has been shown, frequently there are very strong correlations between CDC and FDA results.

The end points of the trial were to asses immune responses, and the following parameters were assessed. The percent of subjects achieving a titer of at least 1 to 40 in their post-immunization sample, was determined.

And, historically, levels of 1 to 32, or 1 to 40, depending on the laboratory, have been considered immunization goals, because of their correlation with protection against influenza.

The geometric mean titer and percent of

subjects with four fold or greater titer rises in serum antibody also were determined. However, percent with rise was not considered a primary end point.

Based on a consensus among the investigators, and other influenza experts, we established what we considered to be acceptable immunogenicity in the half dose group, when compared with the full dose group.

For the percent achieving a so-called protective titer, we considered a difference of 20 percent, or less, between the two to be acceptable. That is percent in the high dose group -- excuse me, percent in the full dose group, minus percent in the half dose group.

For the geometric mean titer of ration of less than, or equal to 1.5, was considered acceptable. And for a percent with rise a difference, once again, of 20 percent or less was considered acceptable.

Now, the study used a similarity design to compare responses in the full dose and the half dose groups. And the sample size of 420 subjects per group was considered necessary to conclude that the response to the half dose was adequate, if the geometric mean titer was no less than 67 percent in the full dose group.

So you heard a little bit about the concept that was proposed early in June. The subject were beginning enrollment at the end of July. By the end of August the full cohort, within three and a half weeks or so, the full cohort of subjects had been enrolled, data were analyzed, and results reported to the ACIP by the beginning of October.

And this slide shows you the enrollment by stratum. Stratum 1, shown in triangles, were subjects who had recently received inactivated vaccine and stratum 2 had not received an influenza vaccine, ever, or at least within the past 3 years.

And you can see, approximately, equal numbers were enrolled into each of the two strata. And in total 1,009 subjects were enrolled over this period of time, three of whom were not evaluable.

The vaccine was extremely well tolerated, as has been shown in numerous clinical trials. The most common side effect was some discomfort at the injection site.

You will note that about 50 percent of subjects receiving either the half dose, or the full dose of vaccine experienced no injection site reactogenicity. And among the 50 percent or so that did, most of this was characterized as mild.

There was a very low rate of systemic complaints, and no differences between individuals receiving the full dose or the half dose.

Now, as has been demonstrated previously, and shown again here, there was a statistically significant increase in the minor injection site discomfort in the subjects who received the higher dose of vaccine, and not shown on the slide is the fact that subjects who received vaccine for the first time actually had a little bit significantly more reactogenicity.

Post-immunization geometric mean titers against each vaccine antigen, here H1, H3, and influenza V are shown in this slide. Geometric mean titer is shown on the Y axis. Once again, half dose is shown as a white bar, and full dose is shown as a blue bar.

We have stratified here because of the significant differences between previously vaccinated and not previously vaccinated, into these two groups. And I would like to point out that, in general, the geometric mean titers were similar, levels achieved were similar.

However, statistically significant differences between subjects given full dose, and half

dose, were observed for H1N1, H3N2, and previously vaccinated, and for H3N2 antigen in subjects who were not previously vaccinated.

Now, when you combine these groups together, and treat them as individuals getting half dose, or a full dose of vaccine, there was statistically significant differences in the mean titers for all three antigens.

Subjects achieving a so-called protective titer three weeks after immunization, is shown here, once again percent achieving this titer is shown on the Y axis, and the three antigens are shown here on the X axis.

And you will see that the vaccine was highly immunogenic and the majority of subjects achieved protective titers against each influenza antigen, and when vaccine strata are combined there are no significant differences between the groups.

Finally present with a significant response to vaccine is shown on this slide. And this is where the biggest difference is between the two strata can be observed. And you will note that in subjects who have been recently vaccinated with influenza virus vaccine, the percent of response is much lower than among subjects who have not recently

received an influenza virus vaccine.

And, from my point of view more importantly, in this panel, we see that there were significant differences in response rates against all three antigens among subjects who had been previously or recently immunized.

So, finally, these data have been combined into a single slide to put them in the context of what we had defined as acceptability criteria. In the first panel the percent achieving a protective titer, second the ratio of post-vaccination geometric mean titers, and then the third, the percent with the four-fold rise. This, for the reasons I've described, being a secondary end point.

Remember we accepted a difference of 20 percent between the two dose groups, and for a percent with rise, and percent with protective titer. So in these two panels the Y axis is the percent difference between the two vaccine groups.

So that for HN1N, there was about a four percent difference in the percent achieving protective titer. And the one sided upper 95 percent confidence limit is shown here.

So this falls well below our -- what we consider to be an acceptable immune response among

subjects given the half dose, when compared with subjects given the full dose.

And the same holds true for HVN2 influenza B. In the center panel the GMT ratio, that is the full dose GMT over the half dose GMT, I will remind you that we had set a ratio of 1.5 as being acceptable in the study sample size. This determined based on the power to detect this kind of a difference.

So, in summary, overall the half dose of vaccine was less immunogenic than the full dose among healthy younger adults. And the immune responses to the half dose met preset acceptability criteria for all three antigens.

So then the question becomes one of in the event of a true vaccine shortage, would a half dose of vaccine administered to twice as many people provide greater benefits than a full dose of vaccine administered to half as many people?

I would like to show some very preliminary data regarding a decision and analysis that was conducted in collaboration with Scott and Donald Berry of Berry Associates.

And I will need an overhead to do this.

(Pause.)

DR. KEITEL: During the -- can you all

hear me, is this one?

During the period between 1983 and 1987 the Influenza Research Center at Baylor and Houston my colleagues and I conducted a randomized control perspective clinical trial of commercial inactivated influenza virus vaccine.

And the goal of the study was to determine whether repeated annual immunization with influenza vaccine continued to provide protection.

Although the public health policy had been to administer influenza virus vaccine, annually, some studies in British boarding schools had suggested that the protection conferred by subsequent doses of inactivated vaccine was inferior when compared with the first dose of vaccine given.

So this clinical trial was designed to test the public health policy. And each year subjects were enrolled and randomized to receive other placebo or inactivated vaccine, which in this case was commercial whole virus influenza virus vaccine.

Once the subject had been assigned, randomized to receive vaccine, then for subsequent years they were given vaccine, so that we had cohorts of individuals with successively increasing numbers of annual immunization.

Subjects enrolled into the study were monitored, prospectively, during the winter season, and were evaluated for the occurrence of any febrile and/or respiratory illness during influenza seasons, which was determined by means of intensive virologic surveillance in the community conducted, and surveillance conducted in our laboratory.

At the time of illness evaluation a sample of respiratory secretions was collected and cultured for influenza viruses. Blood samples were collected at that time, and several weeks later, to determine whether an immune response had developed to the influenza virus, so that we had five successive seasons of illness assessments, paired blood samples.

In addition we collected blood samples before and one month after immunization to assay for the level of antibodies to vaccine antigens.

Now, after the epidemic strain for each year had been identified, and characterized, then blood samples were tested, again, for immune responses to the epidemic variant.

So that we had blood samples to the vaccine variant, to the epidemic variant, on subjects enrolled in this trial.

Each year between 600 and 1,000 subjects

were enrolled into the trial. So that what we ended up with was a large number of sera in which the antibody levels, after immunization, or prior to the epidemic, could be used to determine the level of antibody which would confer protection against influenza.

Now, these are not particularly new data, but these constitute a very large data set. A number of investigators previously had reported either under field conditions, or in the circumstance of artificial or experimental challenged with well typed influenza virus that levels between 32 and 64, or 40, or whatever, were associated with significant protection against influenza.

So the -- I show you, in this overhead, the data set between '83 and '87, and I show you, in each year -- in some years we had two strains. But in these preliminary analysis we only have the results for one strain in each epidemic season. two H1N1, three H3N2, and one influenza B epidemic.

Parenthetically, during this period we had what we would consider suboptimal match between vaccine and epidemic strains. We had seven epidemic strains, and in two out of the seven we had good antigenic match, in the A/Philippines epidemic, and

the A/Taiwan epidemic.

Now, this -- what is shown here is the attempt to develop a model which would predict the likelihood of being infected based on the pre-season antibody level.

Drs. Berry have used a bazian approach to develop a model so that we could use the data collected in the clinical trial to predict what the outcome might be if we chose various immunization strategies.

So shown here is the plots of the five epidemic strains, the proportion of subjects experiencing influenza over the season, as a function of log base to titer, and their post-immunization sample.

And this relationship has been observed previously, but now has been modeled. And without getting into the details of the model, I would like to show you the results of a preliminary analysis, decision analysis, looking at different strategies.

So, let's say there had been a huge vaccine shortage, the question is, well could we, for those healthy younger people, who elect to be vaccinated, could we safely recommend a half a dose of vaccine as opposed to a full dose of vaccine?

And so shown here are various dosing strategy. No one is vaccinated, everyone gets what we consider the optimal dose, half receive a full dose, all receive a half dose.

And so these are estimated cases, or tac rates per 1000 using some CDC data. And over in this column are shown the extra cases, if you had elected to use any of these particular dosing strategies.

So if everybody received a full dose, if you compare this with all who receive a half dose, you can see the number of extra cases, per thousand, is five.

So that it would be better to give everyone a half dose than the circumstance of using a regular does of vaccine, and giving it to half as many people, where 43 extra cases of influenza per thousand might occur.

So we were fortunate in this season that we did not have to utilize the half dose vaccine, but I think we are beginning to look at ways that in the event there were true shortage of influenza vaccine we might approach, one strategy might be to offer a lower dose than is ordinarily recommended.

But before I leave you with that thought, I would like to emphasize our concern about

extrapolating the results of this trial to other populations, older individuals, and persons who are at high risk of death and complications following influenza.

It has clearly been demonstrated that as we age, and as we develop underlying medical conditions, the immune response to inactivated vaccine declines.

And so our group has really been interested in moving the other direction, rather than reducing the dose of influenza vaccine to consider increasing the dose of vaccine.

This is one of the number of strategies which include agivents, topical immunization, increasing the dose, and so forth. And this is the result of a small clinical trial in which we compared the immunogenicity of subvirion vaccine with that of purified influenza virus hemagglutinin in similar doses, 15, 45, and 135 micrograms of purified influenza A, H1, and one antigen. In this case it was A/Taiwan.

And this we conducted in a healthy elderly population that would show, even with very small numbers of subjects, that has a significant dose response with increasing antigen content, both in the

serum, and not shown as well as in respiratory secretions. Thank you.

CHAIR DAUM: Thank you very much, Dr. Keitel. There are one or two burning questions on the part of the committee. We will go with Ms. Fisher and Dr. Ferrieri.

MS. FISHER: Do you know why there was not as strong an immune response in those who had received the vaccine, flu vaccine previously, versus those for whom it was the first dose?

DR. KEITEL: There are several potential reasons for this. And I would say that the first is pre-immunization antibody titer. And when, actually the data that I've just described, if you do a multi-varied analysis, the pre-immunization antibody level is a significant predictor of responding to vaccine, as is age, and dose.

The second caveat that I would like to point out is that subjects enrolled into this trial, reported verbally whether they had received a flu vaccine within the preceding several years.

And they were not randomized to receive yes or no. So there is, possibly, an element of cohort effect, as well.

MS. FISHER: Pre-vaccine antibody titers,

in other words, those who had had the flu, and had had antibodies to the strains, is that what you are saying?

DR. KEITEL: I'm sorry. Individuals who had been recently immunized against influenza have significantly higher pre-immunization antibody levels.

MS. FISHER: Right. I was asking why would there be less of an immune response for those who had been previously vaccinated, wouldn't there be a stronger immune response?

DR. KEITEL: My opinion is that the people who had been previously vaccinated start with a higher level of antibody, and that impairs their ability to respond to that dose of antigen.

MS. FISHER: But what does that say for the protectiveness of the vaccine in that year, for those who had been previously vaccinated, what does that say in terms of people who had been repeatedly vaccinated with flu vaccine, and their ability to mount a proper antibody response and indeed be immune that year?

Am I not understanding this?

DR. KEITEL: In the clinical trial that we conducted we compared the post-immunization geometric mean titers among subjects who had been randomized at

the time of entry into the trial, and got increasing numbers of annual immunizations.

The pre-immunization titers each year were higher among individuals who were previously vaccinated. But the post-immunization geometric mean titers were similar for all years, and antigens, with the exception of one antigen, in the latter part of the study in 1997, 1998.

So I think that when we look at responses to influenza vaccines we have to be careful about which parameter we are looking at. One is a four-fold rise, and you are less likely to experience a four-fold rise in titer after immunization if you've been previously immunized.

And the effect of previous immunization on the geometric mean titer has been variable in study to study.

CHAIR DAUM: We need to move on. Dr. Ferrieri, please.

DR. FERRIERI: Well, that was my question. I thought that perhaps that one would have expected, as Ms. Fisher did, in the animistic response based on some of the homologies of these antigens.

But in reflecting on this there are a number of other models in microbiology where pre-

existing antibody titer may dampen the response.

It asked a group A streptococcal disease where an ASO and anti-deanase B are blunted in those who had higher titers at the time of a new exposure to group A strep.

So it isn't so illogical. But I appreciate, you know, that you might have expected, perhaps, the opposite.

CHAIR DAUM: Dr. Kilbourne, very briefly.

DR. KILBOURNE: It is not so much an inability of these people to respond, it is an inability for you to perceive their response to the geometric progression. That is what it boils down to.

I mean, they are actually making lots of antibody. But when you set yourself an arbitrary definition of four-fold increase, then they may not make it. Yet they also may be losing higher affinity antibody.

And, also, the question I have is whether the previous vaccine was a heterovariant immunization, in which case you would have the problem of regional antigenic sin, and animistic response directing response to the wrong direction in people previously immunized.

CHAIR DAUM: Thank you, Dr. Kilbourne.

Thanks to our three speakers this morning for what I thought was a very enlightening series of presentations.

We would like to move on and call on Dr. Katherine Zoon who is the Director of the whole operation here, the Center for Biologics Evaluation and Research, to make some presentations to retiring members.

DR. ZOON: It is a pleasure to be here. Thank you, Bob.

This morning, as you know, we have several members of our committee who are retiring from the committee, in quotes. And I think it is really very special for the public service that they have provided the FDA, and actually the American people, on these important discussions surrounding vaccine issues.

And it is one opportunity that the Center has to officially recognize their important contribution. So this morning, in appreciation of those members, I would like to recognize them, and provide some plaques.

The first is to Dr. Mary Estes. Mary, are you here? Mary, I just want to say it has been a delight to have you on the committee, and I hope that we will see you in the future, to help us again with

some important issues. Thank you, so much.

CHAIR DAUM: Subsequent plaque recipients, please take note.

(Applause.)

DR. ZOON: The next is to Dr. Alice Huang. Alice, it has been a pleasure to work with you in many different avenues over our careers. And, especially, thanks for your contribution to this committee. Thank you very much.

(Applause.)

CHAIR DAUM: Dr. Huang wanted to take a minute of committee meeting to say a few words, having received her plaque, and now might be a good time to do that.

DR. ZOON: Great, thank you. Please.

DR. HUANG: I just wanted to say that from all of my experience on a variety of committees, that this committee is the best staffed. The staffing is not only most efficient, it always has a view towards cost effectiveness, as we can see in the no-frills meetings that we hold.

(Laughter.)

DR. HUANG: So I want to thank you for this opportunity to have been able to serve with such a professional committee. And I've also enjoyed

working with the very knowledgeable colleagues that I've met here.

(Applause.)

DR. ZOON: Alice, I'm not sure if you are saying we are cheap, or thrifty. But we do serve coffee to the committee members, so I have to say that.

DR. KOHL: The coffee is kind of weak.

DR. ZOON: And last, but not least, I have the honor of presenting two plaques to Dr. Harry Greenberg. Harry has served on our committee, but as well has chaired our committee.

And, Harry, we really appreciate the service and leadership that you have provided to the VRBPAC in dealing with some very difficult issues over the past several years.

So, one, I appreciate your service, and I hope your neck gets better. Thank you.

DR. GREENBERG: This is what happens if you mess around with the committee.

So, Alice really stole a little of my thunder. I would like to say that I have rarely worked with a group of colleagues, that is the committee members, who are so dedicated, and so good at what they do.

The public is well served by this group of people, and I would like to thank all of you who have been very helpful.

Secondly, the staff is outstanding. I can't single out all of you, but basically to a person the FDA staff is outstanding. But, Nancy, who is sort of the point person who many of us interact with, really is the grease that keeps this thing going, and keeps all of us in good humor at times when our humor might be flagging. So, thank you, NANcy.

(Applause.)

CHAIR DAUM: Well, there is a tremendous groundswell of feeling that the committee -- a picture of the committee now needs to be taken. So because of that we will now take advantage of that for a morning break.

We will break for twenty minutes. I have five to ten here in the eastern time zone, and we will resume at 10:15. Committee members do not get to leave the room, however. And please assemble over here to be arranged by our photographer for a quick photo op.

(Whereupon, the above-entitled matter went off the record at 9:55 a.m. and went back on the record at 10:20 a.m.)

CHAIR DAUM: I would like to call the committee back to order at this point, please. We do have a little extra time on our hands today, but if we keep being somewhat lax in our time observance we may end up being behind the eight ball.

So I would like to get moving. We would like to move, again, to another series of three presentations regarding influenza, to get to a point where we can begin our deliberations.

And we will begin with Dr. Fukuda from the CDC, who will enlighten us regarding U. S. surveillance. Dr. Fukuda?

DR. FUKUDA: Thank you, Dr. Daum.

In a couple of minutes what I would like to do is describe what has been going on this season, and then sort of put it in context to the last couple of seasons that we've had.

I think, as all of you know, during the last number of seasons, these have been dominated by influenza A, H3N2 viruses, and they have been quite severe in terms of their clinical impact.

The bottom line for this year, by contrast, we are really seeing a mixed viral season in the United States, similar to what is being seen in many other parts of the world. And the clinical

impact, so far, has been less than it has been in the previous seasons.

Up here, on this slide, what we do is have the numbers from the World Health Organization, and National Respiratory Virus system of laboratories. And basically between October, up until about January 20th, about 30,000 respiratory specimens have been tested for influenza viruses.

And of these seven percent of them have been positive for influenza viruses, for about 2,239 isolates.

Now, among those influenza viruses about 73 percent, or three quarters of them have been influenza A viruses, and the remainder have been influenza B viruses.

Among the influenza A viruses, here are the influenza A viruses. And among those 38 percent of those have been subtyped. And of those which have been subtyped, the vast majority, 97 percent, are influenza A HN1N viruses.

So, again, we are seeing a mixed season, with a quarter of the viruses influenza B viruses, and among the remainder influenza A viruses, almost all of them have been influenza A H1N1.

And this slide here graphically shows,

basically, the information that I just told you. The green bars are the influenza B viruses, the yellow and the blue bars are the influenza A viruses. These are un-subtyped A viruses, these viruses down here are influenza A H1N1.

And, again, you see that there have been some H3N2 viruses, but very few.

Now, we saw, this line here represents the percent positive, cumulative percent positive percentage of the virus of the specimens that are positive for influenza A viruses.

And as of the most current week, right now, about 22 percent of the specimens coming into this system are testing positive for influenza viruses.

When you look at past seasons we typically peak somewhere between 19 percent and about 33 percent being positive for influenza viruses.

This map here basically shows where A or B viruses are predominating in the country. The red represents a predominance of influenza A viruses, the blue represents a predominance of influenza B viruses.

So you can see that most -- in most parts of the country, A viruses are predominating. But on the west coast, and somewhat on the east coast, we are

seeing areas where B viruses are predominating.

Now, another thing that we follow at CDC are the percentage of visits to a group of about 500 sentinel physicians. And what percentage of those visits are for influenza-like illness.

And, nationally, we are seeing that about three percent of visits to this group of sentinel physicians are for influenza-like illnesses.

Again, in past seasons we have seen this peak up at about five to seven percent. And in this map here, what we see are that the rates of visits to physicians for influenza virus, or influenza-like illness, vary by region.

The darker blue states represent areas in which the percentage is higher, and the light blue states represent those areas in which the percentage is lower.

So, again, on the west coast, around the Texas area, and in the mountain states, the percentages range from about four to seven percent. And then in the remainder of the country they range about two to three percent.

Now, another way that we asses influenza activity in the country is to get reports from each of the state and territorial epidimiologists.

And for week three, the most recent week, 30 states are reporting either widespread or regional activity. At the same time last year about 41 states, or 48 states were reporting either regional or widespread activity.

And, again, this map gives a slightly different picture. This is the reporting by the state and territorial epidimiologists. The red states represent states in which activity is being termed widespread. The blue states represent states in which activity is a step down, so-called regional activity. And you can see it sort of scattered all over the country in no clear pattern.

Finally, the last parameter that we follow is the -- are the rates of pneumonia and influenza deaths in the country. You can see that in the previous four seasons, that we have had these pronounced and fairly large peaks in pneumonia influenza deaths in the country, going above the sinusoidal base line.

By contrast, in this season so far, we have not gone above the threshold for PNI deaths. Again, sort of cementing the idea that we are having a milder season than we have had in the previous seasons.

So to put this in context, again, this is a graph of the percent positive specimens coming into the WHO, the National Respiratory Enteric Virus lab system.

The blue graph represents what we saw last year, where we saw a larger number of isolates, and we saw a peak coming earlier in the season.

In the current influenza season we are seeing a slower increase in the number of virus isolates, and in the percentage of positive specimens. And we have not seen the peaking yet.

So we don't really know whether this is going to continue up higher, whether it is going to plateau, or what it is going to do. We just know we haven't seen the peaking yet.

And, similarly, this graph here shows what the visits for influenza-like illness to the sentinel physicians was for last season. That is this blue curve here. And this red curve, here, represents what we are seeing so far this year in the United States.

So I will stop there.

CHAIR DAUM: Thank you very much, Dr. Fukuda. Are there one or two committee questions? Dr. Diaz, Dr. Goldberg, Dr. Katz, Dr. Kohl.

DR. DIAZ: Dr. Fukuda, just out of

curiosity, the 30,000 plus specimens that have been looked at, at WHO referral labs, I'm always curious about the, in this case, 93 percent that are negative for influenza.

Is there any comments, epidemiologically, what those negatives represent, do they look for other viruses, or is it that they were tested as influenza positive locally, and yet the specimen didn't survive in making it to the laboratory; any knowledge of what those represent?

DR. FUKUDA: Yes. It is probably a combination of both of those possibilities. I think that probably some of these represent purely negative test results, because the swabs may have been taken too late to isolate any sort of pathogen.

But if you look at surveillance reports, say from California, from Canada, from a number of other systems, it is clear that there are other viruses co-circulating in particular RSV viruses.

I think we haven't seen big peaks in the pair of influenza viruses. But they are clearly out there.

DR. DIAZ: Likewise, I guess the reason for my comment is that with downsizing of laboratories, and the negative impact of doing viral

cultures on a local level, I think that WHO and others may have to begin to take up the brunt of local surveillance by delving further into those negatives so that we know what kinds of viruses are circulating.

DR. FUKUDA: As an aside, one of the things that we have specifically been trying to do is to get money into those public health labs so that they can continue the viruses isolation.

CHAIR DAUM: Dr. Goldberg.

DR. GOLDBERG: I wanted to just make a comment about the discussion before the break.

CHAIR DAUM: We are having technical problems. Can you speak way into the microphone, please?

DR. GOLDBERG: I just wanted to make a comment about the discussion before the break about the half dose study. In the previously immunized subjects the titers are high at baseline.

Which means, for example, if they have a titer of, let's say, 100 -- this is arbitrary, to have a four-fold increase they would have to exceed 400. Whereas if someone had a titer of one, a four-fold increase is four.

So an absolute difference would be very small, but a percent, or a fold difference would be

very large. When you have levels of protective -- protective levels, it is unlikely that you can increase very much.

And the goal is to maintain the level, and not so much to show an increase. So I think it doesn't mean they are not protected at all, it means they have a level of protection, which is being built upon, but they can't increase very much in any terms.

CHAIR DAUM: Thank you.

DR. GOLDBERG: So I just wanted to clarify that.

CHAIR DAUM: I want to return to questions for Dr. Fukuda. We have Dr. Katz, then Dr. Kohl, then we will move on.

DR. KATZ: Just a quick one. Do they represent the internist family physicians, pediatricians, mixtures thereof?

The reason I ask is that we are seeing a lot of RSV on the east coast in among the pediatric population. And yet that doesn't seem reflected in your respiratory illness.

DR. FUKUDA: Sam, Originally when the system was set up, it was set up exclusively with family practice physicians. In the last couple of years it has really been opened up.

So I think that pediatricians probably represent about a quarter to a third of the reporting physicians now, so that there are internists, family practitioners, pediatricians, OBGYNs.

And you are right, these curves don't reflect RSV activity. But, you know, if we were to pull out other data, clearly, there are a number of RSV viruses out there.

Particularly, I think, the California State Health Department does a good job of showing concurrent activity in terms of those viruses, and flu viruses.

CHAIR DAUM: Dr. Kohl, please.

DR. KOHL: Nice presentation, as usual. Are there historical data that allow us to say that a late upswing in the curve means that it will be a milder season, or is it possible that it will be severe, but it is coming at us?

DR. FUKUDA: I guess the rule in flu is that, literally, anything is possible. I mean, I think -- it is simply true.

So I think that I would guess, I mean, I really hate guessing but I would guess that it is likely that we are going to continue to have lower clinical levels of activity.

But clearly when you look, historically, you can see bimodal peaks, if H3 viruses begin to come out later in the season, as we've seen in Australia. In Australia, initially, there is a predominance of H1 viruses, and then later on there is kind of an upsurge in H3 viruses.

If we see that in the United States we may see, you know, a double peaking of activity. So it could be anything.

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

I would like to move on at this point with our influenza branch trilogy, and call on Dr. Cox, the chief of the influenza branch at CDC for our next presentation, World Surveillance and Strain Characterization.

DR. COX: Thanks very much. We are moving on to the more technical aspects of our considerations this morning. And I want people to try to follow along in the handout that has been distributed, in case you are not able to see the overheads here.

We will be starting on page 9 and then progressing through. Now, I am not going to present the CDC human serologic results today. I'm going to leave the summary of that data up to Dr. Levandowski

in his presentation.

But if you have any specific questions about the CDC serologic data, please let me know.

As usual I'm going to present the three groups of viruses in the order of the easiest, perhaps the easiest decision, you never know for sure, but perhaps the easiest decision, to the most difficult decision.

And we are going to start today with influenza A H1N1 viruses. First of all we will look at world-wide activity due to influenza H1N1 viruses by season.

First we are looking at last winter's season, October '99 to March 2000, then we will look at what happened in the southern hemisphere, followed by what is now currently happening in the northern hemisphere, predominantly in the northern hemisphere.

And I don't know, for some of you who have been on the committee for some time, if you will remember that we really had relatively little H1N1 activity world-wide for a number of years.

But we saw that H1N1 activity was increasing in some parts of Asia during the northern hemisphere season. This was followed by outbreaks and epidemics in South America during our summer. And it

is being followed by circulation of the same A/New Caledonia-like strains in the no in the United States, and Europe, mainly.

We are continuing to see H1N1 activity in Asia, but there really are no striking outbreaks there that we know about.

Now, we move to the next page of the handout, and we will start going through the hemagglutination inhibition test results. I'm going to try to orient you to these tables. I know that they are sometimes difficult to follow.

We have tried to choose representative tables. We, obviously, present a very small subset of the data that we develop over the year, to you, at this meeting.

We try to make it representative and to allow the data that we show to tell a story of what we've been seeing over the past year.

If you remember back to last year's presentation, and previous presentations, you will recall that there are two antigenically and genetically distinct groups of influenza A H1N1 viruses that are circulating globally.

The viruses that are predominating are related to the old Beijing/262 vaccine strain, but are

much better represented by the New Caledonia 2099 current vaccine strain.

In addition to these viruses, which are shown as tests, to viruses like these, which are shown as test antigens 6 through 18, we do have the old Johannesburg 8296-like viruses continuing to circulate in the United States, as well as in other areas of the world.

Now, here we see one other viruses in our reference battery, up here, and that is the Hong Kong 1252 strain. You can see that it had a titer that was reduced four-fold in comparison to the homologous titer for New Caledonia.

And we found that it was reproducibly reduced four-fold, and so we put that virus into ferrets, since that indicates a significant antigenic variation.

And then we developed a ferret serum which we were using to see if that particular ferret serum could distinguish differences among the currently circulating strains.

This was not a particularly representative strain, it was simply one of the viruses that appeared to be somewhat different. And we see that it doesn't, there is a bit higher homologous titer, but it really

doesn't cover the current strains any better than New Caledonia.

So the picture that we were seeing last summer with strains from the southern hemisphere, really had -- did not change in the early fall. We see here we have strains from Texas, which has really provided a tremendous number of the H1N1 strains that we looked at so far.

These strains are all clearly New Caledonia-like, with a small subset of viruses which are like the older Johannesburg 96 vaccine strain.

So we should move through this table a bit more quickly. The first thing I would like to point out is that we've added a different referenced strain here. This time the A/Fujian/156/2000 strain, which was also used as a serology antigen.

I should mention that the strains that have asterisks here were used in human serologic studies.

Here we have another strain, this one from China, that was reduced in titer with the Nanchang ferret antiserum. But the majority of the strains that are in this lineage of viruses are quite well inhibited by antiserum to the Nanchang virus.

And where we have viruses from wide

geographic distribution in the United States, one from the UK, and then a couple from China. In addition, on this slide, we have some of the Johannesburg-like strains shown here, and those strains do not appear to have undergone antigenic drift, including this strain, A/England 192/2000, which was used in serology.

This last table was produced very recently, on the 24th of this month, and actually has some of the most recent viruses that we have been able to test on it.

Again we have a variety of strains from the United States, with a fairly good geographic distribution, along with one from France. I think that is the only strain that is not a U. S. strain.

And, once again, those that are in the New Caledonia lineage are very well inhibited by antiserum to New Caledonia. The strains that are on the Johannesburg lineage continue to look Johannesburg-like.

So in this overhead I'm going to summarize the antigenic properties of the viruses that we characterized. And I think it will be most instructive if we just focus on the bottom half of this particular overhead.

For the time period between April 2000,