FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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VACCINES AND RELATED BIOLOGICAL PRODUCTS
ADVISORY COMMITTEE MEETING

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THURSDAY,
FEBRUARY 21, 2008

The Committee convened at 8:30 a.m. in the Hilton Washington, DC North, 620 Perry Parkway, Gaithersburg, MD, John Modlin, MD, Acting Chair, presiding.

MEMBERS PRESENT:

JOHN MODLIN, MD, ACTING CHAIR
CHRISTINE WALSH, RN, EXECUTIVE SECRETARY
SETH HETHERINGTON, MD, INDUSTRY REPRESENTATIVE
VICKY DEBOLD, PHD, RN, CONSUMER REPRESENTATIVE
LISA JACKSON, MD, MPH
JACK STAPLETON, MD
JOSE ROMERO, MD
THEODORE EICKHOFF, MD
ROBERT COUCH, MD, TEMPORARY VOTING
ROBERT DAVIS, MD, MPH, TEMPORARY VOTING
FRANK DESTEFANO, MD, MPH, TEMPORARY VOTING
BRUCE GELLIN, MD, MPH, TEMPORARY VOTING
WAYNE HACHEY, DO, MPH, TEMPORARY VOTING
PAMELA MCINNES, DDS, MSC, TEMPORARY VOTING
STEVEN SELF, PHD, TEMPORARY VOTING
MELINDA WHARTON, MD, MPH, TEMPORARY VOTING
NANCY COX, PHD, NONVOTING TEMPORARY

FDA
NORMAN BAYLOR, PHD
FLORENCE HOUN, MD. MPH
JOSEPH TOERNER, MD, MPH
JERRY WEIR, PHD

CDC
JOSEPH BRESEE, MD,
NANCY COX, PH.D

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

8:33 a.m.

CHAIR MODLIN: Good morning. We have a quorum at the table, so we'll go ahead and get started.

My name is John Modlin. I'm from Darthmouth Medical School, and I'm serving as the Acting Chair of the Vaccines and Related Biological Products Advisory Committee today, and I'm going to begin the meeting by turning things over to Ms. Christine Walsh.

EXECUTIVE SECRETARY WALSH: Good morning, everyone. I'm Christine Walsh, the Executive Secretary for today's meeting of the Vaccines and Related Biological Products Advisory Committee.

I would like to welcome all of you to this meeting of the Advisory Committee.

Today's session will consist of presentations that are open to the public.

I would like to request that everyone please check your cell phones, pagers

and Blackberries to make sure they are off or in the silent mode.

And I would also like to request that any media inquiries be directed to Ms. Peper Long from the FDA Office of Public Affairs. Peper's over there. Thank you, Peper.

I would now like to read into public record the conflict of interest statement for today's meeting. This brief announcement is in addition to the conflict of interest statement read at the beginning of the meeting on February 20th, and will be part of the public record for the Vaccines and Related Biological Products Advisory Committee meeting on February 21, 2008.

This announcement addresses conflicts of interest for topics 2 and 3.

For Topic 2, the Committee will discuss and make recommendations on the selection of strains to be included in the influenza virus vaccine for the 2008/2009 flu

season. This is a particular matter of general applicability.

For Topic 3, the Committee will discuss clinical development of influenza vaccines for pre-pandemic uses. This is a particular matter of general applicability.

Based on the agenda and all financial interests reported by members and consultants related to Topics 2 and 3, conflict of interest waivers have been issued in accordance with 18 USC 208B(3) and 712 of the Food, Drug and Cosmetic Act.

Related to Dr. John Modlin. Dr. Modlin's waivers include a consulting arrangement with two firms that could be affected by the Committee's discussions. The waivers allow Dr. Modlin to participate fully, and vote on the Committee discussion.

Related to Dr. Robert Couch. Dr. Couch's waivers include a contract with a firm that could be affected by the Committee's discussions. The waivers allow Dr. Couch to

participate fully, and vote on the Committee discussions.

Dr. Seth Hetherington is serving as the Industry Representative acting on behalf of all related industry, and is employed by Icagen, Incorporated. In addition, Dr. Heatherington's spouse is employed by GlaxoSmithKline. Industry Representatives are not special government employees, and do not vote.

With regard to FDA's guest speaker for Topic 2, the Agency has determined that the information provided is essential. The following information is being made public to allow the audience to objectively evaluate any presentation and/or comments.

Tony Colegate is the influenza technical affairs manger at Novartis Vaccines in the United Kingdom. He is a member of several European groups which focus on influenza vaccines and pandemic issues.

This conflict of interest statement

will be available for review at the registration table.

We would like to remind members and participates that, if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Committee of any financial relationship that you may have with any firms, its products, and, if known, it's direct competitors.

That ends the conflict of interest statement.

Dr. Modlin, I turn the meeting back over to you.

CHAIR MODLIN: Thank you, Christine.

I'd like to begin by asking the

Members of the Committee to identify themselves, and their home institutions. And I believe we'll begin with Dr. Eickhoff.

MEMBER EICKHOFF: Ted Eickhoff, University of Colorado.

MEMBER JACKSON: Lisa Jackson, Group Health, Center for Health Studies.

MEMBER HATCHEY: Wayne Hatchey, Department of Defense.

MEMBER SELF: Steve Self, Hutchinson Cancer Research Center, University of Washington.

DR. MCINNES: Pamala Mcinnes, National Institutes of Health.

MEMBER ROMERO: Jose Romero, University of Nebraska Medical Center.

MEMBER HETHERINGTON: Seth Hetherington, Icagen Research, Triangle Park, North Carolina.

MEMBER DeBOLD: Vicky Debold, National Vaccine Information Center.

MEMBER COUCH: Robert Couch, Baylor

College of Medicine.

MEMBER GELLIN: Bruce Gellin, Department of Health and Human Services.

MEMBER DAVIS: Bob Davis, Center for Health Research, Kaiser, Georgia.

MEMBER STAPLETON: Jack Stapleton, University of Iowa.

MEMBER DESTEFANO: Frank Destefano, RTI International.

MEMBER WHARTON: Melinda Wharton, Centers for Disease Control and Prevention.

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

DR. BAYLOR: Norman Baylor, FDA, Center for Biologics, Office of Vaccines.

DR. WEIR: Jerry Weir, Center for Biologics, Division of Viral Products.

CHAIR MODLIN: As you're aware, the topic of this morning's meeting is the strain selection for influenza vaccines for the 2008/2009 influenza season for the United States. We'll begin with Dr. Jerry Weir, from

CBER, who will be giving us an introduction to today's meeting.

DR. WEIR: Thank you. Good morning. I'm Jerry Weir, from the Division of Viral Products at CBER, and I'm going to provide a brief introduction to this morning's session of the VRBPAC.

As you know, the reason we're here today is to ask the VRBPAC Committee to recommend strains that should be included for the 2008/2009 influenza vaccines for the United States. This includes two strains of influenza A, an H1N1, and a H3N2, as well as a B component for the vaccine.

The reason that we consider strain changes each year for influenza vaccine relates to the efficacy of the vaccine. And essentially, the efficacy of the vaccine is determined by vaccine potency, and the immunogenicity that it elicits, as well as a match of the vaccine hemagglutinate, and neuraminidase antigens with wild-type viruses.

As everyone knows, antigenic drift of HA and NA is continuous in influenza A and B, and there was evidence of reduced vaccine effectiveness resulting from antigenic drift noticed within two years of the first licensed influenza vaccines in the United States.

Each year, when we go through this process of selecting the strains to be included in next year's vaccines, the Committee asks itself four questions:

The first, are new drifted or shifted influenza viruses present?

Are these new viruses spreading in people?

And do current vaccines, the ones that are currently in use, induce antibodies against the new viruses, specifically to the HA hemagglutinate?

And finally, last but not least, are strains suitable for vaccines available so that manufacturers can produce vaccines for the next year?

In the next two slides, I want to spend a couple of minutes reviewing what we did last year at this time. This is a review of the influenza strain selection for 2007/2008, in other words, the current year. We were here about a year ago, I think actually in the same room, to go through this process, and select the strains, the H1N1, the H3N2, and the B strain for this year's vaccine.

When we met last February, the vaccine that was in use at that time, the 2006/2007 vaccine, contained an H1N1 that was an A/New Caledonia/2099-like strain. It was observed from the surveillance data that there was an increasing percentage of antigenically distinguishable H1N1 viruses present in the world. And the recommendation that the Committee made last year at this time was to switch the H1N1 vaccine component to an A/Solomon Islands/34/2006-like virus for inclusion in the 2007/2008 vaccine.

For the H3N2 component, at this time last year, the vaccine in use in 2006/2007 contained an A/Wisconsin/67/2005-like strain. It was also noted at this time last year that there was an increasing percentage of antigenically distinguishable H3N2 viruses that were being isolated worldwide. However, at this time there was no emergence of a well characterized variant group, and also at this time last year, there was no candidate virus for manufacture that was available that gave more complete coverage of the entire spectrum of H3N2 isolates.

So the recommendation of the Committee was to retain the H3N2 component of the vaccine, and that was an A/Wisconsin/67/2005-like virus.

And finally, for the B component of this year's vaccine. When we met last year in February, the 2006/2007 strain contained a B/Malaysia/2506/2004-like strain from the Victoria linage of B viruses.

The majority of B influenza isolates at this time last year belonged to the B/Victoria lineage, although, as always, both lineages were present at different parts of the world.

The recommendation last year was made to retain a B vaccine strain similar to the B/Malaysia/2506/2004-like virus.

And so, as a result of all of the deliberations of the Committee and our recommendations last year were for the U.S. vaccine composition to be the same as that recommended by the World Health Organization. The result of this was that the preparation of vaccine for the current season was on schedule, and the supply was plentiful. However, recently mismatches have been noticed between the strains included in this year's vaccines, and strains that are currently circulating now, the winter of 2007/2008. And this is particularly the case for the H3N2 components, and the B components of the

vaccine.

I'll remind everyone that we now have quite a few licensed influenza vaccine manufactures, and so the recommendations apply to an increasing number of companies that manufacture vaccine both here, as well as the rest of the world.

For inactivated seasonal vaccines, we have vaccines from Sanofi-Pasteur, Novartis, GSK, ID Biomedical and, most recently, CSL.

We have one licensed influenza live attenuated influenza vaccine made by Medimmune.

I'll also remind everyone that the entire process of strain selection is fairly fixed, and somewhat rigid. This is due to the nature of the situation of influenza.

If you look at the bottom of this slide, you'll see that the process of surveillance, trying to identify new strains is a year long process. This is ongoing all

the time. However, recommendations for strains to be included in the vaccines typically take place twice a year; (1) the time of year now in February for the northern hemisphere season next year, and then in the fall, in early September, usually the strain selection for the southern hemisphere takes place. But if you notice in the middle, preparation, seed viruses, monovalents, trivalent formulations, all of these take quite a bit of time. And, of course, it's very complex and difficult to get all three strains manufactured for inclusion and distribution of the vaccine in time for use in the northern hemisphere, which is shown at the very top from October through January.

Now recently, last week, in fact, the World Health Organization convened a group of influenza experts in Geneva to make recommendations for the composition of influenza vaccines to be used in the northern hemisphere winter of 2008/2009. Influenza

experts from all the different WHO Collaborating Centers met in Geneva on February 11th through 13th, and there they analyzed the antigenic and genetic characteristics of seasonal influenza strains circulating globally, taking into consideration epidemiological data on influenza obtained from different countries and regions. And at the end of their meeting, they made recommendations for the composition of influenza vaccine for the northern hemisphere 2008/2009 season.

This can be found on their website. But to summarize in this slide, their recommendation was that vaccines for use in the 2008/2009 influenza season northern hemisphere winter contain the following:

An A/Brisbane/59/2007 H1N1-like virus;

An A/Brisbane/10/2007 H3N2-like virus, and;

A B/Florida/4/2006-like virus.

As you will note, all three of these are different from what is currently in the vaccine now in use in the northern hemisphere.

They also noted that, as in previous years, national control authorities should approve the specific vaccine viruses used in each country. And this is why we're here today, because this is the role of CBER and the VRBPAC to select the strains for use for vaccines in the United States.

Toward that end, the agenda that we've set up today will be to focus on the strains that we should recommend, and this slide shows briefly what we will present today.

We'll have a review from Joe Bresee of CDC on recent influenza virus surveillance data in the U.S., as well as some data on vaccine effectiveness.

Nancy Cox, also from the CDC, will review world surveillance data, and provide

some information about strain characterization.

We'll then have a presentation from The Department of Defense by Angela Owens and Thomas Gibson, who will talk about their data on vaccine coverage and effectiveness, as well as some sequence analysis of different virus isolates.

Zhiping Ye from CBER will review serological responses to current vaccines, and Rajesh Gupta will provide an update on the availability and timing of candidate strains and reagents.

And at the end of that, Tony Colegate, from Novartis, but who represents PhRMA, will provide comments from manufacturers.

After that, the Committee will discuss and recommend the strains that should be included in the vaccine. And as a preview, I'll provide this slide now, but then I will come back up at the time the Committee begins

its deliberations and flash this back up. But it's essentially the same question that we ask every year, and that is, what strains should be recommended for the antigenic composition of 2008/2009 based on the epidemiology and antigenic characteristics of the influence virus strains circulating in the human population, the serologic responses to circulating influenza viruses of persons immunized with the current influenza virus vaccines, and of course, the availability of vaccine candidate strains.

I'll also give you some various options to consider, and we then will talk and make recommendations.

And that's all I have for the intro, and I guess unless there are specific questions about this, we'll move on to Joe Bresee.

CHAIR MODLIN: I don't believe there will be now, but let's move on. Dr. Bresee?

DR. BRESEE: Good morning, everybody.

Can I have my slides, please?

My name is Joe Bresee. I'm from the Influenza Division here at CDC.

I hope everybody can hear me.

I'm going to briefly, very briefly, take you through what we know about this season as an appetizer for the meat to follow, maybe.

We're going to start with geographic spread. I'm going to show you a series of maps. These are the maps that we get from state health departments each week. Notice that, even in November, we start counting the season, and they start reporting in early October, the last day of September this year, but even six weeks into the season in early November, there was very little activity in the nation. No regional disease yet, only three states reporting local disease, even six weeks into the season this

year. And I'm just going to flip you through, just to let you know how the season progressed.

Even by December, there were a handful of states with local disease, which just means that they were identifying increased activity in one location in a state, but nobody yet was reporting regional disease, which would mean there is increased influenza activity in at least two parts of the state, or regions of the state. And really wasn't until the last week of the year, when we first started seeing regional activity reported by state epidemiologists in a handful of states, and the season actually really got going about mid-January this year, when the first states started reporting widespread disease.

And I'll flip through the last four weeks, and as you see over the last four weeks, increasing numbers of states have been reporting widespread disease up until this last reporting week, ending last week, where

there were 44 states that reported widespread activity, 49 states reported regional activity, just illustrating that really the same phase, or at the same time, pretty much the whole country is reporting widespread or regional disease in the United States. So a slow start to the season, but over the last four or five weeks, we've seen rapidly increasing levels of disease.

The viruses we're seeing are represented here. And I apologize for this small font for those unfortunate enough to be in the back. But let me just show you what this means.

These are the viral lab data that we get reported to CDC. States around the country will report each week the number of samples they test and the proportion positive, and then report us any information they have on type or subtype. And this is by week this histogram.

The bars represent the numbers of

isolates that are influenza positive. The line graph, which may be difficult to see at the back, represents the proportion of all samples tested that are positive.

And what you see here again is that, early in the season, there was relatively little activity. Most of it was A, and most of that was H1 early in the season. Really since mid-January, we've had increasing levels of activity in the nation, represented here by the increasing in proportion positive, and increasing over time that the proportion of the viruses that are H3, and I'll show you that in two seconds.

Right now, from September 30th, a little over 80 percent of the samples that are the reports coming to CDC are of A viruses, 17 percent are B, and of the viruses that are reported to have been subtyped, about 60 percent are H3, and about 40 percent are H1 viruses. And, again, this represents a shift in recent weeks to H3 from H1.

This is represented, same curve, different box. This is the last week's data that were completed yesterday.

Last week, again, we're getting the 80/20 A/B split, but again, this represents the fact that, over the last few weeks, we've seen increasing numbers of H3s, 90 percent of the viruses that were reported to be typed last week were H3 viruses, and only about 10 percent were H1 viruses.

At CDC, we monitor influenza associated mortality in two different ways. I won't go through all the surveillance systems, because I suspect that folks in here are well aware of them. I'm happy to answer questions about them, though.

This is our 122 cities system, which monitors the proportion of death certificates that pneumonia or influenza listed on them by the week in the United States. This is for each season. Our season here is on the far right side of the screen,

and what you see is that, for six weeks running, the proportion of deaths attributable with a pneumonia and influenza designation on the death certificates have exceeded an epidemic threshold for six weeks running, and currently are about 8.1 percent of deaths are P and I associated deaths.

If you compare this year, both the height of the curve, the slope of the curve and you get a hint of the area under the curve, the amount of excess P and I mortality is not too dissimilar to these two years, three and four years ago, in which H3N2 was the predominant strain. But it's slightly higher than the last two years, which have been relatively mild years.

The other way we look at mortality is pediatric deaths. These are a nationally notifiable disease. All kids under 18 that die that have an influenza positive test are meant to be reported to CDC.

Again, the far right side of this

graph represents data from this season. We've had 22 pediatric deaths that have had an influenza positive test reported to CDC so far this season. And again, I just want you to see this compared with last year, when there were 73 such deaths reported over the season, and the year before, when there were 46 such deaths reported. That the slope of the curve, the height of the curve and the look of curve really is consistent with what we've seen since we've been monitoring this outcome over the last three years.

We're still in the middle of the season, and how this will look at the end of the season is uncertain.

Briefly, outpatient disease, you guys have seen these curves, probably, that have looked at our website, I hope. This is this week's season, again, and just to say that the proportion of visits to sentinel physicians that are associated with influenza-like illness is above a seasonal baseline.

The red curve we're looking at here is CDC data, and it's above baseline in all nine regions this week, again showing diffuse levels of illness, or levels of illness that are increased diffusely across the nation.

We monitor hospitalizations. I won't go through it. Just to say that these red curves here that no one in the back can see at this point represent that the rates of pediatric hospitalizations are consistent with the rates seen in previous years so far this season.

I'll mention briefly a word about antiviral resistance, because it's been in the news lately. These are data that were produced by Dr. Sasha Klimov and Dr. Larissa Gubareva at CDC just yesterday, and updated just yesterday, and shows that, since September 30th, of the influenza viruses that CDC has tested for Oseltamivir resistent, 27 of the 471, or 5.7 percent have been found to be Oseltamivir resistent. All those resistent

strains, all 27 are among H1s. And if you look at just the H1s, you subset those out, 8.1 percent of the H1s tested so far this year are resistent, all with the same point mutation, which is clearly the most common mutation that confers resistance to Oseltamivir among H1s.

Importantly, no resistance has been found, either among H3s, or among these so far this season. The 27 cases come from all regions of the country. The cases for which we have data, which represent about 16 of the 27 so far, don't have any travel history that would be concerning, for outside the United States, at least, and the cases don't have any known Oseltamivir exposure, either personally, or in a household member around the time of the illness.

Importantly, all the H1N1 isolates that -- all 27 that we found that are Oseltamivir resistent are susceptible to Zanamivir and adamantanes so far.

And just to give you a quick update about adamantane resistance. Again, I apologize to those in the back that can't see this, but so far this year, we've tested 282 influenza viruses for adamantane resistance; 99 percent of the H3/N2, I think 98.6 to be exact, are adamantane resistent, and about seven percent of the H1s are.

Principally H1s have been tested, the lion's share of the viruses tested have been H1s, just because that's what's been circulating up until now in the U.S.

Just to compare our 8.1 percent resistance among H1s to what's been seen in other countries, The global proportion of resistance is 14 percent. If you break that down, Europe's slightly higher, really driven by a couple of countries, France and Norway, but the U.K has similar proportion resistent compared with the U.S., and Canada, as you see here, is six percent, not much different than our 8.1 percent. There have been very few

viruses tested relatively from Africa or Latin America at this point.

Just my Public Health brain working. To investigate the Oseltamivir resistant, we've done a couple of things. We've increased surveillance in the United States, we've increased the number of viruses that we've looked at, we've solicited viruses from our Sentinel providers and our state health departments, and we'll continue to do that throughout the season to better monitor where this curve is going.

We've also undertaken a system by which we're collecting fairly detailed clinical and epidemiologic data on each resistant case, with the intention of looking for risk factors and clinical characteristics of these cases relative to susceptible cases.

We've embarked on a fairly aggressive communications campaign, which I'm happy to go through later. But in short, our policy for the use of Oseltamivir hasn't

changed yet, principally for two reasons: (1) because the level of resistance among As, or among flu viruses generally is quite low, and all the resistance is among H1s at this point, which comprise a relatively small, a minor proportion of the viruses isolated, and probably with H3 predominating, even a less major role in the coming weeks.

I want to mention this; Jerry had mentioned that I would, and so I will. CDC, for the last three years, has established mechanisms to look at the effectiveness of the vaccine each year in the United States. This year, for the first time, we are testing methods to measure the effectiveness of a vaccine during the year, at different time points during the year, and we've started that this year.

We're doing it in a population in the midwest that comprises people, or groups, who are recommended by the ACIP to receive annual vaccination. That's our study cohort.

We follow these folks for medically attenuated clinic visits, really, for influenza that's diagnosed or documented by RTPCR. And their exposure history, their vaccine history, is measured or confirmed with a validated vaccine registry.

I won't go through the methods or the results in any detail, only to say that the population we're studying only started getting increased flu about two and a half weeks ago, or we have about two and a half weeks of data. In this two and a half weeks, they enrolled 616 patients in the study; about 30 percent were flu positive, most of those were influenza A, though we don't have the subtype information yet. We do know that, in this area, H3s have predominated this year from other data.

Preliminary results indicate that there is some protection in this population among the influenza A viruses. And again, if that's H3 circulating, that's probably good

news.

There's no protection against influenza B viruses yet that we've seen, though a relatively small fraction of the cases have had influenza B viruses isolated from them.

We're continuing enrollment of the study to build up our sample size, and so that we can make our numbers more precise and more reliable.

The laboratory at CDC is looking at the strains from the study so we'll be able to create type and subtype specific vaccine effectiveness estimates, and we will report these data out in the next few weeks, probably as an MMWR.

There we go.

My last note is next Wednesday the ACIP will be voting on influenza vaccine recommendations for the coming year. I'll just highlight the fact that this year's discussion and the vote will be around whether

or not to expand influenza vaccine recommendations to children between six months and 18 years of age, and so expand to five to 18 year old children -- five to 17 year old children, and whether that expansion will be done this coming season, or in the seasons to come.

That's all I have. Thank you very much.

CHAIR MODLIN: Thank you, Joe. I think we'll go on with Dr. Cox's presentation on global surveillance and then, hopefully, we'll have a little bit of time for questions on this segment right after her presentation.

MEMBER COX: Well, good morning, ladies and gentlemen. Because some of my slides are visually challenging, and I'm visually challenged myself, I'm going to stand over here so that I can point things out more easily.

First, I'm going to start out with the review of the laboratory data for

influenza A H1N1 viruses.

This is a compilation of global data that was done by the WHO Secretariat based on reports from the National Influenza Centers in about 93 countries -- or actually about 120 countries around the world.

So you can see that, for H1N1, the U.S. had quite intense activity during the early part of the year. This is the compilation from September to January. We also have slides going through month-by-month, but that just takes too long. And there was a lot of activity in Europe, and Europe has experienced predominately H1N1 activity.

There was still a bit of H1N1 activity in the southern hemisphere during this period, sort of at the end of their season, and China experienced very little H1N1 activity compared to H3N2.

Okay. Now we start the data dense portion of the talk. And I'll really try to keep this as simplified as possible.

Remember, what we are looking at here, for those of you who have been here before, you're looking at the reference strains up here. These are important strains that have been used in our lab, and often in a number of other laboratories, Collaborating Center laboratories, and we have made reference, ferret antisera to these viruses by infecting ferrets.

Then we have our test antigens, starting here and going down.

We have highlighted in yellow the column here for the Solomon Islands vaccines strain that was included in this year's northern hemisphere vaccine. And so what we're looking for is a difference in titer relative to this homologous titer, that is the way that the Solomon Islands virus is inhibited by ferret serum to itself. And what we're looking for are numbers here, or the ability to inhibit antibody that are actually four-fold or greater reduced in titer. So I hope

that's clear to most of you.

So when we see these viruses that are four-fold reduced, we have taken those viruses and put them into ferrets to really try to see if it's truly an antigenic variant, or just a low reactor of some kind.

Now, you do get ferret-to-ferret variability. Some antigens just simply induce a better antibody response in ferrets. We don't understand the nature of that, but nevertheless, we're looking at titers relative to the homologous titer.

What we have seen at CDC, less dramatically than at other WHO Collaborating Centers, is that, more recently, we're seeing viruses that have four-fold and eight-fold reduced titers as compared to the homologous titer for Solomon Islands.

We were provided with a strain called A/Brisbane/59/07 by the Australian WHO Collaborating Center, and this antiserum to this strain seems to cover those viruses

better. We get higher titers here than antiserum to the current vaccine strain.

We also have another virus, called South Dakota/6, which is considered to be Brisbane/59-like, and it behaves similarly in our tests.

Now, if we just look at CDC data alone, we can see that, of the 184 viruses, H1N1 viruses that we've tested that have isolation dates between October 2007 and the current time, about 11 plus 13, or 24 percent of them have reduced titers. That wasn't terribly dramatic, from our perspective, but other WHO Collaborating Centers were seeing a bit different pattern, and have been seeing a bit different pattern for a few months. So these are data from the WHO Collaborating Center at Mill Hill in London. And here you'll see the homologous titer of 640 with the Solomon Islands vaccine strain, and you'll see that there are a lot of what we would call low reactors down here at the bottom. And

these are relatively recent strains, mostly from November, December and January.

So when they looked at antiserum, they had an antiserum against the Brisbana/59 virus produced in Australia, and they saw much better reactivity here than they did here. And then they produced their own ferret antiserum, and got a similar pattern.

When the data were compiled from all four WHO Collaborating Centers, you can see that, if you look at the low reactors that are down eight-fold or greater, the Australia Collaborating Center was seeing a much higher proportion than we were at CDC at the time these data were compiled. They aren't the most recent data, but they are the compiled data that were available for our meeting in mid-February.

And also, there was a much higher proportion that were low reactors to Solomon Islands in London, as I mentioned. The other two Collaborating Centers saw lower

proportions.

Okay. So now we're moving on to the genetic data. The genetic data are used as an adjunct to our antigenic data, and they're very important because they really help us understand the relationships between the viruses that we use as our vaccine strains, and as our reference strains. And it's very important to note that sometimes you will see quite striking differences in the genetic grouping of viruses, but you do not see a difference in antigenicity. So you have to take the two different types of data together. You have to look at the genetic data, and you have to look at the antigenic data together to make sense of what is actually going on.

Now, you just need to really focus on the colors here. You don't need to strain your eyes and try to read these names, but the most recent strains are shown in pink and purple. So we have our vaccine strain down here, Solomon Islands/3/2006 in a grouping

that we called 2A. This group two has now split out into three groups, 2A, in which the Solomon Islands virus resides, 2B, in which the South Dakota and Brisbane viruses reside, and which compromises the majority of the currently circulating viruses, and 2C. And we do have a few egg isolates up here.

Now the Oseltamivir resistant viruses are all in group 2B. I have designated, using these little triangles, those viruses that are amantadine and rimantadine resistant, and they are in group 2C. So the viruses, as Dr. Bresee said, that are resistant to Oseltamivir, are sensitive to Zanamivir, another neuraminidase inhibitor, and to the adamantanes, as well.

So I hope this gives you a bit of a reference. Once again, here's the vaccine strain, here is the WHO recommended strain, Brisbane/59/2007-like. South Dakota is another potential Brisbane-like strain, and then there's another group up here.

Okay. Here is an evolutionary tree for the neuraminidase genes. Now remember that the neuraminidase gene is the gene that most often carries resistance to the neuraminidase inhibitors, as would make sense.

And the viruses that are resistant to Oseltamivir are down here, and all of their neuraminidases cluster together, while their HAs form three separate groups.

So here's another Oseltamivir resistant virus down here. And Japan, most of the European viruses cluster here. You can see one from Norway, and one from France. And the Japanese viruses, actually, are in a little bit separate group. I think they're falling out somewhere up here.

Now, if we just look at the neuraminidase sequences, we can see there is a lot of diversity here. But the neuraminidase genes have fallen predominately into the group 2B situation, whereas we don't see the neuraminidase of current viruses falling into

the group where the vaccine strain is.

Now just -- I know that Zhiping will be covering the serologic responses, but I thought that it would be nice to put up CDC data for the pediatric serologies that we've done. All of these children are between the ages of six months and 34 months, and these children haven't been immunized before. This group is one that's been recommended for immunization and, of course, they're being immunized in greater numbers. So we really want to know how they respond to vaccine.

We're still looking at responses after the first dose compared to after the second dose. And then, because these children haven't been exposed to a wide variety of influenza strains before, obviously, they have responses that are really very clear cut. And so what we were able to see, and this was reflected in the data for adults and the elderly, but what we were able to see very clearly is that children who had two doses of

the Solomon Islands vaccine mounted a very robust response with the post-geometric mean titer of 202 after the second dose.

When we tested the same serum against the Brisbane, South Dakota and Cambodia strains, we saw much reduced titers of between 15 and 26. Those are geometric mean titers.

The same pattern is shown for this separate set of serum that was provided to us by FDA. Here we don't have the titers post the first dose, but we do have a nice robust antibody response after the second dose, and a clear diminution of titer to the Brisbane, South Dakota, and Cambodia strains.

So in summary, H1N1 viruses predominated in most countries worldwide, and caused outbreaks in some. Many of the viruses were closely related to Solomon Islands/3/2006. There were a few that were New Caledonia-like, which was the previous vaccine strain. But there really was very

clearly an increasing proportion of viruses that were antigenically distinct from the A/Solomon Islands vaccine strain, and more closely to A/Brisbane/59/2007.

The majority of the HA sequences were in clade 2B, and of course Brisbane is in clade 2B.

Now there was, as Joe mentioned, an increasing proportion of clade 2B neuraminidases with this particular mutation, that's been well characterized for a number of years as being a mutation that confers resistance to Oseltamivir.

Importantly, Oseltamivir-sensitive and Oseltamivir-resistant viruses are antigenically similar to each other, so we don't have to consider this in our vaccine strain selection.

So the WHO recommendations, based on data from the four Collaborating Centers, and many national influenza centers, were to change the H1N1 component of the vaccine for

the northern hemisphere, and update it to an A/Brisbane59/2007 (H1N1)-like virus.

We'll move right along now to H3N2 viruses. This is a cumulative map of the H3N2 activity globally from September to January, September 2007 to January 2008. You can see that we've had widespread outbreaks in the United States. Compared to the rest of the world, the United States has really had more H3N2 activity than any other country.

During this period of time, there was some residual activity in the southern hemisphere as their season wound down. And China is actually having H3N2 activity, but their season doesn't seem to be, or hasn't seemed to be quite as intense as ours.

Okay. Now if we look at the data. This is the test that's been done with guinea pig red blood cells, and we do see some differences when we do our H3 test with guinea pig red blood cells versus turkey red blood cells, which is the standard red blood cells

used.

Here you can see the homologous titer for the current vaccine strain. Wisconsin/67/2005, the homologous titer's quite high here, 2560. And you can see down here a number of the viruses with lower reactions, really quite markedly reduced from 2560 down to 160, and 320, and so on.

Here in the second column we have Brisbana/10/2007. The homologous titer is 640. And we can that this antiserum covers the currently circulating viruses very well.

We have a number of other viruses over here. In particular, I would like to point out the Uruguay/716/2007 virus, which is Brisbane/10-like.

Now last year at this time, and I think this is very important, the two groups of viruses that we were looking at most closely were the Nepal/921 and Henan/147 viruses. Now these were in two slightly different genetic groups. We were concerned

about them, but then, in fact, they didn't take off, and Brisbane-like viruses popped up after our decision had been made in February last year.

So in terms of our frequency data, we have tested a total of 90 H3N2 viruses. That number will be going up rapidly as we are receiving an enormous number of packages from state health departments and others. Of those 90 viruses, about 82 percent are Brisbane/10-like, just a few viruses were well covered by antiserum to the Wisconsin virus, and then we have a few viruses that are lower to Brisbane. And that always happens. That's not unusual.

Here I've included an HI table from the laboratory in Melbourne for completeness, because I wanted to make sure that you realized that, when we make vaccine strain recommendations, we're really relying on data from around a world. In Melbourne, they get quite a few viruses from Asia, Singapore, Thailand, the Philippines, and so on.

Here is their 640 homologous titer with the Wisconsin/67 virus. And you can see that coverage here, these titers are relatively low, in the 40s. Many of these in the 40s, and some even less than 40, which is their cutoff.

In contrast, we have the homologous titer of 640 for the Brisbane/10 virus, and we have better coverage, much better coverage, relative to the Wisconsin, of the currently circulating viruses. Although there are, as I mentioned before, some low reactors.

If we look at all of the data collected as of mid-February by the four WHO Collaborating Centers, and this was compiled, as I said, by the WHO Secretariat, the majority really could be characterized as Brisbane-like, but there were low reactors, and in some WHO Collaborating Centers, there were more low reactors than others. And we don't really know the meaning of this. I think that we're going to be doing a variety

of tests in conjunction with the other Collaborating Centers looking at different red blood cells, and a whole variety of different ways to test these viruses to understand what's actually going on.

Now, over recent years, we've been engaged with a group that is at Cambridge University headed by Derek Smith. And Derek, we provide all of our data to Derek, and he does what is called antigenic cartography, which is basically to say he uses some number crunching programs that take our HI tables, and reduce them to a visual display that's actually much easier to understand than the reams and reams of paper, and hundreds and hundreds of numbers that we have to look at. It's not to say that we don't get exactly the same gestalt that he gets, that he presents by looking at all these tables every week, but this is a nice way to display what's going on.

So you'll remember we had a large epidemic caused by the Sydney/97 virus, the

Wyoming/303 vaccine strain is shown here, and you can see that there are some viruses clustering around there in the light, uncolored circles.

Here's the New York/5504, and here's Wisconsin virus here. And we've got a lot of scatter of the current viruses out here when they're plotted in this way. And here's the Brisbane/7 virus. So these viruses are closer to the Brisbane/7, but you do see these outliers. And we're trying to, as I mentioned, trying to figure out what's going on.

I just have one more slide. These are relatively few data points, but again, the most recent viruses were closer to the Brisbane/10 than to the Wisconsin virus.

Okay. I think that my slides may be -- okay. If we now move on to the sequence data, you'll see right along here that you have a lot of viruses that are in what we are calling the Brisbane/10 group, or Brisbane/10

lineage. I'd like to point out that the viruses that we're really concentrating on as potential emergent viruses last year are down here at the bottom of the dendrogram, and we have seen only one virus in recent time that could be put in that group, and that was a virus isolated in September from Massachusetts.

There is, as you can see, quite a bit of genetic variability, as pointed out by these amino acid changes, that are key in terms of distinguishing these different nodes on the dendrogram.

What I would like to point out is that the Brisbane/10 virus is here. It's actually a February 2007 isolate that wasn't on our radar screen last year during vaccine strain selection. But clearly, there are some changes that have occurred that are common to all of these viruses, and then there are some individual differences among these strains.

I should point out that all of the

viruses that have the hatch marks after them or the pound signs after them are egg isolates. And in contrast to what we've seen for H1N1 viruses, we find H3N2 viruses very difficult to propagate in eggs. And so we have to go first into kidney cells, which an acceptable substrate, and then pass on into eggs.

So we have the Uruguay egg isolate here, and it's considered to be Brisbane/10-like.

I'll move on to the neuraminidase genes. We see exactly the same pattern for neuraminidase genes. There are a number of changes that occurred, and are all present in viruses within the Brisbane/10 lineage. Here are the Brisbane/10 isolates, a whole variety of high growth reassortants, as well as the Brisbane/10 egg isolate.

I want to note that, again, the neuraminidases of the older groups, the Nepal lineage groups are down here, and I forgot to

mention, here there is one group that we're keeping a very close eye on, and we're calling that the British Columbia lineage, because it does have a number of changes in antibody combining sites that we're looking at. But these viruses really haven't taken off. But nevertheless, we do have an antiserum prepared to viruses in this group, and we're trying to obtain an egg isolate for this group for the future, and we will watch this very carefully.

Now once again, I'm going to show the antibody responses of children who were vaccinated with the Wisconsin vaccine strain. And once again, we see that we don't get a really dramatic rise after the first dose of vaccine, but after the second dose of vaccine, we have a post-vaccine geometric mean titer of 76 for the vaccine strain itself, as compared with less than 50 percent of that, or 35 to the Brisbane/10 strain, and only 15 to the Uruguay strain. And that is true. There is at least a 50 percent reduction in post-

vaccine geometric mean titers for the more recently circulating strains.

This year, we decided we really needed to move forward and do microneutralization tests on as many of the sera as we possibly could. And here I have a table that was done using serum from two adult populations, one from Japan, and one from the U.S.A. If you we look at the panel for the U.S., we see that we had a nice -- there was actually quite a bit of antibody prior to vaccination with the GMT of 123. But there was a very nice robust response post-vaccination, that titer went up to 854.

In contrast, when we looked at the Brisbane/10 egg isolate, we saw about -- well, less than a third of the post-vaccine geometric mean titer that was obtained with the vaccine strain. So there were reductions.

Interestingly, when we looked at some of the high growth reassortants, we could see in particular that the Brisbane/X171

reacted a little bit differently than the Brisbane/171A. And there was a higher titer, and it looked a bit more like the Wisconsin virus.

We're continuing to look at changes in the viruses themselves for all the high growth reassortants, and really analyze which of these high growth reassortants are most acceptable for vaccine production.

So the WHO recommendations were to update the strain to A/Brisbane/10/2007/H3N2-like virus.

Influenza B viruses circulated in China and Hong Kong, and not very much in Europe, circulated in the U.S., and I think this a bit overstates. This, as I said, was put together by the WHO Secretariat, and I think it a bit overstates the extent of influenza B activity that we've had, although there have been some localized outbreaks.

You'll remember that influenza B viruses are divided into two separate

lineages, both by their antigenic reactivities, and by their genetic patterns. And one of our major problems is that these two lineages of influenza B viruses have been co-circulating in the world for a number of years, and sometimes they alternate, sometimes we have several years in a row where we don't see, for example, B/Victoria viruses. We had almost a whole decade where B/Victoria viruses circulated only in Asia. But right now we do have both groups circulating globally.

The majority of the viruses that have been examined this year are in the Yamagata lineage, which is outlined here by the yellow color, but we do see a few viruses that are of the B/Victoria lineage outlined here in B in green, and you'll remember our previous vaccine recommendation was A/Malaysia/2004-like, and we see a bit of antigenic drift there, although our Ohio serum seems to cover a bit better, and they're considered like each other.

Now if we concentrate on the Yamagata lineage viruses, the predominate lineage globally, we can see that we have this Florida/4/2006 strain that we've had in the lab for a while, and we've actually sent it to all the other WHO Collaborating Centers and the vaccine manufacturers. And these two strains here, Florida/4 and Brisbane/3, just to confuse everyone even more, we have another Brisbane strain, were used in vaccine manufacture for the southern hemisphere.

So if you'll recall, the southern hemisphere recommendations differed from our northern hemisphere recommendations by two strains, and these are the two strains that were used in vaccine manufacture.

So if we look at the CDC data, we tested a total of 97 influenza B viruses. The majority were Florida/4-like. We did have some that were in the Victoria lineage, and they were mainly Ohio-like.

This may be difficult for you to

see, but I did want to include a table from one of the other WHO Collaborating Centers, and unfortunately, I just was able to cut and paste, and couldn't improve the projectability of this particular slide. But here you can see we have the Florida/4 antiserum, and it is covering these strains that are in the Yamagata lineage very well. So I think that's the main message there.

So if we look at the compilation of data, we can see that the majority of the viruses in all of the four WHO Collaborating Centers were in the Yamagata lineage. Actually, Japan had very few influenza B viruses to look at. And so 84 percent overall were Yamagata lineage viruses, and 16 percent were Victoria.

So here we go with the evolutionary relationships among the HAs of Yamagata lineage viruses, and we have a bit of a complex picture here. We have two groups of viruses. The Florida/4 is here. Many of the

more recent viruses are here, but we can't detect antigenic differences between these two groups. And it's not too surprising, there aren't that many changes between them.

And just to be complete, although I don't think it has much bearing here, we have an evolutionary tree for the B/Victoria lineage HAs. And the most recent viruses are showing up down here. Here is the Malaysia vaccine strain, and I don't really think there's a lot more to say about that.

Okay. Now for the neuraminidase genes. All of the influenza B viruses that are circulating, whether they are of Victoria lineage or Yamagata lineage HA, contain Yamagata lineage neuraminidases. But there's been a great deal of diversity that's occurred, and you can still separate them out. So if you have a Victoria virus, in spite of the fact that its neuraminidase originally came from a Yamagata lineage precursor, you can tell where it should go on the tree unless

there's been reassortant. And we haven't seen reassortment among the viruses that we've been looking at.

Here, for your reference, is the B/Brisbane strain, and here is the B/Florida/4 strain. So these are the two Florida/4-like strains that were used for vaccine production in the southern hemisphere.

Again, the pediatric serologic data are really quite clear. When you immunize children, young children, with the B/Malaysia strain, which is on the Victoria lineage, you get a nice robust response post the second dose, and you have post-vaccine geometric mean titers of 55 and 58 for the two Victoria lineage viruses. But for viruses in the Yamagata lineage, you do not see that robust response, and you only have post second dose vaccine geometric mean titers of nine,10 and six here for some of the circulating strains.

The same is true for the serum panel provided to us by FDA.

And we've noted this in children. It's not true in adults, however, but we've noted this in children before that you get very clear delineation between the antibody responses to the two different lineages of influenza B viruses, whereas, in adults who have been exposed to both lineages of viruses, you do see a bump in titer to viruses on the other lineage.

So, summary of influenza B. Influenza B outbreaks were reported in several countries. Viruses of both the lineages were reported in many countries, but Yamagata lineage viruses predominated.

For the Vic lineage minority group, most were related to Malaysia or the Ohio. However, most of the recent B/Yamagata lineage viruses were antigenically similar to B/Florida/4, and the northern hemisphere vaccine stimulated HA antibodies that were similar in titer. And I guess I won't go through this point because, actually, Zhiping

will be covering that later.

So WHO recommended that the vaccine be updated to include a B/Florida/4/2006-like virus.

Okay. So I will stop there. And if there are any questions, I will be happy to answer them.

CHAIR MODLIN: Yes. Great. Thank you, Nancy.

Let me ask if there are questions for either Dr. Cox or Dr. Bresee regarding their presentations. And we'll start with Members of the Committee. Melinda?

MEMBER WHARTON: Nancy, that was terrific.

Has there been any discussion at WHO about potentially having a quadrivalent pediatric vaccine that included both the lineages? I know this is something that this Committee worries about every year, and trying to figure out how one keeps the conversation in sync, given the global nature of influenza

vaccine production.

MEMBER COX: There really has not been extensive discussion at WHO. As you recall, on a couple of occasions, WHO recommended either a B/Victoria lineage or a B/Yamagata lineage virus, depending on the epidemiology of the country. So national authorities could really choose. But I think that WHO's focus is really on making recommendations that are generally applicable, and it would be left to national authorities to decide if they wanted to included two B strains.

On one occasion in the past, the Netherlands actually did include two B strains in their vaccine, and they looked at responses to both lineages of B viruses, and found good responses. But that's the only situation I know where a national authority has decided to go ahead and include two B strains.

CHAIR MODLIN: Dr. Couch?

MEMBER COUCH: Nancy, a couple of

technical questions, just to help my understanding, because I'm not a gene jockey. But I was beginning to assume that the genetic data is complementary, as you've said, to the ferret immuno relationship data. And how tight is that relationship, is my question? In other words, are all 2B strains react the same with ferret sera, and 2C strains react differently, or how do they relate to each other in that respect?

MEMBER COX: No, unfortunately, and many people have suggested that we just go to sequencing to do vaccine strain selection, and frankly, it would save us a lot of work. But the problem is that sometimes you have two genetically quite distinct groups, but they react similarly.

Alternatively, you can have one single amino acid change, and the rest of the gene is the same, and that can cause quite a distinct antibody change, change in antibody reaction.

So there is generally concordance, but sometimes, when you think you should be able to detect antigenic difference, you do not, and sometimes when you wouldn't expect one, you do see it.

So, but we're looking for reassortment, we're looking for low reactors, and do they cluster together. And what we're seeing now is that the low reactors tend to be sprinkled through the evolutionary tree, and they're not clustering together, indicating that there may be an issue of avidity, or glycosylation, or other issues that's actually impacting the reactivity that we see.

MEMBER COUCH: You prompt me to go ahead with my question, then, is that, how do we use that for our selection strains? How do we use the genetic data, then, to make our strain selections?

MEMBER COX: Okay. The genetic data are actually extremely useful. First of all, the genetic data can tell us very, very

quickly whether we have resistant viruses, so that's a public health issue, not a vaccine strain selection issue, but it can tell us if certain amino acid changes are having an impact on the antigenicity. And what we're often looking for is a pattern of what we call signature changes that absolutely confer a difference in antigenic pattern. So many times in the past we've been able to say, these are the signature changes, and this is the antigenic pattern that we expect to see when any virus has those particular signature changes.

Now what it looks like to me is that there is quite a bit of sputtering around that's going on, both with the H3s, and with the H1s. The differences with Bs are not so dramatic, and have a lot more to do with glycosylation right at the tip of the molecule. But it looks to me like we're in one of these periods where the virus hasn't quite decided, if you want to put it that way,

where the virus is looking for the next path forward. Now that puts us in a very difficult position, because we've had B/Brisbane-like strains circulating, but there is no clear emerging new variant, there's just -- if I could go back to that, I won't, but if you look at the evolutionary tree, you'll see that there's quite a bit of amino acid variation within that Brisbane/10 group, but you can't say, boom, that's the one that's going to go.

MEMBER COUCH: Okay.

CHAIR MODLIN: And Nancy, presumably you sequence the entire HA or neuraminidase gene, I would guess?

MEMBER COX: Correct.

CHAIR MODLIN: And so that there's going to be parts of that gene that don't code for antibody binding sites, and some that do.

Would it help if you were to shorten that to a degree with the sequencing, would it in any way -- I was getting at Bob's question, is it more likely to predict --

MEMBER COUCH: You don't do the whole sequence.

MEMBER COX: We actually do.

MEMBER COUCH: I didn't know that.

MEMBER COX: And I don't know if we can go to my supplementary slides. One of the useful things that we can do is to actually plot where the changes are on the three dimensional structure, and we know a lot about antibody combining sites, and receptor binding sites, and so on.

We need to go back. Okay.

So what we've been concentrating a lot on is is to look at where the changes are occurring between the cell grown isolate, and an egg grown isolate. And then where the changes occur when you make the high grow reassortants, and really trying to understand what's going on around the receptor binding site, or the H3 viruses. Because we believe there are changes in the receptor binding site, perhaps subtle changes in the shape of

the receptor binding site.

So the most interesting thing is to actually plot on the three dimensional structure, and this is just a monomer of the trimer shown here with a space filling model. And you see that, right at the receptor binding pocket, you have a change, and this is a known egg adapted change. And every single H3 virus that we managed to get out of eggs, or kidney cells, and then eggs, after putting in hundreds -- literally hundreds of clinical isolates, has one or more changes around the receptor binding pocket that enable it to grow.

And then what we have done is looked at the different Brisbane hydro 3 assortants, and plotted the changes there. And I won't go through this in detail unless we need to.

And then we've looked at the -- you know, from the top of the molecule, we've seen that a number of the hydro 3 assortants

actually have a deletion right here at the top of the molecule. You're looking down at the top, the head of the trimer. And then here's the receptor binding pocket, and we have changes there.

Anyway, so it's really quite informative to see precisely where those changes are, because your antibody combining sites are not contiguous, they're conformational.

Does that help at all, or is that more confusing?

CHAIR MODLIN: Very much so.

Jack?

MEMBER STAPLETON: So would it be -- I mean I think what you're saying, for Bob, perhaps, to clarify for Bob, is that, in addition to those sites, you can have mutations elsewhere: the change of confirmation, the antibody binding sites, or the receptor. And at this point, no clear patterns emerge in any of those sites.

MEMBER COX: That's right.

CHAIR MODLIN: Other questions? Ted Eickhoff?

MEMBER EICKHOFF: Nancy, could you comment a little bit further on the Microneut tests? You've avoided doing a direct comparison of Microneut and HI. But do they track generally in parallel? Is there a Microneut titer level that you can equate in any way with protection, in the way we use one to 40 as a general cutoff for HI as protection, even though it's far from absolute?

MEMBER COX: Yes. We're actually doing a lot of that work in Jackie Katz' lab at CDC. She has been working very hard over the years to do correlations between Microneut and HI, both for H5 and for H3. And, of course, for H5 you really can't detect antibody in the serum of infected individuals using a standard hemagglutination and a vision test. You have to use, of course, red blood

cells and there are a lot of complications.

And there's been an international study and an ongoing study to try to standardize the microneutralization assay because so many different labs use totally different techniques. And so there's an ongoing effort to standardize Microneut and to really look at a correlation.

Now for H5 what you see is about a twofold higher titer for H5 viruses than you do using the HI tests. So Microneuts are about twofold higher. They're always more sensitive for detecting antibody.

And I don't think we really are able right now to say that a 1 to 40 in HI is equivalent to a 1 to 160 or a 1 to 80 for the H3s. But that work is ongoing.

CHAIR MODLIN: Further questions?

Let me just ask if there are any members -- yes, Bruce Gellin?

MEMBER GELLIN: We struggle with this every year and, in fact, the collection

of presentations really helps to put it together. Jerry in his, he commented about where we were a year ago and talked about at this point in time things have not emerged. Joe told us about surveillance, at least in the United States and things are just picking up. So you're somewhat hamstrung by the relatively limited disease activity and the corresponding surveillance that goes with it.

I was just trying to add up what the total number of subtyped isolates are in the WHO Collaborating Centers. It's in the hundreds, maybe, if you look at each one. Are we looking at about the same number of isolates now as we are typically? And then it's also a question of what the disease activity was in other countries. I just don't know whether or not this is -- we're in the place where we always are or if maybe we're behind the curve because the season started relatively slowly.

MEMBER COX: That's for that

question, Bruce.

I think for the United States we're a little bit behind the curve because our season did start slowly. We certainly have more H1N1 viruses to look at than we've had for a long time because H1N1 activity has been relatively sporadic over the past few years. Well, there were certain countries that were effected, but globally we didn't have that many H1N1 isolates.

So I think we're behind the curve with respect to H3/N2s. We would have had more H3/N2s to look at at this time last year. But, you know, each year is different and the total number is probably about the same.

And, of course, one of the difficulties is that there is a lag time between the time the patient becomes ill and the time that we actually do the characterization. And, you know, all of the various steps and how do we speed that up? We keep trying. We send out the message get the

isolates to us or the clinical materials to us ASAP.

And we've had an overwhelmingly positive response from the U.S. labs this year to the point that we have boxes and boxes and stacks and stacks of things to do. But they just arrived last week.

MEMBER GELLIN: A corollary question is, you know this reminds me a lot of watching a Polaroid -- if they still make those -- develop. Where, you know at some point you can actually see what it's going to turn into. And I guess the question then is if you had more time, what's the best date to be looking at? I mean, do you need to buy another month? And I know that you can't answer this specifically and it varies every year, but it's a question of sort of when might you have more confidence of what that picture's going to look at as you get closer to the coming season?

MEMBER COX: Well it's, you know,

it's this tension between wanting to have as much data as you possibly could and you probably would have a better picture by the end of March, or certainly by the end of April you'd have a much better picture. But we really can't wait until then to start vaccine manufacture. So it's this tension between the need to produce vaccine on a given schedule and the need to make a decision so that that can happen.

So in an ideal world, I suppose two more months would be wonderful. But we don't have that time.

MEMBER GELLIN: I'll bring this up again when Tony comes about the other side, the manufacturing end of this.

So, thank you.

CHAIR MODLIN: All right. Dr. Self?

MEMBER SELF: Well, I'm struggling with trying to integrate the space and the time components. The data presented here are

pretty large grain, you know countries, big chunks of time.

But it strikes me that last year certainly viruses were moving a lot faster than the sort of granularity that you're describing here. And there's a lot of variation it seems from Australia to the U.K. to the CDC and they're chucked in time. Do you have anything that tries to separate space and time and gives a little finer grain look at those two components? Because that's the place where I have the most problems?

MEMBER COX: I would be up here for hours, and I could be. But we can look at genetic variation by month, anagenetic variation by month; we can look at all of these things by country and so on and so forth. But you get lost in the data if you have only a few hours to look at it.

So the bottom line is I think that, you know, I'm always open to different ways of presenting the data but I have to give this

Committee an overview. And I think that that's part of the frustration of it. I mean, we have reams and reams and reams of data, and a lot more sequence data but it just won't show up on a slide and it won't make sense. So we really try to focus on what we think will help the Committee understand.

And I'm not sure exactly what kind of granularity would really help at this point.

MEMBER SELF: Well, it's not a question I can answer because I haven't worked with the data. I would suggest that the more genetic data is probably not what we need, but to see some time trends in the antigenicity data by country might be useful, and I think that might be done fairly simply that wouldn't take hours and hours to do.

MEMBER COX: Sure.

MEMBER SELF: But it's a question that we can't answer here. Maybe it's not so much a question that I'm posing, but a plea

for a little better statistical summary in terms of space and time with these data.

MEMBER COX: Okay. I can tell you that for example in the southern hemisphere they were seeing low reactors to Solomon Islands last when we made the recommendations for the southern hemisphere last October. So they had H1N1 viruses, they were already seeing low reactors. We weren't.

There's variation from ferret serum to ferret serum that also has to be taken into consideration. And some of the centers have a lot more difficulty obtaining ferrets than we do, so they don't put so many viruses into ferrets, and they're much more limited where we can really do a lot more ferret work.

So what I would say is that there are definitely time trends that I can describe that we knew even last year at this time that there were low reactors to Wisconsin. We didn't have a good alternative. Brisbane/10 emerged in February and the viruses have

generally speaking been well covered by the Brisbane serum.

What I think is more important than sort of kinds of time trends that you're talking about is to look at where the low reactors actually fall on the tree. So you want to know, okay, if there's an increasing proportion of low reactors, where are they, can we correlate that reactivity pattern with something very concrete like the sequence? And if we can, then that really tells us something about an emerging new group. However, in my slides the low reactors are scattered throughout the tree and that tells us that there's really not a temporal or geographic trend emerging within the low reactors.

CHAIR MODLIN: Bob?

MEMBER COUCH: To keep this discussion going.

CHAIR MODLIN: Well, I want to keep us on time, but if it's an important question,

then yes.

MEMBER COUCH: Well, no, I don't know if it's an important question. Just a comment for Dr. Self -- for both. That I've been on this Committee, been doing this for a long time. And you always try to reduce the decisions to a scientific basis as possible. And it reminded me of one time in the past we had a statistician on the Committee who wanted it reduced to numbers. And there's too much art and too much to be considered in this to make it that simplified.

And so we always end up with a best guess. And we ought to appreciate that that's what we are doing, but still try to make that a scientifically a best guess as possible. And always try to keep learning, despite the fact that I've done this a long time.

Now what I did to try and teach myself something I'll pass along to you. I went back to last year's data that we had here and asked myself why did you miss, you see.

Because why did we not pick -- we talked about Nepal, remember. And that was based on the serologic data that we had last year. And we were concerned about H3. There were a lot of us on the Committee that were concerned about sticking with Wisconsin for a subsequent year.

And so I went back and looked at that data again. And what I came out of that one with was a feeling was that the virus was there and in what we looked at last year, and it was Canada. It was a Canada isolate. Well, you know, we've had isolates from Thailand here and so forth. So what do we do with a single isolate?

Well the missing data the last year was the outbreak data in Canada to go with those isolates, and we did not have that. And I thought that would straighten it out for me if we had outbreaks with a new virus in Canada, then that would point us in a direction, you know, to move away from Wisconsin.

And the WHO data which was sent to us that time says there were outbreaks in Canada. And, you see, we didn't have that data here. And if we're missing something now -- we're not missing, but if we don't have an adequate amount of information now, I would make the plea for it being epidemiologic data.

We've got a lot of virologic data. Just huge amounts, as you see. For a while we dealt without pediatric data, which everybody thought was crucial. Now we're getting that routinely again.

I think we're not getting the detailed epidemiologic data we want. And even the WHO summaries just say quickly it occurred in this country, that country and that -- that doesn't help you. I mean, we got a isolate in Thailand. So what? We got an isolate in Nepal. If Nepal didn't have any outbreaks and there was no spread and there was no problem with the virus.

So my plea would be for more and

better epidemiologic data to feed into these decisions each year. And that's the best I could do for why we missed last year, and might have actually been able to move forward with that correction. On the other hand now, you also have to remember as was pointed out by Jerry, where it was too late. Things are already in the pipeline. Industry had already committed to Wisconsin and the reagents and all that sort of thing. So there's so many things that hamstring you here with even what you would like to do. But we would have pinpointed that out, I think.

CHAIR MODLIN: Bob, those are all good points. I don't want to prolong this, but I want to do point out that many, many, many countries don't have the public health infrastructures to provide the data on a timely basis like we would like to have it, which is often a problem as well. So we're hearing about this much after the effect.

MEMBER COUCH: Yes. The alternative

to that, as best I can tell, now we're all aware the alternative of that would be that you get a whole set of isolates from one location, even if they really don't know what went on epidemiologically. That's the surrogate, hopefully, for an epidemiologic outbreak in those countries that don't know that sort of thing.

CHAIR MODLIN: Thank you.

I think we do need to move on. Nancy, thank you very much both to you and Joe for a very detailed and, obviously, informative presentation.

Our next speakers will be Drs. Angela Owens and Thomas Gibbons, who will be talking about giving us a vaccine effectiveness report.

DR. OWENS: Hello. I'm Angela Owens, and these are my colleagues, Dr. Tom Gibbons and Dr. Chris Myers. I'd also like to point out there are other people who are involved in this presentation, and that's

Jason Garner and Mr. Anthony Hocksworth.

We're going to describe the data from the DoD Global Laboratory Based Influenza Surveillance Program.

And just a little history for you all who do not know about the seasonal influenza and DoD. There are two main lab-based components to monitor seasonal influenza in DoD. The Sentinel site surveillance takes place at DoD military sites worldwide. There are also sites in countries where collaboration efforts take place with DoD overseas research labs such as Thailand, Nepal, AFRIMS is one of them, and it's Armed Forces Research Institute for Medical Sciences, among others.

A second component is the population-based component, and that takes place at mainly at the DoD recruit training sites and also Navy ships and the Board of Health surveillance. And both maps actually show the different sites. The map to the left

shows the eight recruit training sites and the map to the right to the right shows the Sentinel sites.

As far as the background for our collection methods, we request the sites to collect specimens from patients meeting the influenza-like illness case definition and within 72 hours of onset of illness.

Along with this we request questionnaires to be completed. And here's an example of one. It includes the patient's history: travel history, vaccination history, symptom history.

Although we collect vaccine data from the DoD, our beneficiaries, the dependents the children, don't always have a good vaccination status. So this is a good secondary option.

Once we receive the specimens they go through RTPCR for universal A and influenza B and we do viral culture on all of our specimens and they culture for a panel of

respiratory viruses.

All influenza isolates are subtyped and sequenced, and the sequence information is shared with CDC.

This is this season's data up to 19 February. As you can see, the last bar is not a representation of that week because the week was just last week. We're still getting specimens in this week as I speak. So that's bar going to exceed. You can see there's a definite peak.

In the beginning of the season we've seen a lot of H1s and toward the end of the season, right now we're seeing H3s. About 23 percent of our specimens are positive for influenza at this time. And this graph only shows positive viral results.

As far as vaccine effectiveness, we can describe that in our recruit populations. We describe vaccine coverage in our Sentinel sites. You can see the period of review is this season, although for the recruits because

of their sessioning, it takes place in August -- August to now.

The populations vary. In the recruits it will be population-based surveillance, and that will include the vaccine effectiveness. And for the active duty members and DoD beneficiaries it would be the coverage.

Our outcome in lab confirmed influenza, and we identify those patients covered by the vaccine if they were vaccinated greater than 14 days prior to the clinic visit.

So by eliminating those non-DoD beneficiaries we have 2,570 specimens, of which 21.9 percent were positive for flu, 36 percent had an identified vaccination status. Again, the reason why the low percentage is because our population includes DoD beneficiaries which is hard to track the vaccination status.

Seventy-seven percent were

identified as covered by the vaccine, also known as potentially vaccine breakthrough. And although we have a list of breakdown of vaccine type, just know we're dealing with military bases. These populations don't necessarily have an option to choose which type of vaccine they receive. It's what the base has, other than the recommendations.

This particular graph was those vaccinated patients who had influenza by the week that it was collected. The majority were influenza A, and of those each one was identified.

So for the population based data surveillance this would be the vaccine effecting this data. 205 had live confirmed influenza cases. Now that's of all the season of all of the recruits. Twenty-nine percent were identified as A/H1, 36 percent were identified as H3 and we still have pending types for 35 percent because they were the recent weeks collected.

As you can see this graph identifies those vaccinated and those unvaccinated.

Here's the calculation that NHRC, which is the Naval Health Research Center, used to identify vaccine effectiveness. They only considered periods when all trainees on the base were vaccinated. All the trainees get vaccinated upon the sessioning. And at any given time they consider about 25 percent of the population not vaccinated because of the 14 days that it takes.

For the previous years they've had estimates anywhere between 86 and 94 percent of vaccine effectiveness. And this year they have 85 percent vaccine effectiveness based on the 102 lab confirmed cases that were included in the analysis. Most of those were actually H1, and then you see also the H3s or the Brisbane strain virus.

So based on NHRC's population-based survey elements among the recruits the overall

vaccine effectiveness remained strong among basic trainees, but when compared to the previous four years it's on the low end, because it's 85 percent. It's reduced effectiveness against influenza A/H1 subtype.

Now as far as the sequencing goes, that's where Dr. Gibbons and Dr. Myers will describe a little more information about the sequences of these since this only describes the subtypes.

MAJOR GIBBONS: I'll ask Andy to continue to drive, and I'll just give what's a quick snapshot of the HA1 hemagglutinin and phylogenetic analysis.

First of our influenza B field isolates and our lead molecular biologist Jason Garner prepared these slides for us. For the B isolates they include all of the specimens identified as influenza B. For the H3 and H1 he attempted to give a representation using both genetic and geographic data. In other words, to fit it on

a single slide he would keep the same picture but maybe omit some sequences instead of showing the exact same sequence over and over. But you can extrapolate back on the data that Andy's presented.

These specimen are from July 2007 up to present, but present being the last couple of weeks. You'll notice that spike obviously wasn't able to get sequencing data completed and forwarded to the CDC.

Seventy-eight percent of the isolates were collected in Nepal, Thailand and the Philippines. And four of six of the isolates collected within the U.S. are of the Yamagata lineage and 29 of the 50 isolates belongs to the B/Victoria lineage. And all of the isolates that are in the B/Victoria lineage are extremely similar. So overall we are seeing close to a half and half of both the Yamagata and Victoria lineage.

Let me stress that this is only sequence data. This is all submitted to the

CDC and they, based on looking at that data, will request clinical isolates for further testing.

Now with regard to the H1N1 field of isolates, as I mentioned earlier, this is not all of the isolates. What he did here to get it all on one slide and kind of fit in our time constraints is kind of give a geographic representation and maybe omit some sequences that would only be redundant in the tree here.

Only 5 of the 51 isolates represented here were characterized as clade 1. The bulk of the isolates are characterized as clade 2. And if you go to the first green box there, so everything above is glade 2 of H1N1.

DR. MYERS: So this is our sequence data from NHRC and in contrast to the variation that they see at AFIOH. You know, we're predominately seeing one strain in the clade 2B section of the tree.

Most of our sequences -- this is

all the sequence data we have, but we haven't sequenced every single H1 sample that we've gotten in. You can see the majority of these are from a couple of different outbreaks at Fort Lewis and Fort Leonard Wood. So the majority of what we're seeing, and again the vaccine effectiveness data on the H1N1 was about 54 percent are the single strain that we see going around.

MAJOR GIBBONS: With regard to H3/N2, 85 percent are the Brisbane. In other words they have these key amino acid changes indicative of the A/Brisbane. So we are continuing to find predominately Brisbane. Now of those isolates we are seeing some additional changes, and they're located at the very top of the tree there. And we do have some hemagglutinin inhibition data from the CDC, and those have basically shown that these are characterized as A/Brisbane-like.

DR. MYERS: And in contrast to the H1s, we do see a lot of variation in the H3s

that we're collecting from the recruit training sites across the country. Again, those are shown here. All Brisbane-like in nature, but a lot of variation within them from different sites. And just to reiterate it again, all this sequence data is sent to the CDC. They do make requests for specific samples and do the HAI data and provide that back to us.

DR. OWENS: So we take knowledge, of course, of the Global Emerging Infection Surveillance and Response Systems, which is GEIS, the Centers for Health Promotion and Preventive Medicine and the Air Force Clinical Information branch, of course, CDC, Marshall Regional Medical Center and all of our Sentinel sites and recruit training sites that take part in this program.

Thank you.

CHAIR MODLIN: Thank you.

Are there any questions? Dr. Couch?

MEMBER COUCH: Do you have any serologic data on the recruits with regard to particularly the HI antibody responses and a cross reaction with your isolates?

DR. MYERS: We've sent those to the CDC recently. We haven't gotten that back yet. I'm sure they're working on it.

MEMBER COUCH: But they were collected? We just don't know the results of the vaccine responses?

DR. MYERS: Right.

CHAIR MODLIN: Dr. Davis?

MAJOR GIBBONS: I believe there is some preliminary. I know some of the AFIOHs have been sent to the CDC. And I think there has been some hemagglutinin inhibition data on our H1s. Is that incorrect? Since it's not our data, we didn't want to present it.

MEMBER COX: Right. Sure. If I understood Dr. Couch's question, he was actually asking if serum pre and post vaccination serum had been drawn from the

recruits and if those sera had been tested against some of these recent strains?

DR. MYERS: Actually, no. That happens in rare cases. We did that once last year, but we haven't done it this year.

MEMBER COUCH: Well, you alerted us to the fact that that vaccine may not have been very good for H1.

CHAIR MODLIN: Bob?

MEMBER DAVIS: I'd like to go back to the vaccine effectiveness calculations. Do you mind? I was having trouble understanding the setup of the study. Is this a cohort study, a case control study? Could you walk us through how the calculations of vaccine effectiveness were done?

DR. MYERS: Right. So, again, we have the denominator data because we know everyone that's at the recruit training site at any given time. We have FRI data. We have people on the ground at each one of these sites that count every FRI case. They only

collect a certain number of samples. And so that's where we get our influenza numbers from and our FRI numbers from.

The assumptions are, you know again this starts once everyone at the base has been vaccinated, so a couple of weeks after vaccination has started. We assume, you know, that for 14 days they are unvaccinated and that gives us the percentage of the population that's unvaccinated and from that we make the calculations.

MEMBER DAVIS: If everybody's vaccinated, though, is it really fair to assume that the unvaccinated are exposed? Because there's a lot of herd immunity going around.

DR. MYERS: Sure.

MEMBER DAVIS: Do you just accept that and --

DR. MYERS: Right. And we can do the calculations with different ways with different assumptions. And I have some of

that if you want to see it with the 7 day vaccination or a longer time period, and things of that nature.

MEMBER DAVIS: Yes.

CHAIR MODLIN: Okay. Let's move on to the next presentation. Thank you all very much.

The next speaker will be Dr. Zhiping Ye from the FDA who will be leading us into this next issue that Dr. Davis was just getting at, which is vaccine responsiveness.

DR. YE: Okay. Nancy Cox in her presentation the antigenic characteristics of the circulating virus has been analyzed by using ferret and the sera to the vaccine strain as well as to the representative recent isolates.

In this presentation I will focus on the antigenic characteristics of the newly isolated viruses to the human sera which immunized with current vaccine.

So unlike the data presented by Dr.

Nancy Cox, the human sera only has the serum against the vaccine and does not have the serum against the newly isolated viruses. So what we're going to see is that we see the difference of the antigen against the serum to the vaccine strain and how the difference between the vaccine strain as well as the newly isolated viruses.

Okay. There are four serum panels from adults and the elderly. The four serum panels, one has come from Australia. Another one from E.U., Japan as well as from U.S.

The serum panel from Australia was the individual who immunized the vaccine against H1N1 for New Caledonia, this is old one, and Wisconsin for 83/N2 and the B/Malaysia. Then the rest of the serum panel contains who immunized with Solomon Islands, the current vaccine, Wisconsin as well as Malaysia. Only the difference is that the serum from Japan instead of use Wisconsin, they used the Wisconsin-like strain, which is

a Hiroshima/52/2006.

And in addition there is the one serum panel from pediatric, that's nicely or a dimension -- another serum panel was collected by CDC.

And each serum panel contains around 24 to 32 individuals. So you start off with seeing the individual to the serum, but here we seeing is a group of the serum reaction to the vaccine strain -- to the serum against the vaccine strain.

And then the antigen for serology study was chosen on based on a few criteria. First of all, they said the vaccine strain we have to use this one as the control. And the representative current -- the strain was chosen by a few criteria. One is, of course, the reason doing this one is to choose the suitable vaccine for suitable candidate of a full vaccine. And we were basically focused on the isolates from eggs. And also we have to cover the geographic difference and some of

Japan and Europe as well as from U.S. And also we have some italic font as we present the isolate from cells.

And the color coded Brisbane/59 is the strain crossed to different centers. I have to mention that the five centers doing the serology studies, so the percentage is the combination of all the studies.

So this is, Brisbane is everybody uses as antigen for serology studies. And the rest of them it depend upon the availability of the different centers.

Here I cannot present every one of them. I only choose the one of the representative strain. Since I do the presentation, I choose the sera panel from CBER.

Okay. So here I present three different sera panels. As I mentioned, the sera panel from Australia does not contain the current vaccine for H1N1, so we didn't use this one for H1N1. Only choose the three

panels contains the vaccine strain to Solomon Islands.

Okay. Nancy already mentioned this, but I want to go through a little bit. So each panel we have 24 individuals. Okay. Then since the panel contains pre and post-immunization so we can compare the pre and the post. So here is the antigen we used in serology studies. And here is the vaccine strain. And here is the representative strains.

And here we can see this column which shows the percentage of rates of four-fold increase because we have a pre and a post-immunization. And here it shows -- this column shows the GMT, pre GMT titers to the vaccine strain and to the isolated viruses.

And skip the third one because I will focus on this one later. And also we have the percentage of the individual contains 1 to 40 HI titers antibodies.

And here you can see here the pre-

immunization, the percentage of 40 percent of the individual.

Now let's focus on the post-vaccination GMT titers. I think Nancy already mentioned that. I just wanted to focus on the adult/elderly and later on mention on the children.

So here we can see that GMT titer like strains for this -- this is panel is 724. And then here we focus on the difference of the isolated virus, the GMT to the representative viruses versus to the vaccine strain. So I don't think you can read that from the back of the audience. But here for the vaccine strain it's 724 GMT titer where the newly isolated it's between 160, 20, 13 and 44 GMT titers. And so they can see there's the reduction of the antibody against the vaccine strain is very, very low. We use arbitrary titer to see how the 50 percent reduction compare to the vaccine strain. So here we can see the -- of the newly isolated

virus has significant reduction of GMT titer compared to the vaccine strain.

The same picture for the Japan sera panel.

I have to mention that to increase the sensitivity of the study, the sera panel from EU, U.S. as well as from Australia has to be preselected to choose the -- strain. So the absolute data here, the number here does not mean much, but the comparison of the antibody to the vaccine strain and compared with the new isolated virus is meaningful, it's here.

So you can see the GMT titer for Japan is relatively low, 109 virus to the EU 700 or the U.S. about a 1,000.

So bottom line from this study is that the newly isolated viruses, the GMT titer to the new isolated viruses compared to the vaccine strain is very, very low.

Here it shows the elderly population. I'm not going to go through that

again to show the same picture as those from adults.

Okay. Here Nancy already mentioned on the HI antibody response to the vaccine strain from children. Here she shows the first two rows was from the study from CDC, the last one from U.S. I'm not going to go through that again since it show the same picture that the newly isolated viruses, GMT titer is very low compared with vaccine strain. And overall of reduction, like 74 percent reduction compared to the vaccine strain.

So the conclusion from this study for H1N1 is that they have significant reduction to the vaccine strain.

Here is a summary to give you whole picture. Since we have five centers, this serology study, one from CBER, CDC, U.K., Australia and Japan. So here is to show the whole picture how many strains and what's the outcome of the study from different centers.

Here at the CBER we used Lisbon, we used the South Dakota and Cambodia as our antigen for the serology studies. And the same as the CDC. NESC choose the Brisbane, Egypt, Hiroshima and the Netherlands.

So what we can see here is the frequency of these sera panel have a reduction of 50 percent reduction. So as we can see here, the three panels, three out of three has 50 percent reduction. So here this last column shows the actual percentage of reduction. Here you can see 87 percent of reduction of the newly isolated viruses compared to vaccine strain. So indicated as the antibody against the vaccine strain does not cover well for this Brisbane/59. Same as the rest of them. Only one exception is Netherlands/345, and it's no reduction. I think the one reason is that this may not be representative of the whole picture. But this virus is isolated from cells. But none of the viruses from Norway also isolated from cells,

but they have significant reduction, which is 97 reduction compared to vaccine strain, where the Netherlands have 25.

So put the whole picture together, 45 out of 50 cell panels shows 50 percent reduction. And overall average of the reduction is 79 percent if you put a whole picture together and compare it to the vaccine strain.

So bottom line from this study shows that newly isolated virus does not cover well by vaccine strain.

And here this shows the reduction from elderly and for children, and I mentioned this at 74 percent of reduction. And for the elderly it's a 67 reduction. And 44 out of 50 sera panel shows a 50 percent reduction.

Okay. Here we go move on to H3/N2. Again, the vaccine strain, as I mentioned, that everybody use Wisconsin itself but Japan use Hiroshima as the alternative vaccine strain.

And the representative current strain as follows: Is the Brisbane/10 itself and the Henan and Jinshui/147, Taiwan and the Texas and the other one was isolated from cell isolates. I think Nancy may not mention this. This H3/N2 egg isolated is very limited. And the Uruguay one is everybody used for this antigen for their serology studies.

And here show, this representative study was choose from the U.K. And again there are three sera panels. And here is the GMT titer to the vaccine strain, which is Wisconsin is the 563, then the new isolated virus include Brisbane/10 it's 93 versus the vaccine strain GMT total vaccine strain 563.

And the rest of the viruses had similar picture that have more than 50 percent reaction. And the same thing from Australia as well as U.S. So this is the picture from adults from U.K. study. And next one it shows the elderly. Again, I'm not going go through the details. You cannot see this one

anyway. And it shows the same picture that the newly isolated viruses include the Brisbane/10 and the Uruguay has more than 50 percent reduction compare those to the vaccine strain.

And here is the pediatric population and shows the HI antibody response to H3/N2. And, again, Nancy already mentioned that, so the conclusion for this one is that you get the viruses not only in from adult, but it's in the children has a very significant reduction to the vaccine strain itself. So the percentage of reduction for children is around 80 percent reduction compared to this vaccine strain.

And here just a summary table from different centers. And the bottom line is the 55 out of 61 had 50 percent of reduction. And the average of reduction is 75 percent compared to the vaccine strain. To that is again that the GMT reduction is very significant.

Now here just shows the elderly and the 55 out of 61 had a 50 percent reduction. And the average of the percentage of reductions is 71. So, again, the picture's very clear. It's different.

Here we move on B. The current vaccine strain is B/Malaysia, and the representative current strain that basically we chose two that's Victoria-like because it's controlled for the serology studies, and we choose Hiroshima and Pennsylvania/5/2007. And the rest of them are the Yamagata lineage. So the one color coded is B/Florida/4, and that antigen has been used for all the centers.

Okay. As Nancy mentioned, B a little bit it's not clear cut like H1 and H3 and also different from different sera panels. But here I choose two, one from U.S. and one from EU.

As you can see here the post the GMT titer to vaccine strain is 222. And as you can see here the Victoria-like strain

B/Pennsylvania/5 pretty close have 252. So very close to the vaccine strain. However, B/Florida has 240 GMT titer and Delaware had 101, and Sendai had 247 and Bangladesh had 104 GMT titer to the sera immunized B/Malaysia. And however, the EU panel shows a little bit different result that the GMT titer to the Malaysia is 202 and the similar Victoria-like strain, Pennsylvania 202, whereas for the -- representative strain it's 92, to the Florida/4 30, to Delaware and 28 to Sendai and 43 to Bangladesh.

And here shows the elderly. So I think this is a similar picture as those from adults. And I'm not going to go through this one again, but it shows a similar picture as those from adults.

And here is the pediatric. The pediatric, unlike the adults and elderly, give you pretty good clear picture. And here I just mention again from U.S. we have for the GMT titer to the Malaysia the 22, but then for

the rest of the Yamagata lineage and less than 50 percent.

So overall summary for the pediatric study that the reduction to the GMT titer over newly isolated viruses is 83 percent compared to the vaccine strain. So it's very significant difference.

And here again to show the whole picture across the different centers. And this only showed the reduction to the Malaysia itself. I didn't include the reduction to the Yamagata lineage. So here it shows that 40 out of 60 panels it showed 50 percent reduction. And the average reduction is 52 percent for the adults and 39 out 50 sera panel has 50 percent reduction in elderly. And the average of 50 percent reduction -- average of the reduction is 58 percent in whole picture.

Okay. Here is the summary. The study with human sera collected after immunization with the current vaccine strain

shows that for H1N1 representative recent viruses was less well inhibited by HA antibodies to the current vaccine strain, which is Solomon Islands.

And for H3/N2 the representative recent viruses was less well inhibited by HI antibody to the vaccine strain.

For the B strain it depend upon the lineage. For the Victoria lineage it represents the recent viruses was less well inhibited by the HA antibody to the vaccine strain, which is a Malaysia/2506/2004, which is the Victoria-like. However, for the Yamagata lineage the representative recent viruses generally were less well inhibited by the antibody against the current vaccines.

Thank you.

CHAIR MODLIN: Thank you, Dr. Ye.

Are there any compelling questions for Dr. Ye? None at all. If not, I'm going to suggest that we take our break now. And let's try to be back at 11:00 sharp and we

will continue on with Dr. Gupta's presentation.

(Whereupon, at 10:48 a.m. a recess until 11:03 a.m.)

CHAIR MODLIN: Our next speaker will be from the FDA, Dr. Rajesh Gupta, who will be speaking on the availability of strains and reagents, a very, very important topic and one that's critical for us in our discussions later on today. So could I please ask everyone to be seated?

In order to select strains, we have to know if there are strains available that will grow in eggs. That's what Dr. Gupta's going to be leading us through that discussion.

DR. GUPTA: Good morning. My name is Rajesh Gupta. I'm in the Division of Product Quality in the Office of Vaccines. And we are responsible for providing potency reagents for the seasonal flu vaccines. And as you know, the potency reagents are critical

for the formulation of vaccines. So I will give you some update on the availability of reagents for this season.

So for influenza A (H1N1), as all you know, that the current vaccine strain is the A/Solomon Islands and reagents for this strain are available from our lab, from the NIBSC in the U.K. and the IGA in Australia. These are the agencies including the NIID from Japan. We do the calibration and collaborate on the calibration of the reagents so that the quality of the vaccines in a global setting can be I think consistent.

And as you know also that for this year the WHO has recommended the A/Brisbane/59 strain, 59-like viruses. And the possible candidates which I think reassortments are being made or are available are A/Brisbane/59, IVR-148 and then the A/South Dakota and the reassortments are in preparation for that strain.

We have estimated that if this

strain is selected today, we are estimating that we can have the potency reagents available by late May of this year.

For the H3/N2 strain, the current strain is A/Wisconsin and the like reagents are available from three agencies. And, again, as the WHO recommended strain for H3 is the A/Brisbane/10-like viruses. And the possible candidates are the A/Brisbane, then the IVR-147 and then the reassortments. Probably we will have some discussion on these reassortants this afternoon.

And then the A/Uruguay strain, the assortments are in preparation.

The potency reagents for these strains are available from TGA, as most of you know that. This strain is being used as a vaccine strain for the southern hemisphere. So they already have the potency reagents available. And based on our estimates the CBER will have the potency reagents available by the end of the May this year.

For the influenza B strain the current strain is B/Malaysia and the potency reagents are available for this strain. And the WHO recommended strain is the B/Florida-like viruses. And the possible candidates can be B/Florida and the B/Brisbane.

And again, this is one of the strains which is in the southern hemisphere vaccines and reagents are available from TGA, which are for B/Brisbane. And we have already started working on these reagents as our best guess based on the southern hemisphere information. So these reagents may be available from CBER if this strain is selected by the end of next month.

I think that's all about the three strains.

CHAIR MODLIN: Thank you, Dr. Gupta.

Are there any questions?

Dr. Gupta, we can assume that these are all strains if you say that they're

available or expect to be available, that they do grow well in eggs?

DR. GUPTA: I know that there will be portions there. I do not want to go into the details of the -- like the deletion reassortment for the H3 and some growth issues. So probably that can be taken during discussion.

CHAIR MODLIN: Is there anyone else that would like to go into detail? Okay. Well, we probably will need to address those issues.

Thank you, Dr. Gupta.

Are there any further questions? If not, we'll go onto the next item on the agenda, which will be comments from the manufacturers. And I understand that Tony Colegate will be representing the manufacturers.

MR. COLEGATE: Good morning. Thank you for the opportunity to give the industry perspective in this work. I think it's going

to be a very, very difficult year for us.

This presentation last year was given by Al Thomas, and basically have updated his presentation because I thought it was very good. And I'll give you insight into the time pressures and the benchmarks that we have to follow through to get the vaccine out on time. And then kind of update where industry thinks we are as far as producing vaccine for this year.

So what do we need? Well, the critical factors to produce the millions of doses that we need to produce for the U.S. market. I guess probably the most essential one is the gross potential of the seed virus. And what is often forgotten is that the quality of trivalent vaccine that can be produced is limited by the least productive one available strain. So the more information we've got about the strains and how they grow, we can best plan our production. This year we're in a very good position.

The timing of the strain selection is also important. Because we have a limited production time due to the necessity of distributing and administering vaccine prior to the influenza season. And new working seeds require at least four weeks from receipt of seed candidate for development to use in large scale manufacturing.

Now following on from that we need to the potency test reagents, and they are obviously limited to a large extent by the strain selection. Because the antigen used in those potency test reagents is usually supplied from the first production batches produced by the manufacturers. So these things are linked.

These potency reagents are required to determine the potency of monovalent components prior to formulation in the trivalent vaccine. They're also required for us to know how much monovalent we've used. And this year it would appear we're going to

be processing blind until these reagents are made available to us, which makes life a little bit difficult.

And these reagents have to be produced and standardized for every new strain.

And then the final thing is the timing of the annual license ultimate approval. We can't release the product onto the market until we have that.

What I'm going to run through quickly is the ideal model for influenza vaccine manufacturing. I hope you can see that. It's not that very clear even from here.

Basically we have a time line to work to which is the delivery of the vaccine. It's becoming increasingly clear; it was always said that if you haven't got the vaccine there for people to have by Thanksgiving, they don't take it. I think that's probably being demonstrated again this

year despite a quite extensive campaign to try and get people to get vaccinated in December/January.

So how do we achieve that? We start early, basically. We manufacture one strain at risk. Now in hindsight I can see you're thinking well which strain did they produce. Well, at the time Solomon Islands looked good. Towards the end of January it became clear that it wasn't so good. But there we are.

And then rather about this time we like to start on the second strain. That's going to be challenging. And we normally have seeds and everything prepared ready for that. And then round about the middle of April, and the latest in May, we start the production of the third strain. And in the meantime we're producing, or people are producing reassortants for us and we're producing the working seeds. But this year we're still in that same situation for the second strain. So

we're already in some delay.

And then we try to balance the strains. Because up until the point at which we have the potency reagents, we don't actually know how many doses of each of the three strains we've produced up until that time. So until we have that information, we can't balance the strains. And as I said before, we're limited by the strain which grows the last well or produces the fewest doses. We have to do a longer production on that than the ones that grow well.

Once we have the reagents we can then start to formulate and to fill. And when we have the annual license approval, then we can start to distribute. That's how we would like it to be.

Where are we this year? Well production is underway as usual. We started at risk of strains that would not be selected for 2008/2009 northern hemisphere just to make sure that we could have sufficient vaccine in

the marketplace when it was required. And based on publicly available surveillance information at the start of this production, manufacturers have chosen to produce the A/H1N1/Solomon Islands. And, as I said before, when it became not so sure that this strain would be chosen, we changed to B/Florida/4/2006-like strains.

Now as we've said before, there are two strains here available. There's the B/Florida/4 and the B/Brisbane/3. And, again, I guess to show how difficult this product is to produce, some manufacturers favored the Brisbane/3 and others favor the Florida/4,

And you could argue well why didn't we start with the B in January. At that time we were faced with this dilemma that Florida was good for some manufacturers and Brisbane good for others. And we also had three new B/Florida-like strains from CDC to evaluate. And until we evaluated them to see if any of those were better than these two, because

these strains are adequate but they're not good. So we would really have preferred there to be something better, but it would appear there isn't. And as you know, WHO have not recommended Solomon Islands for the next season.

So it looks as if there could be three new strains for 2008/2009. And this is unprecedented for the northern hemisphere. And in the last 20 years this has not happened before. So we have a very, very challenging year.

So we're all busily evaluating new strains at the moment. You've heard about the IVR-148 Brisbane/59 reassortant from CSL -- sorry. I'm talking H1N1s. I've gone on to H3/N2s.

The H1N1, the Brisbane/59 there is a reassortant that has been received by manufacturers only recently and is current under evaluation. But it does appear to grow reasonably well and is a good candidate.

Last Monday and Tuesday of this week from New York Medical College we received South Dakota/06/2007 and we have one, two, three, four reassortants there to look at. But I understand they have not yet been fully characterized and therefore, may or may not be of use to us. The Brisbane/59 I believe has been characterized and should be an acceptable strain.

The B strains, both B/Florida and Brisbane where we use production for the southern hemisphere and other viruses were received from CDC or NIBSC, CDC through NIBSC by most companies. And these viruses don't appear to offer any yield advantage over B/Florida or B/Brisbane. But I think the plea from the manufacturers is can you please give us the option to use either/or as they are both like-strains. That will cause a problem in reagents, of course, but we can sort that out, hopefully.

So as far as the H3/N2 is

concerned, IVR-147, A/Brisbane/10 was used for the souther hemisphere. And the one good thing that shown us, I guess, is that it is not suitable for production for the northern hemisphere. It does not grow well and we have no possibility of producing sufficient doses if we use that strain.

New York Medical College have been trying also to produce a Brisbane/10 reassortant and out of four or five that they produced, only one grows reasonably well. That's 171B. But it has a deletion A193 and is under evaluation at the moment. Additional serological studies have been taking place at CDC. So we don't know whether we can use that or not.

Better news, I guess, is that since the Uruguay/716 egg isolate became available, that was received by the three reassortant laboratories that produce reassortants for us, CSL, NIBSC and New York Medical College, and they have all been working on this particular

strain to try to produce reassortants for us. And New York Medical College is due to ship the beginning of next week. Is that 25 or 26 of February? And CSL and NIBSC should be available the week beginning the 3rd of March.

So we have things in the pipeline, but we're not in the situation where we would like to be at this time of year with two strains, with working seeds ready to go and reagents in late stages of preparation. So, as I said before, it's going to be a difficult year.

So this year, more than any other I guess, we will need public/private cooperation. And what we need is a timely Committee selection of the appropriate antigens. And we ask you here to consider not only the antigenic match, but the ability of the strains you select to enable us to produce sufficient vaccine for the marketplace. We need seed viruses, especially the high growth reassortants.

Normally we have more opportunity to evaluate the growth characteristics of potential strain candidates. This year we're right against the wire and it's going to be very difficult. And we need the potency test reagents. And we need all three of these by early June.

I was encouraged to hear that we could get them by the end of May. I just wonder if that's a little bit optimistic. If manufacturers don't know which strain to produce, they won't produce the antigen. And if you've got the sheets here that's good. But if you haven't got the antigen, you can't produce the reagents and then there's the standardization question which always seems to take longer than anyone anticipates. And then following on from that we need a timely approval of annual license supplement.

If you'll bear with me, I have a colleague in Liverpool who likes putting information together and producing tables. And

so he looked at the northern hemisphere strain changes since 1989. And the ones he read are where the strain changed. And you can see if you look right at the bottom that never before has an H1N1 not run two years running. So we thought we were on pretty safe ground with starting with that, but we've been caught out this year.

If you look at the H3/N2s, you can see that that changes far more frequently. And the B strains.

When we have the question about the quadrivalent vaccine, I thought not this year. But I think it does bring home the problems that we have and that would potentially give us producing a quadrivalent vaccine. Years like this would be -- I don't know if Bob Couch has had further thoughts about his suggestion last year that we do the B strains year-on-year; one year Yamagata lineage and the next year Victoria. And that would also help us with the bank of strain right at the

beginning. It would give us something to go at. And it's a thought. Anyway, I was quite taken with the idea last year and I wish we'd done it.

So this is just a summary, but you can see that if you go down to the bottom, zero strain changes in the single years happened four times and all the manufacturers are happy you do that. A single strain change nine times, which again we're happy with. Two strain changes happened six times, but three strain changes in a single year hasn't happened to date.

And I will end with that.

CHAIR MODLIN: Thank you, Mr. Colegate.

Let me ask if there are questions for the manufacturers from Members of the Committee and our guests. Bob?

MEMBER COUCH: Well, just one comment for Tony. And I think the manufacturers know that this Committee has

always given serious consideration to the availability of vaccine. And we don't make vaccine available. You make vaccine available. So that always, quite frequently, enters into our decisions on what to recommend, as well. Not just the selection of strain now.

I thought, when I looked at what had been done to the southern hemisphere, we weren't doing what you're saying we're doing to you, and you've suggested that maybe the B strain for the southern hemisphere, maybe that one's already relatively in place. But you're looking at two new changes, and, as you've said, that does occur, but that's not quite as unusual.

And I had thought that the A/Brisbane, you had that one for the southern hemisphere. But you've indicated that was a poor grower, so you've got to go back to the drawing board to make the H3N2 strain for that recommendation. And that you'd only have an H1N1 strain.

I don't want to accept it's quite as bleak as you say, but for the northern hemisphere, very clearly as you said, is three new strains.

I want to ask you a question. I don't know whether you'll want to answer it or not but, see, WHO now has given you those three strains. And influenza vaccine and manufacturing is very international now; distribution, manufacturing, what have you. What if we selected a different strain from the WHO recommendation, what would be your reaction to that?

MR. COLEGATE: It would depend on whether there is a reassortant available, how it kind of affects our production schedule, really. I think, because the U.S. market is so big, it can go into low, as it were, really, as far as manufacturers are concerned. Because all of the major manufacturers are now looking to this market to use.

MEMBER COUCH: You want the market,

so you'd try to meet it. But then you'd be, perhaps, making two vaccines; one for the U.S. and one for Europe, for example?

MR. COLEGATE: Well, certainly we've done it in the past in Liverpool.

MEMBER COUCH: And that would reduce doses, correct?

MR. COLEGATE: Not if you plan it properly. Again, it depends on how well the strain yields. If you choose something that yields better than is being produced for Europe, then in that same time frame, you produce more doses. I mean, it's down to well, how well the virus grows, and how many doses you get out of every batch that you put into production.

I mean, the southern hemisphere really has been a dress rehearsal for us -- well, it should be a dress rehearsal for us every year, and usually it puts us in good stead to start. But this year our star performer, Solomon Islands, is sick. And we

found that the IVR-147 reassortant didn't grow well enough, so we need it more, and the B strain, neither of those grew particularly well. But we have found that we could live with those particular two, the Florida or the Brisbane. So at least we've got something to use.

I mean, what we are doing as an industry group, just for information, is that we are currently talking to WHO Collaborating Center in Australia with a view to have an egg crate with them, as well as with CDC, so that we can, hopefully, pick up egg isolates in the southern hemisphere. And maybe if that had been in place this year, we may have been in a little better position. I don't know. But we're trying the whole time to make this situation better where we can.

CHAIR MODLIN: Bruce?

MEMBER GELLIN: Tony, building on your last comment, if you had a wand, and could wave it and improve the system so that

things got to you faster, or there were more choices, what would the system look like? How would it look different than the one we currently have?

MR. COLEGATE: Dare I say? The biggest problem we have, and it is improving, is coordination within WHO, basically, to make sure. I mean, we now have three industry-funded facilities, institutes, that are producing reassortants for us. So we've got CSL, who have been producing them for years. We've got Doris Brooker at New York Medical College, and last year, we set up NIBSC, we funded them to start producing again.

They can't produce egg reassortants for us if they don't get the egg isolates to do it. But we, as industry, can't decide which egg isolates they should be looking at. They need some kind of WHO prioritization and timely supply of those. I don't know if Nancy wants to comment on that.

It is a wish list, really. Because

I know the difficulties. It's easy to say, this is what we want, but I appreciate it's not easy to do.

MEMBER COX: Sure. I'll just make a couple of comments.

I think that there was a lot of discussion at the IFPMA Roundtable and within the WHO Collaborating Centers and other reference labs, as well, about how to really improve the communication within the system, and also with manufacturers. Because, for example, although I was aware that the IVR-147 strain was not growing well at first, I certainly was not aware, until very recently, that it would be unacceptable. So my assumption was that it was being used for southern hemisphere production, therefore it must be okayn and there were reagentsn and so on. So that kind of feedback needs to come to us.

One of the things that we've experienced over the years is a plea for more

egg isolates to be sent. And then we send a lot, and then we get told "That's too many to look at." So we're trying to find that balance so that the viruses that we send are those that are most likely to be useful to you.

And I want to emphasize that, for the H3N2 viruses, I believe the statistics are something like this: we put 488 original clinical specimens into eggs, or into kidney cells and eggs, and got something like three or four or five egg isolates. So it's very, very difficult to -- it takes a huge amount of effort to derive one. Then, when you have an isolate, you find it always has changes for adaptation to eggs for the H3. So it's not always true for the other subtypes. But right now, it's true for the H3s.

So then you need to be sure that it's suitable, it's in the right genetic and antigenic group.

So we've all been really, really

struggling with this renewed effort to provide timely information, and viruses that are truly going to be useful, not just flood the industry with viruses that might never come to fruition. And I think there's a balance there that we're getting closer to. But I agree, there's room for improvement.

MR. COLEGATE: Yes. I mean, that was, I guess, the main reason for setting, or trying to set up an egg grate with WHO. Now, we're open to trying to get more H3N2 egg isolates available. And maybe that will pay off.

CHAIR MODLIN: Bruce?

MEMBER GELLIN: Yes. Let me ask a couple more things.

Your animated graphic was really quite helpful. The boxes have looked the same for a long period of time, as far as their dimensions, but the manufacturing capacity has expanded significantly recently. And so I guess the question is, we're all faced with

the same calendar, and we can't lengthen it. So that's the biggest problem.

So within that, can those boxes, can they get fatter? And I guess I'm not quite sure if we're going to have excess vaccine this year, and the growth curve of the amount of vaccine that's produced for the U.S. market has been tremendous. The question then is, how is that being accommodated by potentially shortening the time when each of those boxes is running?

MR. COLEGATE: Well, I mean those boxes, I think, have been getting fatter in recent years to accommodate the increased market requirement. But you still have all these time points that you have to follow, and you've got to balance the strains. And the fatter the box, the bigger chance you've got of going dangerously wrong by producing twice as much of the fast growing strain before you've got potency reagents to tell you what it's yielding.

It is a very, very exacting -- well, it's not exacting, in some respects, it's kind of bucket science as far as flu production is concerned, because it's an old product. But it does take a lot of management to try and get everything lined up, and the vaccine out on time.

CHAIR MODLIN: Other questions?

If not, I'd like to thank Mr. Colegate. Thanks very much for an eye-opening presentation.

At this point in time, we will move on to the open public hearing for this session, and I'll turn things over to Christine.

EXECUTIVE SECRETARY WALSH: Thank you, Dr. Modlin.

As part of the FDA Advisory Committee Meeting procedure, we are required to hold an open public hearing for those members of the public who are not on the agenda, and would like to make a statement

concerning matters pending before the Committee.

Dr. Modlin, would you please read the open public hearing statement?

CHAIR MODLIN: Yes. Both the Food and Drug Administration and the public believe in a transient process for information gathering and decision making. To ensure such transparency at the open public hearing session of the Advisory Committee, FDA believes that it is important to understand the context of an individual's presentation. For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or your oral statement, to advise the Committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting.

For example, the financial information may include the company's or group's payment for your travel, lodging, or

other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

EXECUTIVE SECRETARY WALSH: I have received one request from Ms. Manon Cox, representing Protein Sciences Corporation.

Ms. Cox?

MS. MANON COX: Okay, Thank you. I am Manon Cox, I'm Chief Operating Officer at Protein Sciences, so I'm employed by the company.

And the reason for this public statement is that I would like to update the Committee and the public here of the fact that Protein Sciences is planning to submit a BLA application for a novel recombinant

hemagglutinin vaccine within the next couple of months, and we hope to be able to have some vaccine in the market later this year.

We also expect to come to the Committee with more detailed information on our clinical studies. But I just wanted to give you a brief update on our plans in the next few minutes.

First of all, for those of you are not familiar with FluBlok, it is a recombinant hemagglutinin protein-based vaccine, so it only contains hemagglutinin, and instead of the licensed vaccines, it contains 45 microgram, as determined by the ID of the hemagglutinin, versus the 15 percent that is present in the licensed vaccine. These recombinant antigens are produced using the baculovirus system in insect cells, and the manufacture does not involve inactivation, thus, of an influenza virus.

The recombinant protein is highly purified, and does not contain egg protein,

and as a result, we expect this vaccine to be providing beneficial benefits for people that are egg allergic.

We also, in using this technology, it's not necessary to select or to adapt an influenza virus to growing in eggs, because you basically use a virus that is very well suited to grow in insect cells, and you use a kind of pluck and play mechanism to produce your antigen of interest.

The cloning expression and manufacture of FluBlok can be accomplished in a relatively short period of time, less than two months. So, for example, we only received the latest H1N1 isolate from CDC yesterday, and we expect to be able to go in production within two or three months with that antigen.

FluBlok provides an alternative to the currently available licensed vaccines. And in principle, one of the major advantages is that you don't need so many embryonated eggs. And another advantage would be that

biocontainment, since a baculovirus is not really harmful for people. It's less of an issue than using live influenza viruses.

So we are planning to use four clinical studies to support our BLA. Well, we are looking for approval for those in 18 years and older using the accelerated approval mechanism, and what I want to do today is I want to share very briefly results of two of those studies which have been fully completed.

The first one is PSC01, which was an efficacy study in healthy adults, where we had 451 subjects, which were randomized to receive either placebo or one of two doses, a low dose and a high dose. I want to speak briefly about an efficacy study that we performed in adults older than 65. This included 868 subjects that were randomized one to one to either receive FluZone or FluBlok. And then there's two very large studies ongoing, of which we will use interim day 28 safety and immunogenicity data to support the

accelerated filing. And in principle, those reports are in production, but I don't want to share the results here today yet, since our investigators in the field are still blinded, and this study is ongoing, since it's a formal efficacy study.

The first study is PSC04. It's a field efficacy study in healthy adults where we have enrolled 4,650 subjects in 25 centers across the United States, and they were randomized to receive either placebo or FluBlok. And then the other study is a study called PSC06, which is a non-inferiority immunogenicity and efficacy study in 600 healthy adults of the age group 50 and 64. And here we compare FluBlok with FluZone, again.

So very briefly, study results from PSC01 was that the commercial dose, where we used four times 45 microgram, protected 100 percent against cell culture confirmed influenza. We also observed a little over 50 percent reduction in CDC-ILI, and what we

observed was the lower dose, which contains the same amount of the licensed vaccine, but only 45 microgram of the H3 component, since that causes most of the illnesses and hospitalizations in elderly subjects.

We saw that this vaccine component had an efficacy of a little over 70 percent, and resulted in a 30 percent reduction of CDC-ILI versus placebo.

We further noted that there was a significant dose response effect between having more antigen present for the B and the H1 antigen, and that led us to conclude that it would be useful to develop a vaccine that would be based on three times 45 microgram.

What we saw was that the vaccine was highly immunogenic. We had protective levels of antigens for at least six months, and particularly the H3 component showed very high and sustained immunogenicity, with GMT levels of over 500 at the month six.

Very importantly, we isolated ten

H3 isolates. This study was conducted in the 2004/2005 season. And as you may recall in that season, the vaccine component of the vaccine which was A/Wyoming did not really match very well with the circulating virus, which was a California-like virus.

Part of these results were published by John Trainer et al in *JAMA Journal,* for those who want to take a closer look at that.

And then, also very briefly, PSC03, this was a study that was conducted last year. And what I'm showing here -- what I've tried to do is to look at the criteria that were described in the May guidance document of 2007. There's two criteria that you need to meet for non-inferiority. And the criteria in this age group is that the lower bound of the two sided confidence interval for the percent of subjects achieving sera conversion should meet or exceed 40 percent.

And these slides, the picture is a

little smaller than I had imagined, but maybe I'd like you to focus on the yeses in this slide, because what you can see is that, in principle, FluBlok meets this criteria in all cases.

I do want to point out that FluZone does miss this endpoint in one instance.

What is even more interesting is that, if you look into a subset of 280 -- approximately 280 individuals that are over 75, that this difference even becomes more pronounced. So having more antigen appears to be of greater benefit to people that are older.

Now in PSC03, we were faced with a problem because, during that year at VRBPAC meeting, it was decided that the vaccine should contain a B/Ohio component, and because the manufacturers couldn't make B/Ohio, CBER decided to produce B/Malaysia reagents for the SRID assay, which we also used for the release of our product. And as a result, it's really

very difficult to compare the immune response that you obtain against a B/Ohio component and a B/Malaysia component, because FluBlok contained B/Ohio, and FluZone contained B/Malaysia.

So I would like you to focus in this slide on the GMTs, and the GMT ratio that relates to the New Caledonia, the H1, and the A/Wisconsin. And again, for GMT, the criteria is that the upper bound of the two sided, it's 95 confidence interval, and the ratio to GMTs does not exceed one and a half. And it turns out that this criteria is met for FluBlok for both antigens.

As I mentioned, study PSC04 and 06, we have done an interim analysis. The reports are being produced. We do meet all the endpoints. We plan to submit this BLA filing within the next couple of weeks, and we hope to be back later this year to present those data in greater detail to this Committee.

Thank you.

CHAIR MODLIN: Thank you, Ms. Cox.

One question? Bob?

MEMBER COUCH: Yes. Manon, I want to be sure whether I understood or misunderstood. I thought one of your slides suggested that, in your healthy adult one, you were giving two does of FluBlok. It didn't say how many doses in the other blocks.

MS. MANON COX: We only give one dose.

MEMBER COUCH: One dose to a healthy adult?

MS. MANON COX: Right. It's one dose, but in the healthy adult study, we had a low dose and a high dose that we were comparing.

MEMBER COUCH: I see. That's what you meant by two dosages, if you'll permit me, rather than doses?

MS. MANON COX: Yes. Two different doses.

Thank you.

CHAIR MODLIN: Thank you.

At this point, I'll have Dr. Weir return to the podium to set up the rest of the discussion for the session.

DR. WEIR: Thank you. So I guess we're at the stage of our meeting to where we deliberate which strains should be recommended for inclusion in the vaccine for the United States for the upcoming season.

In this slide, I've sort of framed the overall discussion that will take place. In other words, what strains should be recommended for the antigen and composition of the 2008/2009 influenza vaccine based on the epidemiology and antigenic characteristics of influenza virus strains circulating in human population, the serologic responses to circulating influenza viruses of persons immunized with current influenza virus vaccines, and finally, of course, the availability of suitable vaccine candidate strains.

The final slide, which we will leave up, Dr. Modlin can decide how he would like to do this, but generally we go through them one strain at a time.

What I have put on this slide is the listing for what is in the current vaccine, that's the top sub bullet in each one. For example, H1N1, we have a current vaccine strain, A/Solomon Islands/3/2006-like virus. I've listed the WHO recommended virus strain in the case of the H1, an A/Brisbane/59/2007-like virus. And, of course, left open the possibility for your consideration of other strains that should be included.

So I'll leave this up, and turn it over to Dr. Modlin.

CHAIR MODLIN: Thank you. Some of these are going to be easier than others.

Why don't we go ahead and take them in order, as we've done in the past. Dr. Couch and Dr. Eickhoff, you are the experts on

the Committee. I think we're going to rely heavily on you. But why don't we go ahead and open up the discussion, and we'll focus on the H1N1 strain to start with.

Ted?

MEMBER EICKHOFF: A question for Nancy. In your discussion this morning, I thought I detected a hint that maybe we should seriously consider a strain in the 2C clade, rather than 2B. That may be a misread on my part. On the other hand, the 2C strains that were in your big reference table didn't really look that all different from the several 2B strains there.

So what do you see as the future of the 2C clade? Is it spreading within -- is there epidemiologic data to support consideration of such a move?

MEMBER COX: We can't distinguish the two antigenically. So there really isn't a reason to suggest at the moment that, until more change occurs, that that would be

advantageous. So while there are a number of strains in the 2C group, the 2B group is predominating. And I think that, since we can't tell them apart, it's kind of a moot point.

CHAIR MODLIN: Bob, maybe you could help us out with, starting off with what you're thinking about with the H1N1 strain?

MEMBER COUCH: The H1N1? No, I was a little surprised that the changes that we've been looking at appeared. Because I would have thought industry, if you hadn't shown me any of this data we received, I would have said A/Solomon Islands was probably a pretty good guess, if you had to do one up front, but it turned out not to be quite as good as I would have thought it might be.

I accept the variation, and we had a major outbreak in this country this year that, if we can change the H1, we need to, and the suggestion to WHO, I will go along with. I have no problems with that one.

CHAIR MODLIN: Ted?

MEMBER EICKHOFF: I will certainly second that motion.

Well, nothing further at this point. I'm sensitive to the comments that we heard from Tony Colegate. If we can accomplish a timely selection of candidate strains, if we can do it today, so much the better.

That's all I have to say.

CHAIR MODLIN: Okay. Dr. Jackson, you can help us out here, too, as well. As an influenza person, how do you --

MEMBER JACKSON: I'm not in the same league.

CHAIR MODLIN: Yes, Jack?

MEMBER STAPLETON: Well I think, if you look at, particularly ay the CDC ferret data, that there is certainly no other candidate that looks superior. So I don't see that there's a lot of argument against this WHO strain.

CHAIR MODLIN: Is there anyone on the Committee who feels that we should not accept the WHO recommendation for H1N1? Yes, Seth?

MEMBER HETHERINGTON: I just wanted to raise a question here. You know, there are two key points I think from the industry presentation. One is that -- and this is globally. I don't want to necessarily focus on H1N1. But what I'm trying to get at is, where is our greatest risk in each of these three strain considerations, and where can we minimize the risk that, at the end of the day, we're not going to have enough doses of a suitable vaccine for distribution. We may end up in a position where we're looking at some sort of a compromise of efficacy versus numbers of doses and coverage.

The two things that I think that really struck out were that it's unprecedented to do a three strain change, and anytime you get a new process and a new series of

challenges, you're just increasing your risk. And the risk that we might fall down at any single step, when you multiply them all together, the total risk becomes quite large.

And the second is that there's a difference between two of the slides we saw, and that has to do with delivery of the vaccine. Not delivery in the sense of, it's on the shelves, but in terms of usage.

Initially we saw a slide where the distribution of the administration of vaccine goes through December. And what Tony Colegate mentioned was that, really, there's not much usage after Thanksgiving. And I'm not sure how much of a restriction at that end of things there really is, but clearly, there's a hard stop in terms of when you're going to be able to effectively use a vaccine, and where that is I think adds another dimension to the level of risk. It just makes your window of opportunity even shorter.

So I guess what I'm trying to get

at is, as we go through each of these three strains, is there a way that we can identify what's a much have change, and what's a, well, we may need to give a little bit here, because otherwise the risk is going to be great. And the risk may be difficult to quantify, but perhaps either Dr. Couch, Dr. Eickhoff can give us a little bit of history lesson here on how we might best balance that.

CHAIR MODLIN: Let me ask -- I'll push back just a bit, but first of all, what do you think -- what is your best assessment of which of these strains we must have, and which would be the one that we could least do without?

MEMBER HETHERINGTON: Well, I'm not sure I can give that kind of a recommendation at this point prior to the discussion. I think that one of the key issues I wrestle with is I saw some of the data on the antibody responses is trying to decide what's a suitable antibody response? What's the

correlate of efficacy for a vaccine?

We saw information on reduction in titer from some baseline, which is a response of a vaccine to its homologous strain. But it's unclear to me where the HA greater than 40 titer comes into play. Are we trying to get everybody above a titer, or are we trying to get the least decrease from baseline? And I don't know which is the best correlate, because they are very different answers.

The reduction from the baseline was quite dramatic for some of these strains. But if you looked at the proportion of subjects greater than 40 for their HA titer, it wasn't that bad. It was more like 80 percent.

So I'm wrestling with trying to assess what's the correlate of protection, because that may influence how we decide what ends up being something we can deal with.

CHAIR MODLIN: I would just point out, one of the things we haven't discussed in any detail, but obviously it's a major factor,

and that is making some -- you can't guess as to when next year's influenza season will occur. We have had data presented to us in the past about the timing of peak influenza activity during different years, and it's my understanding it's more likely to peak January or February than it is in December. But of course, we can't predict that will be the case.

I will tell you that, up at Dartmouth, we have been pretty good about following a recommendation to continue vaccination well into January. And I think there's more and more attention to the fact that we may have an opportunity, at least in most seasons, to extend the vaccination season beyond what we've done in the past. And so I think that is yet another factor that needs to be taken into consideration, recognizing that you're still rolling your dice.

Jose?

MEMBER ROMERO: Well, let me echo

that. I mean, as a practicing pediatrician in NID, we are immunizing well into January, and even into the epidemic today.

The other issue is that we are educating our pediatricians to start earlier and earlier, to the point that we're telling them that we want to start during those school physicals that are going on during August. So, you know, whether it'll happen or not - I see John raising his eyebrow - but that's the issue is that I think the windows are going to shift, and they're going to shift because pediatricians are really getting the idea that this is important, family practitioners, and that we are vaccinating well into the influenza season.

CHAIR MODLIN: Melinda?

MEMBER WHARTON: Yes. I wanted to just make a comment about this issue of extending the influenza season. With support from HHS, CDC has, for the last couple of years, sponsored national influenza

vaccination week, following Thanksgiving, with the specific intention of trying to focus on extending the influenza vaccination season. And we've only done this for two years now. This is not anything that had been done previously, and we do have some evidence, albeit still preliminary that, in fact, that there has been some increase in later season vaccination in the last couple of years.

So I just want to support what my colleagues around the table have presented.

I don't think we should give up on extending the influenza vaccination season. And just as we've seen this year, where it was well into 2008 before the influenza disease season really took off, I think we do have more time, and both in the clinical and public health realm, we can do better with extending vaccination later to make sure that some of this later season production can be used.

CHAIR MODLIN: Dr. Couch?

MEMBER COUCH: No. I just want to

thank Seth for that question. That's an excellent question, because we get caught up in the practical aspects of this, not just in the scientific, as you said. And I understand and appreciate what's being said, that extending the vaccine season is, indeed, worthwhile almost certainly for a lot of individuals. But I want to emphasize that this vaccine really still needs to be available the 1st of September. And when we've had it in the past, on occasion, the middle of August, that's a whole lot better off for delivering. And so we'd like not to compromise on that anymore than possible.

Even though we advise recommending late, I still advise everybody to get your vaccination before Thanksgiving. And that guarantees almost always, actually there's one exception. We had a November H3N2 massive outbreak. But that's only one exception in a couple of decades. Then you'll be all right.

Otherwise, you're running the risk.

And this year, it was H1N1, with a risk of not having that vaccine delivered until after the epidemic was already here.

And so that's important for us not to compromise that part of the vaccination need for a strain selection which is desirable, perhaps not essential. And if you would have told me I'm reducing the dose so that we can't start vaccination until the middle of October, only half as much like we've had to live with, Solomon Islands is fine with me. That would have been a relatively easy decision for me.

CHAIR MODLIN: Any additional discussion?

If not, I'm going to call a vote. For those of you who have been to past VRBPAC meetings, we have changed the way in which we vote. Rather than going around and asking for each individual voting member's vote one-by-one, the procedure has been changed in that we'll be voting all at one time. And we will

ask you to raise your hand, either as an affirmative or a negative vote.

We don't have a specific question, but the issue is, in essence, to accept the WHO recommendation for replacing the current vaccine H1N1 strain with the A/Brisbane/59-like virus, if I understand it correctly.

So I'm going to ask that those in favor of accepting this recommendation raise their hand. For H1. This is just H1. We're doing this one at a time.

EXECUTIVE SECRETARY WALSH: And please keep your hand raised until Dr. Modlin calls your name.

CHAIR MODLIN: Okay. Dr. Cox is not voting.

Dr, Wharton, Dr. Destefano, Dr. Jackson, Dr. Davis, Dr. Gellin, Dr. Couch, Dr. Modlin, Dr. Debold, Dr. Romero, Dr. McInnes, Dr. Self, Dr. Hachey, Dr. Jackson, and Dr. Eickhoff all vote, yes.

Those voting, no? Those

abstaining?

EXECUTIVE SECRETARY WALSH: Just for the record, I think you said Dr. Jackson --

MEMBER STAPLETON: You called me Dr. Jackson, I believe.

EXECUTIVE SECRETARY WALSH: Instead of Dr. Stapleton. So it was Dr. Stapleton.

CHAIR MODLIN: My apologies. It's not been the first time, it will not be the last time, either.

Dr. Eickhoff?

MEMBER EICKHOFF: Just a point of clarification. The slide reads A/Brisbane blah, blah, blah dash like virus. This gives the manufacturers, I presume, a little bit of latitude in selecting the best like --

CHAIR MODLIN: That's certainly my understanding. Jerry, is that the case?

DR. WEIR: That's always the case for us, yes.

CHAIR MODLIN: Thank you.

Let's move on to the H3N2 strain. And again, I think we'll open up the discussion as we have in the past. The recommendation is to replace the current H3N2 isolate with the A/Brisbane/10-like virus.

Dr. Couch, you want to start us off again?

MEMBER COUCH: Not much discussion, again. We wanted to change the Wisconsin last year to something else, we just didn't get the chance. So there's no question about changing it this year. The concern is that we've got it right again this year, but I think with the data we've got in front of us, we don't have much choice. We have to accept the recommendation for A/Brisbane.

H3N2, I will say the same thing I think I've said two or three times, is the major decision each year.

CHAIR MODLIN: Jack?

MEMBER STAPLETON: Yes. I have a question about, is the Uruguay/716 isolate

considered to be Brisbane/10-like?

CHAIR MODLIN: Jerry or Nancy?

MEMBER COX: Yes, it is.

CHAIR MODLIN: Seth?

MEMBER HETHERINGTON: Yes, just a comment. I mean again, getting back to risk, from Tony Colegate's presentation, this seems to be the strain that could be the limiting factor. And remember, the total number of doses is dependent upon your weakest of growing strains, and it sounds like there will be some shipment of some reassortants, if I got it right, sometime in late February for the Uruguay strain. So that's still a big question mark, but it sounds like it is a potential solution to a problem. The IVR-147 Brisbane strain was declared as being not viable. And I think we just need to understand that this may be where the biggest risk resides for vaccine production in this year. And I hope Dr. Couch and Dr. Eickhoff have a comment on that, or anybody else with -

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MEMBER COUCH: Well, we can comment on that, but I think we all take it as A/Brisbane-like. And the chart, as Nancy says, Uruguay is a Brisbane-like. And Dr. Gupta gave us the alternatives that are being sought. And Dr. Colegate did with around three sites in the world trying to get those reassortants to go. So it doesn't have to be A/Brisbane. A/Brisbane-like is the decision.

CHAIR MODLIN: Further discussion? So we'll call the vote on this.

Those in favor of accepting a WHO recommendation, would you raise your hands?

Those voting yes are Dr. Wharton, Dr. Destefano, Dr. Stapleton, Dr. Davis, Dr. Gellin, Dr. Couch, Dr. Modlin, Dr. Debold, Dr. Romero, Dr. McInnes, Dr. Self, Dr. Hachey, Dr. Jackson, and Dr. Eickhoff.

Easier than I thought it was going to be so far.

Let's move on to the B strain. The

recommendation is to replace the B strain with an alternative B/Florida-like isolate. The data here were a little more murky.

MEMBER COUCH: I've got a comment.

CHAIR MODLIN: Bob?

MEMBER COUCH: I had a comment for B that I carried with me that I want to make. I'm going to go ahead and make it.

I went back a little bit like, maybe like Tony did, and a couple of others, that what's going on with the Bs. And I went back to 2000 trying to see if we can get any patterns out of that.

We got selected correctly out of the eight years they've both been circulating that I read. We selected correctly four of the eight. We missed four of the eight. We might as well flipped a coin, to see, for selecting the Bs, if we couldn't do any better than that. I think that's still somewhat where we are with these things still circulating around the world, both of them,

which one is going to be dominate. And if we talk about guessing, this is the one that we do the most guessing on currently.

And so I go back to what -- I was about to say what Tony introduced earlier. You look at some of those responses in adults and elderly, you see, and either one, they do very well against the other strain. And in the absence of attacking it head on, which we discussed to some extent last year, I made up my mind that I'm going to come into the meeting, if I keep coming to the meeting, every year with the decision that I want to change the B to the one we didn't use the previous year.

And that, at least, will improve the circumstance for the elderly and the adults. And if those children, at least the older children, got their vaccinations as they should have the previous year with Malaysia, they'll get the right one this year, and then they'll be in better shape, as well.

And in the absence of being able to guess better than that, I think that's the decision we have to make. Well this time, based on circulation, it says, pick a Yamagata, and we picked Malaysia, based on a circulation. And we had a Yamagata, so I think it's an inexact science.

CHAIR MODLIN: Your point's well taken, and I wonder if that shouldn't take us back to Melinda's original question about whether or not you can, in some respects, obviate this as an issue by including both lineages in the vaccine. Obviously, this is not something we're going to impose upon the manufacturers this year, and it's likely that the only way in which that would happen, if we thought it was a good idea to happen, is to signal our intent to do that at some time in the future. Maybe next year, maybe two years from now. I don't know what that time interval would be. But that might be something that would be worth discussing, and

I think probably should.

But I also don't want to get off on that right now. Obviously, we've got another task here. But maybe, if we have time, maybe we can come back to it.

Is there further discussion about the B strains? Again, Ted, do you have a strong opinion?

MEMBER EICKHOFF: No. I had a thought similar to the thoughts that Dr. Couch had, mainly, maybe we should select the non-dominant strain for this past year in anticipation of the fact that it may be the dominant strain next year. But you're right, it is a guessing game.

I think Nancy pointed out that this strain, the Yamagata strain, could be dominant for the next five years. We just don't know.

CHAIR MODLIN: Bruce?

MEMBER GELLIN: Well, let me put a slightly different proposal on the table, as well. I think that it's not necessarily that

we're imposing on the manufacturers, but I think we're going to provide a roadmap, and maybe an opportunity. And so what if we were to think about priorities?

That we think that for sure they should make X, but if they have the wherewithal, they should consider a second strain, which would then get to a tetravalent.

Without getting into naming names, a lot of companies use the number of valencies in their vaccines to say that they have a better vaccine than the next guy. So I guess I would like to think that that's something that we want to at least start to put down some markers for, and not to compromise, but to then have this prioritization there that everybody should make this one, but if others want to get into it. Now that would, obviously, get into a whole complexity of not everybody having the same vaccine, which is a larger discussion. But then it might help to move the field.

CHAIR MODLIN: Further discussion on B, at least on this particular point? If not, I will call for a vote. And the question again is, do we accept the WHO recommendation for the B strain? Those in favor of accepting the recommendation, if they'd raise their hands?

Those in favor, Christine, or Dr. Wharton, Dr. Destefano, Dr. Stapleton, Dr. Davis, Dr. Gellin, Dr. Couch, Dr. Modlin, Dr. Debold, Dr. Romero, Dr. McInnes, Dr. Self, Dr. Hachey, Dr. Jackson, and Dr. Eickhoff.

Thank you.

We got through that a whole lot faster than I had anticipated, particularly given the difficulty.

I think, in the interest of time, I I think it probably would be worthwhile having a little bit further discussion about the possibility of extending the number antigens, particularly the B antigens. And I'd be very interested in actually having the

manufacturer's perspective on that. I don't know if Mr. Colegate, or anyone else representing any of the manufacturers would like to speak to that topic. And you're welcome to do so using the microphone right there, if you'd like to do it.

Anyone else?

MR. COLEGATE: I think the presentation last year at this meeting, or the one following on the implications of tetravalent vaccine, apart from the obvious time constraints, and you can see with the situation we're in this year, we just could not do it.

With three strain changes, we are at risk now of falling down on two of those strains, because two of them are totally unknown to us. I guess the Brisbane/10 is not totally unknown, we know that IVR-147 will not work for us, so therefore, we have to look for an alternative. But there are three possibilities there ready and waiting for us.

Well four, I guess, if IVR-171B is not completely out of the picture. And I'd like you to remember that. If it does come good with the additional serological studies, if we could use that, maybe that could help us to get to a flying start, if there's some uncertainty over the Uruguay.

I think we ended up last year with saying really what is needed now is we need some help with the regulatory pathway. Because a tetravalent vaccine would need all kind of regulatory, and I thought somebody from the Committee was going to come back to industry and tell us what we needed to do to actually get this tetravalent vaccine off the ground, because we obviously will need some kind of guidance on clinical studies.

We discussed, do we put seven and a half micrograms of Yamagata and Victoria in, or do we put a full 15 in, and we really need some kind of discussion, and some program to work this forward. But I think we do need

some help and some guidance, and then I'm sure we can -- if it's in the public good, we'll do it.

CHAIR MODLIN: This sounds like naivetè on my part, and probably is, but I would think, if there were two B antigens, the likelihood of having to change the B antigens on an annual basis might decrease, would they not? Bob, you're the B expert.

MEMBER COUCH: Well, actually, I wanted to ask that question, maybe much the same question, a little bit different way. I want to remove it from this year, Tony. Because this came up about, let me guess, six or eight years ago. And I can remember that the industry -- because the proposal was, which is actually, if we had to make a change right now, that would still be number one on my list is to give seven and a half of each one, so your total is still 15. We brought that up for discussion, and the industry representative said, well one of them we did

last year, and we've got the reagents, and we're only using half of it, so we only have to make half as mach of a new one. That will delay us, but not significantly. Would you share that kind of view?

MR. COLEGATE: I think so. I mean, we need as much warning as possible. I mean, it just needs to be planned. I guess we can do all of these things, if it's planned in, and I guess, if it means we have to increase our capacity, then we increase our capacity.

MEMBER COUCH: But you only make half as much of the one you made the previous year.

MR. COLEGATE: Yes. If it's seven and a half micrograms, have we got any clinical data to show that that is --

MEMBER COUCH: Yes, that's the problem. FDA wants was a clincial --

MR. COLEGATE: Yes.

CHAIR MODLIN: Any other discussion?

Melinda, did you have a comment?

MEMBER WHARTON: Yes. You know, this issue has come up every year that I've been at this meeting, for however many years that's been, and just from having gone through the annual agony of trying to flip the coin, or get out the crystal ball regarding what strain is going to -- of the two co-circulating lineages of type B, which one will predominate, and seeing, once again, that the issue really has to do with children. It seems to me that, if there is a public health case to be made for improving influenza B protection of children, and there are people around this table who know those data better than I do, and then the next question is what is the scientific base that needs to be brought forward in terms of clinical trials to tell us what the vaccine should look like.

And then, what do the manufacturers need to actually make that happen.

And, you know, where this Committee

sits vis-à-vis other advisory committees, I'm not completely sure, but I would really like to have a pathway forward by which we could get there so we're not having the same conversation every year.

CHAIR MODLIN: That's a great point. Norm, obviously we're not going to settle this now, but do you have any thoughts? Would this be something that would be a proper role for this Committee to take up in another forum, another time?

DR. BAYLOR: I think it would be very useful. I mean, I echo what Melinda said. You know, we bring this issue up every year, and it sort of drops. And maybe it's now time for us to say, let's just tackle this issue. Let's have the discussion. We can put together a VRBPAC and discuss and supplement this Committee with other experts, and discuss what kind of data would we all recommend to, say, form a quadrivalent vaccine containing two B strains, what kind of safety and

effectiveness data we would require. I think we can have that discussion in this type of forum.

CHAIR MODLIN: Yes?

MR. COHEN: Hilal Cohen, Novartis.

Going back to last year, we raised a point that we have to mentioned again, which is that we'll need a legislative fix, as well as just the pure science. The current legislation covers for reimbursement, and for insurance, a trivalent vaccine. And while I certainly personally like the idea of the fourvalent with two Bs, we'll need that other fix, as well.

So I second the idea with Dr. Baylor. It does pay to put together everything at one time and view it as a whole. Because even if we had a recommendation today for a second B, I'm not so sure that manufacturers would be able to deliver, be willing to deliver.

CHAIR MODLIN: And one option would

be to consider to having a quadrivalent vaccine only for children. We do have other pediatric formulations for the vaccine, and I recognize that that introduces all kinds of other complexities, as well. I'm not sure we want to get into that discussion, but at least that's yet another thought there.

MR. COHEN: That would be basically a new vaccine that we would have to bring forth to the agency for licensure. That's certainly doable, but it is a new product completely, and would require an extensive safety database. So again, I would like the idea to do something like that, but I think it would require industry working with CBER to define the needs. And then we can move forward.

CHAIR MODLIN: Any further discussion? Yes, Pam?

MEMBER McINNES: I just want to second what Melinda said. I mean, I've also been coming here for a long time, and I think

the Committee, these are not frivolous decisions that are made. And there is always this dynamic of, oh, don't change the decision, because we might not be able to deliver.

There's risk on both sides. There's risk of not having sufficient antigen, and there's risk of us really not having the right strain.

So this is not a risk-free business, and I think we need -- one of these years, we're going to have a B year. And I'm personally quite concerned about that. And this is, in fact, maybe a year we should have two Bs in the vaccine. And for a whole host of reasons now, we can't appear to even sort of move in that direction. But if we don't step into the water, we're never going to solve this, because there will always be the push back.

So I just, absent having the proof of a decision that, yes, this is the year you

need two, and you'd better pretend this is the year you need two, what is it going to take to move this discussion forward?

CHAIR MODLIN: Jack?

MEMBER STAPLETON: I have a kind of an historical epidemiology question for Drs. Eickhoff and Couch, and that is, since I've been paying attention, since I'm not a flu person, there has been this mix between Yamagata and Victoria lineages, and for the last, at least eight to ten years. Is there, historically, a time when one has emerged where there's been a single B lineage?

CHAIR MODLIN: Nancy, you may be able to address that, as well.

MEMBER COX: Yes. When the B Yamagata lineage emerged, of course, it had been circulating in Asia - it was detected first by the name in Asia - we saw, for a couple of years, and it was more prominent in Europe, co-circulation of the previously circulating B/Victoria strains with the

Yamagata. In the United States, there was a pretty clear transition, a pretty sharp transition to B/Yamagata-like viruses.

Then for the next ten years, B/Yamagata circulated very little, if at all, in Europe and North America, South America, but remained in circulation in Asia. And first it was really only in China, and then we would see it in China and Japan. And after ten years of its absence, as far as our surveillance was able to detect it, we had a resurgence of the B/Victoria viruses. And we anticipated that, I think, through our surveillance. I would have to go back and look and see for sure. And I think we did move to B/Victoria lineage vaccine.

Since then, it's been a mixed bag. And it's been very difficult to determine what to do.

I agree very much. We do see that going on right now in Hong Kong, approximately 50 percent of the viruses are Victoria, and 50

percent are Yamagata, whereas, in Mainland China, there's a different picture. The rest of China, there's a different picture.

So it is a very difficult forecast to make, and there's not, one year it's Yamagata, the next year it's Victoria, which would make it very easy for us. But also, just in line with what others have said, it's really the young children where you see this dichotomy of antibody responses, where basically it's all or nothing. In the adults, you see a much more -- because the adults have been exposed to both lineages, you do see that bump in titer to the opposite lineage.

So I think the public health focus really is on young children where we would not expect them to be proactive. And we do see childhood deaths associated with influenza B viruses.

MEMBER STAPLETON: I mean, I just want to comment that, given that epidemiology that we've observed, and I don't see how we

can avoid, like others have talked about moving towards a tetravalent.

CHAIR MODLIN: Bruce.

MEMBER GELLIN: So Tony Colegate, as usual, told us very many important things. He started by giving us this cautionary note about the tetravalent. But then he came back to the microphone and said, if it's in the public good, we'll do it. And we can do all these things if we can plan. And then sort of put out this regulatory challenge.

So my question is really to Norman or the FDA is that, if a manufacturer wanted to come in this year, and to produce, for some segment of the population, a tetravalent vaccine, do you think that -- I guess the big question is, would it require a phase three trial which would take it off the map for bringing it into the next year, but do you think that there's enough time to be able to perform the kind of studies that might be needed to bring such a product forward?

DR. BAYLOR: To bring a product forward, say if someone said it today, and to bring that product forward in the fall? That would be cutting it close. That would be very difficult to do. But there's another complication here, and it's not insurmountable, but influenza, as we all know, influenza vaccine is very unique. It's really the odd vaccine out, because it follows into all the manufacturers, the public health; we follow in step. So this one is very close. And to have a manufacturer -- this has come up a lot this year about quadrivalent vaccines. To have one manufacturer out of step from the others, so we have one manufacturer who wants to make a quadrivalent, and the others do not. I mean, that is somewhat difficult.

I mean, it can be done. But as far as the way our influenza system has gone all these years, I mean it's a partnership, and we try to keep everything in step with all the manufacturers, with all the government

recommendations. So that would be a challenge.

From a regulatory point of view, we could do it. But how would this be implemented as far as public health policy, that's another question.

MEMBER GELLIN: Yes. I didn't say it was simple, but I guess you want to have a core vaccine, and then in some way you may want to add to it. I mean, it's not the only product that different manufacturers have different numbers of valences.

DR. BAYLOR: No, but it's really the only product where we sit here and make a recommendation on what will go into that vaccine. If you wanted to make a hib vaccine, and you put a different conjugant in it, that's up to you.

MEMBER GELLIN: Another, not a different. So they have to meet these three, and then they may have, you know, FluPlus, or whatever they want to call it, but they now

have something that has an additional component.

I'll stop.

DR. BAYLOR: It's doable from a regulatory point of view. We could do it.

CHAIR MODLIN: Bob?

MEMBER COUCH: I would like to urge, I'd certainly support a discussion, serious discussion, of how to move forward on these issues. But I would personally not like it to be restricted to Influenza B. Because I think some of us have had the view for quite some time now that we've got one vaccine for all you say, as though that's all you got to have, and reduce the dose for reactions in young children, and you're fine. We've been at the point for quite some time that we need vaccines tailored a little bit better for different individuals. We've got the elderly, my view, and it won't surprise many people, the vaccine dosage is not high enough. Now it's fine for perfectly healthy young adults,

and the military has got the beautiful data on that for a long time, and we've addressed questions that are unique for children here on influenza B, and that also applies to children on H1 and H3 to an extent, as well.

So you see, we've got these different considerations, and some of us are now worried about how do you immunize immuno-compromised individuals? See, there's another group, that that's a part of the discussion of how to make -- well, I know Dr. Baylor said a minute ago that we've got one system. But look how many cephalosporins we've got? Now that won't mean that we want that many different versions of influenza vaccine, but that sort of circumstance would not be unique for our country, if they're picked and they're tailored for the right populations.

CHAIR MODLIN: If flu vaccines made as much money as cephalosporins did, then we would have no problem.

Yes, Lisa?

MEMBER JACKSON: Well, Bob, along those lines, I'd just say I was a bit surprised by the sort of suggestion that we might consider reducing the dose of B to include more strains because to me, if anything, maybe you would want to have more B than we currently do. I mean, especially in young children where the serologic response, if that's meaningful, is obviously not what we'd like to see, and really necessitates two doses, which still, a very substantial proportion of children do not receive.

I think the other thing we'll run into as we go down this road is the realization that there's quite a dearth of information on how well the B component works. I wondered if you would agree with that.

It seems like in young children, especially of the relatively small number of studies that have done a good job evaluating efficacy in general, the B circulation hasn't been extensive enough in those years to allow

a reliable calculation of effectiveness, specifically against those strains.

MEMBER COUCH: Again, maybe I sound like an industrialist here, but the regulatory requirements are of major importance, and you remind me of that one because of how strict we want efficacy to be proven for these various things. Because that's difficult and time consuming for influenza, and when a company asked me about this, I said, don't ever plan for one year. You'll almost certainly won't make it. That's the unpredictability, and you're talking about investments that go in large numbers over three years to prove -- I don't mean to be sounding like I'm picking on FDA -- to prove a surrogate that was established decades ago. Now how many times do we need to prove it?

But, you know, I want supported data. I'm not arguing against that, but how rigorous should that data be to prove that same surrogate that we've had for decades?

CHAIR MODLIN: Norm?

DR. BAYLOR: And at some point, Bob, I'd like to have that discussion. Because I don't disagree with you, but I think we need to have that discussion.

CHAIR MODLIN: It sounds like we've got a topic for another meeting.

DR. BAYLOR: And if we want vaccines to be tailored for the population, we just have got to have some discussion about, what is the minimum requirement, as opposed to what is the desired data.

CHAIR MODLIN: Okay. We'll let that be the last word.

We've gone from being behind to being considerably ahead of time. I'm going to suggest that we start up at 1:30 rather than 2:00, if that's okay with everyone. So we'll start the afternoon session at 1:30.

(Whereupon, at 12:34 p.m. the meeting was adjourned, to reconvene this same day at 1:36 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

1:36 p.m.

CHAIR MODLIN: I would like to welcome everyone back to the afternoon session of the VRBPAC Committee meeting for February 21st.

We'll be moving on to the next topic, a very interesting critically important one, and that is the development of the influenza vaccines for both the pre-pandemic and for pandemic uses. And I understand that Dr. Golding from the FDA is going to, first of all, provide a summary of a government workshop on pandemic preparedness, influenza preparedness that was conducted this past December.

Dr. Golding?

DR. GOLDING: So we are moving from a game to looking for the crystal ball when we are starting as the world to be prepared for the unknown, which is a potential of pandemic influenza.

So it become apparently in the past couple of years that we cannot just sit and wait to see what happen, but rather there is a very big push both by the World Health Organization, the U.S. Government and really globally to try and prepare for the event of the avian influenza starting to move from one person to another. And in order to best be prepared there is a need to prepare some vaccine and there is real mandate to prepare stockpiles of vaccines trying to at least partially protect and curtail pandemic in the case that it started. But as we were starting as an agency to decide how to address it from a regulatory point of view, we realized that there are a lot of scientific gaps that need to be answered. And that was the reason for organizing a workshop that took place back in December. It was co-organized by scientists at the FDA, NIH and the World Health Organization and it took place in Bethesda. And I just want to take a couple of slides to

summarize what was the nature of the workshop and what was the general recommendation.

I do want to make it very clear that none of the slides will present any formal FDA viewpoints or standpoint. This is just reflecting what came out of that particular workshop.

So, as we all know, the common situation, which is still good in that very limited human-to-human transition of avian influenza have been reported or confirmed. We'll hear more about it from Nancy, but the current situation is not conducive to traditional vaccine clinical trial. Therefore, evaluation of pandemic influenza vaccine is relying on immunological measures that currently have evolved from the seasonal influenza vaccines that we're all very familiar with.

And as you know, the principle correlate of influenza vaccines efficacy at the moment is the hemagglutination and

inhibition antibody titer as the real doubt, and we saw many slides with type of data today.

But the big questions are, of course: Is it appropriate to extrapolate what we know from seasonal influenza vaccination to pandemic influenza vaccines when most of the population are lacking in preexisting immunity?

Is it also possible that due to the higher pathogenicity of the H5/N1 what will be protective against seasonal vaccine may not be fully protected against these viruses?

Most specifically, is an HI titer of any antibody measurement appropriate to predict clinical benefit from new types of influenza vaccines such as live attenuated vaccines, plasma DNA vaccine, virus-like particles and vector vaccines, all of which are currently under development by many different manufacturers and sponsors?

And we know already even from the

seasonal vaccines that the live-attenuated vaccine using the HI titer was not always a good predictor of protection.

And, of course, the big goal is therefore how do we establish the protective level associated with newly defined immunological endpoints and accurately quantify the responses following vaccination, which is what we will eventually need to license such vaccines.

So the goals of the public workshop were, first, to identify the gaps in our knowledge and abilities in addressing the unique challenges encountered in the development evaluation of vaccine intended to protect against pandemic influenza and then to facilitate implementation of global research agenda to improve efficacy assessment of pandemic influenza vaccines.

There were four sessions. The first session was chaired by Dr. Robert Couch, who is with us today. And this session

included descriptions of humoral and cell-mediated responses to influenza with an emphases on immune mechanisms that contribute to protection against influenza infection or disease.

Of course, I cannot cover all the talks that were discussed. But this is sort of trying to just summarize this particular session in that probably both antibody responses contribute to protection against seasonal influenza. May an analysis of human challenge studies support the conclusion that HI antibody titer of 1 in 40 is associated with at least 50 percent reduction in the risk of contracting influenza infection or influenza disease. That was published by Dijon in 2003.

In the second session we moved to avian influenza. This was chaired by Dr. Jackie Katz from the CDC. And we tried to cover information that was gained from people who were either exposed to H5/N5 and other

avian influenza as well as early vaccine trials. And the main data that was shared came also from information on poultry workers. And it turns out that immune responses to several avian influenza vaccines candidate both an activated LAIV were presented from clinical studies performed in the U.S. as well as in Europe.

What was I think the most important note by Jackie Katz is that in poultry workers that were indeed exposed the titers of antibodies were relatively low. Only in very high exposure one found 1 in 80 titer of microneutralization. And in many cases they did not last for very long. So you really had to capture them in the right time.

This is a very important initiative by the World Health Organization that was presented by Dr. Fred Hayden, describe the Southeast Asian Influenza Clinical Research Network that will facilitate international collaborative epidemiology and immunologic

studies of pandemic influenza. And most of the centers are in Asia in about five different countries. And, hopefully, they will be able to get access to post-exposure samples from infected individuals and start to gain some more insight of what type of antibodies may be correlated with level of protection.

In session three we started to really hone down on the assays that are used to evaluate vaccine immunogenicity. The assays that are used in clinical trials. So it included a discussion of the limitations of the current assay to the antibody responses to NNA and described new assays to evaluate cell-mediated immunity in M2 specific antibody responses. Novel assays that used pseudotyped viruses of H5/N1 as well as genomic -- display libraries were also described.

It was expressed quite repeatedly that the traditional H1 curves based on chicken or turkey red blood cells are not optimal for H5/N1/HI. Horce red blood cells

seems to have more sialic acid -- which are the preferred receptor for H5/N1 strains. However, Horce HI needs validation.

In the fourth session we looked at the value of various animal models, and it was chaired by Kanta Subbarao from the MAID, which was also one of the co-organizers. And in this session animal models for pandemic influenza were described. Results of wild-type virus challenge in mice and ferrets to determine the immunogenicity and efficacy of new vaccines were also presented.

These animal models provided important information about vaccine immunogenicity and correlates of protection including heterologous protection. The vaccine effect included reduced viral loads in the upper respiratory tract and the lungs, lower morbidity and less lung pathology. However, it was felt that lethality as an end point is often not an optimum endpoint for vaccine effect and/or dose findings.

The workshop, the two day was actually then there was a panel discussion and a general sort of recommendations that came out of it. So I think the sentiment was that it may be premature to extrapolate what we know from seasonal influenza vaccination to pandemic influenza vaccine, particularly the use of a given antibody endpoint to predict pandemic vaccine efficacy.

Specifically, the use of HI hemagglutination in addition they say may not be appropriate for all types of pandemic influenza vaccines. Additional immunogenicity measurement need to be defined and the protective levels associated with the newly defined endpoints determined.

Moreover, novel assays should be developed to measure mucosal immunity, cell-mediated responses and antibody responses to neuraminidase and other targeted antigens.

Animal models, both mice and ferrets, can provide important insight

regarding correlates of protection against emerging avian strains. In order to facilitate the standardization of assays to evaluate and compare vaccine responsiveness there is an immediate need for standard reference reagents, low pathogenicity of viral stock, working cell banks and very importantly shelve SOP. I think Nancy referred to one such working group that now has been sort of initiated by the World Health Organization and CDC and try and validate at least the microneutralization assay.

So in conclusion, we felt the programmatic approach to pandemic vaccine trials was use of standardized assay should facilitate comparison of vaccine candidates and expedite pivotal studies and licensure of pandemic and pre-pandemic preparedness.

And that's it.

CHAIR MODLIN: Thank you, Dr. Golding for a very nice and concise summary.

I'm going to suggest that we go

ahead with all three presentations and then maybe open things up to discussion and I ask you to participate with the full Committee discussion when we do it all at once.

So, Nancy, would you like to summarize H5/N1 surveillance?

MEMBER COX: Okay. Thanks very much.

I will try to quickly go through some of the latest epidemiology and virologic results for H5/N1 viruses.

This is a slide that is a composite slide showing, first of all in green, all the reported, OIE-reported outbreaks in birds. And, of course, we know that this is an under representation of the true number of outbreaks. Because there are many that are reported in the press. Many that are confirmed by a reference lab that are never actually reported to OIE. But you can see there are outbreaks throughout Europe and the Middle East, and certainly in Bangladesh right now

there are a lot of outbreaks being reported. And they have been reported throughout China and this part of Russia.

Also in Africa.

And then there's the color coding so that the most recent human cases are in the yellow triangles. And you really can't see those very well because of the color overlap. The purple shows the 87 human cases identified in 2007 and so on.

And you can see that there's a lot of purple down the Nile River in Egypt. There's a confirmed case here. One confirmed case in Pakistan, and so on. But the majority of the cases that you see here in the purple color, which is last year, are in Indonesia, in Egypt and a few cases in China and then a few cases in Vietnam, and so on.

Maybe you can advance the slide for me. Okay. I think we'll skip this slide and that slide, please. Okay.

So as of February 20th there were

362 human cases reported to WHO, 228 of those were fatal giving a case fatality ratio of about 63 percent.

Now we've already had 13 cases that have been reported to WHO, and we know that there are additional suspect cases in 2008. So it seems that we're getting off to quite a rapid start to counting how many cases or to accumulating cases of H5.

So you can see here that the case fatality ratio hasn't really varied that much over time. It's been about 60 odd percent. But if you look country-by-country you'll see some striking differences. We won't go into that today.

So just for the most recent cases, we had a case in Vietnam in a 40-year old male reported on February 15th. And then yesterday China reported a new H5/N1 case in a 22 year old male from Hunan Province.

Next, please.

And this just shows where the case

occurred. There are a lot of poultry outbreaks now being reported in the northern part of Vietnam. They had instigated or put in place a very aggressive poultry vaccination program and really had human cases until last year again. And there's a fairly high case fatality rate. So just from the wave that's been occurring in Vietnam, 8 of the last 12 cases have died.

Now if we look at cases in Indonesia, which is another hot spot as everyone knows, we're seeing cases reported in January. And there have been a 127 cases reported in Indonesia.

Next slide, please.

This is Vietnam. My talking points were a little bit out of order. So you can see this is the wave of infection starting in May of 2007, the current wave and extending into 2008.

For the majority of the cases that we hear about there has been exposure to sick

and dead poultry prior to symptom onset. So that has not changed in the last year or so.

I think I probably showed a similar slide. We're really trying to get a handle on the nomenclature for the H5 viruses. If you read the literature, it becomes extremely confusing. And the nomenclature's a bit arcane, but we feel that we have a much better handle on the amount of genetic variation that is occurring. And the new nomenclature will allow us to go forward using a standardized format so that we will be able to relate what's circulating at a given point in time with what has circulated in the past.

So if you look at the viruses that have circulated in birds during the past three years, you can systematically divide them up into nine clades. There are actually ten clades if you count the 1997 era of viruses.

This evolutionary tree was based on public domain sequences. So there's a lot of sequence data in the public domain, and over

800 HA sequences were used to draw that particular tree.

Now this is going to be harder to see. And I have tried a whole variety of ways to display these things. And if you really want to get down to the nitty-gritty you need to have a certain number of viruses on the tree.

So the nomenclature is quite simple, except that for some of the clades we are now talking about third order. So we have clade 2.1.1, 2.1.2 and 2.1.3. So it becomes quite complex. But for those of us who are looking at the data on a weekly basis it really helps us to keep a handle on where we are going.

Now in yellow I've highlighted those viruses that have been used to produce candidate vaccine strains. So you can see that we've covered parts of the dendrogram pretty well. Now we haven't seen human cases caused by viruses in clades 8,9,6,5 and 4.

But we are keeping a close eye on those. And 7 as well. So there are a number of clades that haven't actually been in humans, as far as we know.

So there is a very good correlation between the genetic information and the antigenic information in that if you look a the clade designations, at least to the second order, you can really divide the viruses into groups. And there is more cross reactivity generated by the Indonesia/5-like viruses, the clade 2.1 viruses than some of the other clade viruses. But there are really clear distinctions in the reactivity patterns of these viruses, thus necessitating having a variety of different vaccine candidates so we don't know which, if any of these, will take off.

This is a table that was put together trying to look at very closely at what's been happening more recently. And it was a compilation of data from a number of

different tables. So you'll see that there are data points missing here.

What I want to emphasize is that we do need to fill in some gaps. We have these viruses here that are clade 2.3.2 which are not well inhibited by anti-sera to any of our referenced viruses.

There are a couple of other things that I would like to point out. We've seen some viruses from Egypt that have reduced reactivity to the referenced viruses. And I'll amplify on that when I get to my last table in this presentation.

Another thing that I would like to point out is that we do have a virus that's in clade 2.1 that is the Indonesian clade that looks like it's a progenitor of the Indonesia viruses. It was isolated from a duck in Hunan Province in 2002. There are other viruses from Hong Kong that appear to be very similar to this duck Hunan viruses, and you can see that the cross-reactivity with the Indonesia/5

antiserum is very good.

So I'll move on to the next slide. This, again, is very difficult to see except for the colors. I hope you can see the colors in the back of the room. But the red colors indicate the viruses that are available to vaccine manufacturers for use in clinical trials. The blue colors indicate viruses that are actually in progress. So we may have a reverse genetics modified vaccine strain, but not all the safety testing has been done.

So this is the last side, last data slide. And these are the reassortants with completed regulatory approval. So, of course, all of these are reversed genetics modified viruses on a PRA backbone. And we have representatives from clade 1.2.1, 2.2, 2.3.4 and so on. And then these are reassortants that are prepared and awaiting regulatory approval or safety testing. And we have a number of viruses here that will expand the antigenic diversity among the viruses that are

available.

And then in Geneva a week ago we decided that there was a need to make some additional reassortants and it would be prudent to go ahead and make duck/Hunan/2002-like virus and clade 2.1. That would be done at St. Jude, and then eventually hopefully would be made available through NIAID. And as I mentioned before, we needed to include an Egypt virus. It appears that there's quite a bit of diversity. The clade 2.2 viruses are geographically the most widespread of all of the groups of viruses. And it appears that there is enough diversity occurring so that we're probably going to put a third order designation and have 2.2.2.1 and 2.2.2.2

And then we have this virus, which is the only -- represents the only human case in China, that was from the north and is a 2.2. virus. We're working with our Chinese colleagues to make the reverse genetics modified version of this.

And then we didn't yet have a clade 2.3.2 virus, and so St. Jude is going to use this virus to round out our collection.

So I just would like to acknowledge all the people in my group, especially Ruben Donus who worked so hard on revising the nomenclature. There was actually an OIE/FAI/WHO working group that came up with the nomenclature. I guess it looks like a nomenclature that a committee came up with.

And then, of course, I'd like to acknowledge all of the WHO Collaborating Centers, the WHO H5 reference laboratories, the National Influenza centers, the Ministries of Health, the Ministries of Agriculture around the world for making it possible for us to do these kinds of analyses and to become better prepared should H5 turn into the pandemic strain.

Thanks very much.

CHAIR MODLIN: Thanks, Nancy.

Let's go on to the next

presentation, which will be by Dr. Joseph Toerner from the FDA on pandemic and pre-pandemic influenza vaccine development issues. And then we'll open the floor up for questions for each of our presenters.

DR. TOERNER: Good afternoon. My name is Joe Toerner. I'm a Medical Officer in the Division of Vaccines in the Office of Vaccine Research and Review. And the topic of my talk this afternoon is evaluation of insulins and vaccines and pandemic and pre-pandemic indications.

And when I ran into my friend Zhiping this morning, who gave one of the marque presentations this morning, he said to me "Joe, you're giving the hot topic presentation at today's meeting." And I hope I can live up to that expectation.

So the overview of my talk today I'll be providing a summary of last year's Advisory Committee presentation where we began to discuss pandemic influenza. And then I'm

going to clarify the indications of pandemic vaccine versus a pre-pandemic vaccine. And there are very limited amounts of data available on immune responses. And I'll be sharing those data as well. Then, again, the goal of my talk is to help the Advisory Committee focus their discussion this afternoon. And so we'll be reviewing then the discussion points.

At last year's Advisory Committee meeting we introduced the topic of development pathways for pre-pandemic vaccines. And an important part of that discussion was the determination of immune responses following the initial immunization with a pandemic vaccine as well as the subsequent immunizations. And as a part of that discussion the longer term follow up of subjects to receive subsequent immunizations was encouraged. And as a result, we're now seeing clinical development studies where subjects are followed for longer amounts of

time in order to gain data on the immune response determinations to the subsequent immunizations.

And we also view today's discussion as an ongoing discussion of pandemic and pre-pandemic influenza vaccine development.

As this has evolved over the past year, we found important to clarify the definition of a pandemic indication versus a pre-pandemic indication. And the reason why this is important is because the proposed indicated or intended use of an influenza vaccine under development will determine the type of clinical data needed to support the safe and effective use of the vaccine. And this has been a source of confusion because we're currently in an inter-pandemic period, and so these vaccines are being developed. And so we, again, find it important to clarify this nomenclature for regulatory purposes.

So the pandemic indication this is a vaccine that's intended to be used to

immunize persons who are at high risk of exposure to an influenza virus strain with pandemic potential. And what do we mean by that? Well, it's immunization of anybody during a pandemic. But it also covers the immunization of laboratory workers who might be exposed to H5/N1, for example in the course of their laboratory work.

Persons who are deployed to areas where there have been documented human cases of an influenza virus of pandemic potential, they may desire to be immunized.

And so pandemic indication, we've outlined in our guidance document for industry, which was filed in May of 2007, the types of data and the clinical trials that are necessary to support that indication.

So now I'd like to move on to the pre-pandemic indication and define for you what we mean by that indication. And this is the vaccine intended for the active immunization of persons against influenza

virus subtypes with pandemic potential during the inter-pandemic period. And this is an immunization as a strategy for population-based pandemic influenza preparedness.

And so I'm going to come back to this indication later in my talk. And I'm going to shift gears back towards the pandemic indication.

And before I go on to present some immune response data, I just wanted to reiterate the immune criteria that we feel is reasonably likely to predict clinical benefit. And that's a hemagglutination inhibition antibody titer of a four-fold increase that the lower bound of that two sided 95 percent confidence interval should be 40 percent or greater, and the proportion greater than or equal to a titer of 1 to 40 that the lower bound of that 95 percent confidence interval should be greater than 70 percent.

And we've outlined for the geriatric population a bit lower criteria.

So data that are included in the approved product, Sanofi-Pasteur H5/N1 vaccine. And you've heard these data presented last year. And to use our adult immune response data 28 days after the second immunization. And you can see here in the blue that 43 percent of subjects that achieved a four-fold response in the HI antibody titer. And you can see that number is beginning to approach the criteria that we've outlined in our guidance document.

And I'm going to move on. I just wanted to pause for a moment to say that this slide is the only slide in my presentation that contains data that have been fully reviewed by the FDA.

So on this next slide of a representative example of other H5/N1 vaccines. And again, this is summary data that have been shared with us. And you can see that with what might be considered a standard amount of antigen, that we can all

agree we're not achieving robust immune responses. In only example we're beginning to achieve some of those numbers that are outlined in our immune response criteria.

So our concern is that a standard amount of antigen might not meet our current immune response criteria for the pandemic indication. And so what can be done to enhance that immune response?

Well, you saw data last year that there was a dose response that was observed with the Sanofi-Pasteur H5/N1 vaccine, but that might not be practical because the highest amount of antigen was approved for use in that product.

And I'll go through data that demonstrate that adjuvants may enhance the immune response. And then finally I'll talk a bit about cross reactivity to the different influenza virus subtypes.

Before I represent data on the enhanced immune response to an adjuvant, I

just wanted to outline in our guidance document for industry that the added value with the adjuvant that we describe. And this is an early development, phase 1 or phase 2 studies, where we expect the immune response that's solicited by the vaccine with adjuvant is greater than the vaccine used alone. And we define that as a difference in immune response rates as the lower bound of the confidence limit of the difference that excludes equality.

Alternatively, you can demonstrate the added value of the adjuvant by showing noninferior immune responses between a dose optimized non-adjuvanted vaccine in comparison to an adjuvanted vaccine containing a lower amount of the antigen.

And so, again, these are summary data that have been shared with and source data has not been submitted to us for review. But I just wanted to use this to illustrate that in this particular instance the addition

of an adjuvant to a low amount of antigen resulted in an immune response criteria here in blue that appear to meet or exceed our immune response criteria outlined in our guidance document for a pandemic indication.

In a different study on the next slide, again what might be considered a more standard amount of antigen did not elicit an appropriate immune response, but with the addition of an adjuvant you see enhancement of the immune response so that you begin to approach some of the numbers that we've outlined in our guidance document for the immune response criteria.

And this is just to demonstrate that not all adjuvants are created equal. And that why we do ask for a demonstration of the added value of the adjuvant. In this particular study the addition of a different adjuvant did not enhance the immune response.

And now I'd like to shift gears a bit to talk about cross reactivity. And

again, these are summary data that were shared with us. And again, a low amount of antigen did not elicit an immune response to a heterologous HI antibody response.

In contrast to the addition of adjuvant, where you started to see some immune response to a heterologous antigen. And the higher the amount of antigen with the adjuvant, you see an even greater immune response. Although to point out that these don't approach the numbers that we outlined in our criteria, it's beginning to demonstrate some evidence of cross reactivity.

Are there data from other studies that might help understand cross reactive immune responses? In a study of a small number of subjects there appear to be broad cross reactive immune responses among subjects who receive an adjuvanted vaccine in comparison to subjects who receive an unadjuvanted vaccine.

And can we glean any information from animal studies that have been conducted?

There have been two published studies using the ferret model. And these are ferrets that had received an H5/N1 vaccine and then subsequent to that a heterologous H5/N1 virus challenge. And small numbers of animals in both of these studies, but one study demonstrated the higher antigen content appeared to be ameliorate signs of clinical illness. And in another study, the addition of an adjuvant to a low amount of antigen in the vaccine appeared to be a survival advantage.

So these are data that are beginning to show the potential for cross reactivity.

And so with the pandemic indication what are some of our current regulatory challenges? And these are questions that we've been asking ourselves and that we're faced with. Not necessarily questions for you to discuss in the Committee. Later on in the talk I'll try to focus the discussion. But these are issues that we're faced with.

How will we know that the pandemic vaccine will provide protection during a pandemic?

There's no correlation of immune protection that's known and so how can we address of efficacy of a vaccine that has a pandemic indication?

What levels of human immune response should be achieved?

What are the roles of animal data that might help us to understand vaccine activity?

What role do studies with seasonal influenza vaccine where the manufacturing process is identical to pandemic vaccine, what role does that have to infer effectiveness of the pandemic vaccines?

And, are there other options to evaluate a pandemic vaccine?

And so before I leave the pandemic indication, just some summary considerations and things that we've identified that might be

the optimal pandemic influenza vaccine:

And that's one immunization that would provide protection;

There would be a rapid development of an immune response;

And that immune response would be sustained for the duration of the pandemic to offer protection for the duration of the pandemic;

There would be a demonstration of broad cross reactivity and the evaluation would be completed in special populations;

The vaccine would have an ability to be stockpiled during the inter-pandemic period;

And finally, the vaccine would have an acceptable profile.

And I think we might agree that these are lofty goals for an optimal characterization and, therefore, the pre-pandemic indication is what's being considered.

And now I'd like to shift gears to discuss the pre-pandemic indication. And again, our working definition of this indication is immunization is a population preparedness strategy against influenza strains of pandemic potential during the inter-pandemic period. And it's important to recognize that the immunization may not provide immediate benefit or immediate efficacy, but it's an immunization that would enable a robust boosted response or a robust immune response to a future immunization with a pandemic strain.

And again, with this indication it's important to recognize what types of data that we would like to see and the clinical evaluations that would be necessary to support that indication. And so the immune response criteria to the initial immunization:

Should that be the same immune response that we've outlined in our guidance document for pandemic?

Would we be willing to accept a less robust immune response so long as you can identify an adequate immune response to the subsequent immunization?

And what should that immune response to the subsequent immunization?

Again, should it be the same criteria or more robust criteria than what we've outlined for the pandemic?

And what if the subsequent immunization is with the same subtype or whether it's with a different subtype, what should those immune response criteria be?

Again, for the pre-pandemic indications, safety is an important consideration. So we would expect some large simple safety studies to be conducted. But what level of serious adverse events should be ruled out? At last year's presentation I had gone through a series of slides outlining the experience in 1976 of Guillain Barrè Syndrome that was associated with the swine flu

vaccine, and it was one event per 100,000 persons vaccinated that brought that population preparedness program to a halt. So what level of serious adverse event rate should be ruled out for the pre-pandemic indication?

So the components necessary for this indication include the immune response following the initial immunization, the immune responses following subsequent immunization and an assessment of effectiveness of the population preparednesses and an acceptable demonstration of safety.

This slide is just meant to illustrate some of the different options that we've considered in population preparedness followed by a subsequent vaccine that might be administered during a pandemic. And so when the initial immunization does not include an adjuvant and the subsequent immunization does not include an adjuvant, I've shown you data that you may lack an appropriate immune

response with that approach, but perhaps there are less safety concerns because we don't have a new adjuvant with potential safety concerns.

The current focus of activity in this area has been the use of an adjuvant vaccine for the initial population preparedness and an adjuvanted vaccine for immunization during the pandemic. Now I had shown you data that an adjuvant can enhance the immune response. So that might be the best approach in terms of the immune response considerations. But the addition of a new adjuvant, what potential safety concerns might arise? And so we view that as a disadvantage with this particular approach.

And then are there hybrid approaches that we might consider that might offset some of the safety concerns that we might have with a new adjuvant? For instance, the initial population preparedness without an adjuvant where there may be diminished concerns about safety is an advantage, but

with the adjuvant during the pandemic you'd have the advantage of an enhanced immune response.

And so these are some considerations that we've had internally on a design for population preparedness strategy.

So the optimal characteristics for a vaccine that has a pre-pandemic indication for a population preparedness strategy would be a robust immune response to the subsequent pandemic immunization. It would be a vaccine that has a low adverse event profile. A vaccine that would be capable of having a long duration of immune memory. And it would be a vaccine that could be given with other vaccines including other influenza or seasonal vaccine.

And so now I have two slides to present the topics for discussion for the rest of the afternoon.

And topic 1: Please discuss the criteria to evaluate the immune response with

an adjuvanted vaccine.

Now the first two bullet points under that are the criteria early in development for the added value of the adjuvant with the difference in the immune response criteria that would exclude equality and not inferior immune responses with the lower antigen plus adjuvant. But if we were to lean toward licensure, would you expect a robust difference in the immune response rate with an adjuvanted vaccine?

For instance, an adjuvanted vaccine having a geometric mean titer twofold higher over the unadjuvanted.

Topic 2 is, please comment on the options to confirm clinical efficacy of a vaccine for pandemic or pre-pandemic indication.

And topic 3 is, please discuss the immune response criteria for the pre-pandemic, or again this is a population preparedness strategy, for that indication and the

relevance to the criteria that are outlined in our current guidance document for the pandemic indication.

And so please discuss whether a lower immune response to the initial priming, if you will, so long as subsequent immunization results are acceptable. And then what should those subsequent immune response characteristics be to define acceptable immune response? And should those differ whether you administer the subsequent vaccine that contains the same antigen or that contains the heterologous antigen?

And then topic 4: Please discuss the size of the pre-licensure safety database for the pre-pandemic indication. And in your discussion please comment on the population preparedness and the role of large sample size studies to rule out a rare serious adverse event rate such as 1 in 100,000.

And that concludes my talk. I'm just going to put this slide back to the

discussion items. And I'll turn it back over to Dr. Modlin.

CHAIR MODLIN: Okay. Thanks very much.

Before we launch into a discussion and the public comment, I'd like to ask if members of the Committee have questions for any of our three presenters, Dr. Golding, Dr. Cox or Dr. Toerner regarding their presentations?

MEMBER COUCH: I only have one quick question for Dr. Toerner. All of the data you presented was H5 antibodies? You gave some FDA privileged data. It was all H5?

DR. TOERNER: Yes, that's correct. It was all H5.

CHAIR MODLIN: Jose?

MEMBER ROMERO: For Dr. Cox. Could you give a little bit more detail on the breakdown of pediatric versus adult cases of avian influenza and then mortality rates? Are there differences in the two groups?

MEMBER COX: I think Joe will try to answer that.

I think the bottom line is that there are more cases in young adults and children than older adults. But I don't really think that there are differences in mortality overall.

The most striking differences in mortality that we've seen have been in Egypt where at the time they did the analysis they had fewer cases than they do now. But it was very striking that the mortality in the children was much lower than the mortality in adults. And that was because the adults when they got sick thought, oh it's nothing, yadda, yadda, yadda. But when their child became ill and they knew that they had dead chickens, they got the child in for early treatment.

So I think the key is really whether or not the individual gets early treatment. And so many of these cases, as we see, have been referred from a local clinic to

a local hospital, to a district clinic and so on before they really get proper care. And they're so seriously ill by the time they get to one of the treatment facilities that actually specializes in treating cases, that there isn't really a hope.

CHAIR MODLIN: Joe, did you want to add to that?

Lisa?

MEMBER JACKSON: Well, a question for Dr. Toerner. There's discussion in the document and your presentation about boosting, you know later boosting and so forth. I wonder, do you all have a working definition of what you mean by "boosting" or "booster response"?

DR. TOERNER: Well, I think that was one of the items for discussion today to help us understand what immune response criteria should be for that subsequent immunization.

I think what we mean by the boosted

response, if you will, is the immune response to a subsequent immunization of either the same vaccine or a different vaccine that contains a different subtype and what immune response would be elicited with a vaccine of a different subtype in subjects who earlier received the population preparedness initial immunization.

So it would be the immune response of the vaccine during a pandemic that we would be interested in hearing your feedback on.

CHAIR MODLIN: Other questions? Dr. Davis.

MEMBER DAVIS: I was intrigued by the last point of your last slide which called for a large simple safety studies. I'm wondering if you could expand upon that a little bit? Are there discussions underway in the FDA about setting up the infrastructure for such large simple studies?

MEMBER COX: I think that the issue arose if you're engaging in a large population

preparedness strategy and you're immunizing hundreds of thousands or millions of people with a new agent. So something previously not licensed in the U.S. or maybe not licensed in the world, maybe a new adjuvant in a preparedness strategy to reap benefits it may be decades in the future or, we're hoping, a long time in the future. And so to understand safety was very important.

And in terms of what kinds of monitoring. I mean, we're open to hearing uses of different kinds of databases to monitor during clinical trials, you know what you have in terms of ideas.

The usual kinds of safety monitoring that are in the clinical trials that you've seen for like Roderick's yesterday are very intense. And would you recommend that or would you recommend other types of data sources, such as maybe through claims data or other automated sources?

CHAIR MODLIN: Other questions?

Could I raise the issue of --I'm sure there's been an awful lot of discussion about this. We haven't brought it up for the topic today. And that is what truly is the goal of pandemic influenza immunization. Obviously, we're never going to be able to test a vaccine well prior to a pandemic. And so you inevitably all recognize that we're going to need to rely on surrogate data to make judgments regarding the ability to employ such a vaccine. But is the goal to prevent disease? Is the goal to prevent hospitalization, or is the goal to prevent death? We might look at a vaccine differently according to what those various different goals may be for a vaccine.

Norm?

DR. BAYLOR: I'll start out addressing that. John, I think it's going to vary. But if we think about this, if we think about a pandemic in general, the ultimate goal is to save lives. And so looking at protection

from influenza-like illness, I mean that's a higher goal. That's a goal that we wold expect for seasonal. But I think that at a minimum we want to be in a position to save lives and decrease hospitalizations as much as we can. So that's sort of the bottom. If we can achieve better than that, that would be good.

Let me back up a little bit. Because I think we've heard a lot and used a lot of the term "pre-pandemic versus pandemic." And if you think about where we were in the past with swine flu, with Hong Kong flu, we were looking at making a pandemic vaccine. In the midst of a pandemic then we would use that vaccine. We've historically used a two dose 15 micrograms of a pandemic vaccine, and that's what we've deployed.

What's new I think now is we're trying to say is how do we prepare for a pandemic. So agreeing in the concept of pre-pandemic immunizing individuals prior to a pandemic, preparing those individuals for the

inevitable pandemic. And so that's really where we're having challenges, and I think the industry and all of us are having challenges in these areas. Because how do you evaluate a vaccine that's going to be used in a pre-pandemic or in the pre-pandemic period if you will?

The vaccine that we license, the sanity vaccine as we've said and Dr. Toerner has shown in his earlier slides, that vaccine would be used in high risk when a declaration of pandemic has been declared or the laboratory workers, what have you.

So the goal of the pre-pandemic vaccine is really to prepare for the inevitable pandemic. And there are challenges with that because what will be the next pandemic? Will this vaccine that we license as a pre-pandemic provide any use preparing those individuals in advance of the pandemic?

CHAIR MODLIN: Fair enough.

Other questions? Dr. McInnes?

MEMBER McINNES: So, Norm, just to follow up on that. So if you're thinking in that you want some measure then of immunologic priming whether it takes one dose or two doses or three does, however many doses it takes to show some incremental immune response which we've narrowed to a neoantigen like H5 is surprisingly disappointing, but you know you can see an increase in immunologic readout with the second dose compared with the first dose. And then you want some evidence of memory recall at some time remote from the priming event. Is that sort of conceptually what we're thinking about and how we might measure what that memory recall parameter is?

And then you want some ability to characterize safety. And I'm using those words carefully because I'm not sure we can promise that it's 100 percent safe. But you want to be able to have a profile that you can tell people who agreed to have this vaccine that this is the risk, this is what you can

expect?

Is that really what we're talking about?

DR. BAYLOR: Yes. And let just say a few words about that.

In essence, yes. I mean we're priming that population, and we might prime that population with one dose. And we want to know what level of immune response should we achieve. I mean, should we achieve an immune response that we require, as we've stated in our guidance document, 1 to 40 level? Is that necessary for that prime or is a lesser response adequate knowing that you're going to give a boost, if you will, and we use that term not in the sense of the pediatric vaccines? But you may give those boosts six months, a year out, maybe a year and a half out. And there are variations on that.

So it is a type of memory recall, but also part of that is cross reactivity. Because you can prime with the heterologous or

homologous, a neoantigen, if you will.

The other part of the equation, as you've mentioned, is characterized as safety. And in particular because we're using new adjuvant, nonaluminum salt adjuvant, we're seeing those come back I think the bar for safety is going to be higher. So we want to make sure that we do characterize that because we're actually immunizing individuals in the absence of that real disease. And so the benefit where you have to really define the benefit. Because benefit is really I'm preparing you for something that we believe will come, but if it doesn't.

MEMBER McINNES: Just two follow ups. I mean, I just want to be sure we're open to the idea that priming may take more than one dose. And we tend to sort of think we're going to put one dose in and everybody down the line is going to come back and mount a magnificent response to it. But they may not. So identifying the parameters around what

might constitute priming sort of seems to be important.

The other issue around the safety profile of novel adjuvant, I mean obviously it can also be addressed in the framework of annual influenza. It is not exclusive to the domain of characterizing in pandemic, right? Okay.

CHAIR MODLIN: Bob?

MEMBER COUCH: Well, you asked if CBER wants us to discuss this. So let me just address a few items here.

First of all, I've not been that close to pandemic considerations and H5. About three or four years ago I was asked to review what we knew about past pandemic circumstances and with regard to vaccination. And I'll give you the bottom line of the conclusion I came up with looking at '57, '68 and '77, which is where the data was for the three.

And that is that I cannot tell you,

I could tell you what was needed to protect against that pandemic strain, unless a lot of the seasonal data where we have some pretty good guidelines. I simply couldn't do it.

So I said to myself well if I can't say I've got to have 50 percent or 70 percent, 1 to 40 or a GMT of 150 or something like that, what would be a reasonable criteria to say I have a useful and potentially effective vaccine. And I came up with the same one people keep hearing from me: I want to see an immune response. If I've got a immune response in 100 percent of the individuals who received the vaccination. And you've maybe also heard me, I believe some antibody is better than no antibody. And that's the starting point I've got a vaccine that may or may not be useful.

Because I can't give you a number. I tried to see if I couldn't come up with some numbers, and I could not do it. That's one.

And the second is that no matter

what the numbers are, the present state of science says that antibody must be directed in optimal quantities against the hemagglutinin. Whether it's an HAI or some other assay, that's a different discussion. But it must be anti-hemagglutinin.

If we want to say an anti-M2 vaccine is okay, that may be true. But that data is yet to be developed. So at the present day where we stand, it must be anti-HA. And if it must be anti-HA, and I don't know how much of it is required to protect, I want as much of it as I can get.

Now, see, that doesn't help the regulatory authorities very much, unfortunately. Because they want a criterion that they can say it has been met. But that was the best I could do when I reviewed the science to try to come up with that answer.

CHAIR MODLIN: Well, I think that helps out a tremendous amount. Because I think that gives us a floor to begin our discussion.

I truly do.

Are there questions.

MEMBER COUCH: I got other discussion if you want to let me go on.

CHAIR MODLIN: Go right ahead.

MEMBER COUCH: Primed boost came up a year ago, too. Because, see, priming is an immunologic phenomenon. And if you really want to say somebody's primed, you're looking at the lymphocytes. But that's probably not practical. And if we start looking at the lymphocytes, we then have to validate and discuss what priming consists of when we do that, you see. So we end up with operational definitions is the phrase I like to use for priming. And that is measuring--we do measure a specific immune response, see. It doesn't have to be HI. But a specific immune response. And if a 100 percent of people showed that, I would say they're primed. The level of priming and all that, it's another discussion. But they are primed.

And since we're dealing with operational definitions, then boosting is the same. We've got to say that needs a new unprimed at the same time you're testing the primed to show that that group up here was indeed primed. And those, again, are operational definitions that don't give you hard numbers that can be used as criteria for having met a level, you see. But getting those levels is a problem.

I can keep going with a couple of more here if you want me to.

CHAIR MODLIN: Well, we actually have plenty of time for discussion later on. I intended for this for questions to the presenters. But I still think this is a useful discussion, so please go straight ahead.

MEMBER COUCH: Well, pre-pandemic there has got to be a risk benefit consideration. I can't see that one any other way. And there's another source of great

uncertainty because look how much uncertainty we've lived with for four or five years about the risk of H5 pandemic. And it hasn't materialized. It may yet materialize. It may not materialize. You know, what was the risk, you see? How can we assess that risk? And that's not very easy.

And then if we can't assess the risk, how hard to assess the benefit? And so if it's out there on its way, it's a little bit easier. The pandemic is a little easier decision than the pre-pandemic is. But I consider that one a risk benefit discussion.

Safety. I guess, again, a little bit of the same kind of plea I did this morning. If we want to make the safety requirement -- we're talking about licensing requirements. We want to make the safety requirement something that is doable and reasonable. And, you see, now we live with safety pre-licensure in appropriate numbers, but not a 100,000. That's always been a post-

licensure consideration. And that if that's still where we end up, which is the way I would lean, I would not want to require a -- actually, there's one circumstance we may come back in which I might want to see that, but otherwise not want to require a 100,000.

The post-licensure must be set up ahead of time ready to go and you are monitoring that so you don't miss the Guillain Barrè at 1 in 100,000 rather than let a mercy occurrence determine what your post-licensure safety was.

CHAIR MODLIN: All good points.

Are there questions, other questions? If not, I think probably this is the optimum for public comment.

Christine?

EXECUTIVE SECRETARY WALSH: As part of the FDA Advisory Committee Meeting procedure we are required to hold an open public hearing for those members of the public who are not on the agenda and would like to

make a statement concerning matters pending before the Committee.

Dr. Modlin, will read the open public hearing statement?

CHAIR MODLIN: Yes. I'll do this again.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the Committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting.

For example, the financial

information may include the company's or group's payment of your travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

EXECUTIVE SECRETARY WALSH: I have received one request to speak from Carol DeRosa and Fran Lessens from Passport Health.

MS. LESSENS: Hi. My name is Fran Lessens. I'm President, CEO and founder of Passport Health.

We have no financial receipt of any kind. We're here on our own. I didn't have to go far. I live in Baltimore. And it's a quarter tank of gas.

We're on the front lines of

providing flu, and that's why we're here today. We wanted to hear what the strains were.

I have been in the vaccine business for 20 years and we have over 160 locations with doctors, nurse, nurse practitioners, PAs. And we give vaccines on a daily basis. We answer Department of Defense Call Center 365 days a year. Vaccines are our passion, so we're here today to find out what's going on.

We also want to enlighten you. I've heard here today that it's partnership between the government and the manufacturers. I'd like to add that I think it's a partnership with the providers out there who are vaccinating people daily. And we've been involved in many years of giving flu vaccines through contamination, shortages. And we get the message from the consumer. So we're hearing their complaints on the front line on a daily basis.

We have responded to pandemic

emergencies. Any vaccine that's developed needs to be put on people in a pandemic. We have the search capacity. And I wanted to enlighten the folks here as to our past experience. Two days before Christmas in 2001, in two days we responded to anthrax and we had sites from New Jersey from Florida covered with medical personnel, doctors, nurses.

Katrina, we were in and out before FEMA ever showed up. We vaccinated first responders for our clients, utility companies, oil rig companies.

Tsunami, we vaccinated volunteers to go over there.

And we have done clinical trials as well. The Protein Science trial we did the 65 and over. We secured the vaccine for sites. Not the study vaccine, but it was compared to the egg-based vaccine and we secured that vaccine and disseminated it. That year was very rough because the Sanofi-Pasteur product

was out late.

So anytime there's any vaccine out late, we hear about it; frustrated, angry patients, angry corporations.

My message here today is we'd like you to know that we're here as a resource. We're here to help you. We have no financial -- if we don't have vaccine, we don't make any money. And no one sent us here today.

Thank you very much.

CHAIR MODLIN: Thank you, Ms. Lessen.

Yes, Paul Melman.

MR. MELMAN: Paul Melman, Infectious Diseases.

I have no financial ties to any company working on pandemic. But two questions with regards to safety. Because recently there's been the licensure of two vaccines that are only going to used if there's an urgent emergent situation. So based on the internal deliberations at FDA and

the negotiations with the manufacturers, as a starting point I think it would be very useful for us in the audience as well as for the Committee to understand for the Sanofi-Pasteur 90 micrograms H5/N1 a month apart, what's the size of phase 4? How many phase 4 trials? How big is it? Are they vaccinating first responders? Is it an attempt to get kind of, maybe I'll call it prime boost, but just get additional data? And if they go back and get them again what's -- it may be about the design, but how big is the designer phased for?

For the ACAM 2000, which we heard or at least my memory was, 1 in 100/150 recruits will get myocarditis from the vaccine. So maybe that's a smaller safety study, but define that target. But how big is the ACAM 2000 phase 4? And that's licensed to be used when it's been determined there's been a serious exposure.

So I think the FDA has already

thought this through because they told the two companies thou shalt do phase 4. So I'd just like to know how big phase 4 is for those two programs, and that might be the starting point for the pandemic vaccines.

CHAIR MODLIN: Thanks, Paul.

DR. HOURN: For the ACAM 2000 smallpox vaccinia vaccine live they have committed to do some extensive active surveillance and myocarditis registry studies. And actually they're powered in terms of trying to accumulate enough case events of myocarditis so that we could try to understand more risk factors associated with development of that adverse event.

That vaccine, because of its identified safety concern with transmission as well as development of myocarditis was approved under restricted distribution. So the controls for safety are quite extensive.

In terms of the Sanofi-Pasteur H5/N1 vaccine that, as you know, was approved

with a very small safety and efficacy database that was presented before this Committee last year. And the discussion was that the manufacturing being unchanged from the Fluzone influenza vaccine and the difference being primarily the micrograms. I think that's the only difference. And did folks feel there was sufficient data to understand if there was going to be a risk associated with 90 micrograms versus 45 micrograms that you get of different antigens every year. And I don't think we heard that there was that safety relative to its indication for use in a high risk situation.

That vaccine is in the national stockpile and is not for distribution commercially and is being intended to use for when there's a declaration of pandemic.

CHAIR MODLIN: Thank you.

If we could, why don't we put the questions back up on the screen, if we may. And I think that we'll ask the Committee to

focus in one-by-one on each of the questions.

We have talked about this and around this to a degree, but I think we need to focus on it specifically.

Please discuss criteria to evaluate immune responses with an adjuvanted vaccines. Differences in HI antibody titer that exclude equity, noninferior immune responses with lower antigen plus adjuvant and adjuvanted twofold higher over unadjuvanted.

So these specifically criteria to compare two different types of vaccines?

Bob?

MEMBER DAVIS: I'm probably just coming out on the end of a long conversation. But I just was struck by the nonequality of those first two bullets. They're very different conclusions to make about a vaccine and they really imply different things.

And speaking as a complete naive observer to this arena, I would say that I would prefer the first bullet than the second.

But be that as it may, it just seems like those are very different statements.

CHAIR MODLIN: I think, indeed, that's why they put them there.

How do others feel about this topic? Lisa?

MEMBER JACKSON: Well, I agree that the second bullet, for one thing, lower is sort of a qualitative term. But you could have no effect of the adjuvant and still meet that criteria potentially. so that seems not optimal.

CHAIR MODLIN: Seth?

MEMBER HETHERINGTON: Well, more questions, actually. I guess the point is what are you trying to accomplish with an adjuvant. And there are many instances where adjuvants have been used in the past.

One is to get a broader range of responses among your population. So it has not so much anything to do with titer as it is just getting a higher percentage of people to

respond. And maybe that's really the criteria you ought to be using.

Another is that you know what sort of titer you need to achieve immunity and you want to get above that. And I guess this gets back to I mean if Dr. Couch doesn't know what to predict a level of antibody is, I don't think any of us do. So I'm not sure how you come to that conclusion.

The last of the three sub bullets I'm puzzled by. It almost sounds as if you think that antibody raised by adjuvant vaccine is somehow less adequate than an equivalent amount of antibody generated by an unadjuvanted vaccine. So I'm not really sure what that third sub bullet means.

I think you need to define what you want out of your vaccine first and then make a decision as to how does an adjuvant play into this. Because one thing's for sure, you're probably going to get more side effects with an adjuvant. And the question is what do you

get for that, do you get some sort of benefit?

CHAIR MODLIN: Bob?

MEMBER COUCH: Maybe we need the second bullet clarified. Because my assumption with the second bullet was let's say you have a response with 15 micrograms, then the second bullet would be what would be inferior if you're using 3.8 plus an adjuvant so much so it's an antigen sparing approach to getting the same way. And then how would you define it as inferior? And I wasn't aware that it looks like the FDA defines it as plus or minus 10 percent, which is I think a little tough. But okay.

CHAIR MODLIN: Dr. Toerner, do you want to respond to that?

DR. TOERNER: I think Dr. Couch was right, we are talking about an antigen sparing approach with the second bullet point.

CHAIR MODLIN: Dr. Self?

MEMBER SELF: Yes. So I guess -- I'm having trouble. I see this question not

so much as a comparative one but evaluating a whole series of different possible regiments, some including and other maybe not including adjuvant. So I don't like any of those hypotheses that are working underneath the three sub bullet points. And probably the criteria that Dr. Couch described, albeit it pretty subjective, is the best that we can do. You know, whatever the regiment is should be subjected to that and try and ratchet that up as best you can.

CHAIR MODLIN: Perhaps I can summarize and we get the sense from whatever is saying. I think I heard Pamala say the same thing. I certainly heard Bob say it.

And that is is that the quantity of antibody may be less important than evidence that there's been a response in the first place. I certainly would tend to agree very much with that.

Norm?

DR. BAYLOR: Yes. Just to clarify

a little bit. I mean, where we are struggling here is looking at the added value of that adjuvant. And there are a variety of areas where you might propose that there's an added value. But just on the surface if I have a vaccine that's a 50 microgram vaccine and it's nonadjuvant and I get a 1 to 40 response. And I add an adjuvant to that product and I get the response, then there's really no added value there, although one could then ask -- you could get into other things like well maybe there's a T-cell response or something like that, but I mean the scientist was early on that.

CHAIR MODLIN: I think what we're saying is it's not so much the response of 1 to 40 that's important, but it's the sera conversion rate. It's the number of participants in the study that actually show an evidence of an immune response. And if by adding an adjuvant to the vaccine you raised your sera conversion rate from 20 percent to

50 percent or 70 percent, that may be a more important measure than the actual level of antibody that you achieve.

Am I getting that right?

DR. BAYLOR: And we understand that, John, because that's the other side of it; the sera conversion rate. But, again, how do you evaluate the value added? Again, if I put an adjuvant in there and I'm seeing the same sera conversion rate, or say I see a five percent increase in sera conversion rate, is that really enough? But then you'd have to know something about the adjuvant and the risk that may be associated with that adjuvant before you could make that decision if that's adequate.

So there are a lot of factors involved here. But just to add an adjuvant with no added benefit, regardless of whether it's the titer or the sera conversion rate, I think that we have to consider that.

CHAIR MODLIN: Ted?

MEMBER EICKHOFF: I think that the primary reason for talking about adjuvants in this setting are the considerations of global vaccine production capacity. As we heard here in this meeting last year, as David Fedson writes about all the time, we're never going to make enough vaccine in the event of a pandemic unless we have some antigen sparing device, which right now is an adjuvant.

So I think the primary goal of even considering an adjuvant is the antigen sparing effect. Indeed, I think we're forced to consider an adjuvant in this setting.

If you get out of it the additional benefit of both reducing the amount of antigen and increasing the GMT or the four-fold conversion rate; so much the better. But even if we got the same thing or the same thing in terms of serologic titer and with sparing of antigen in significant quantities like 5 micrograms of antigen rather than 90, so much the better.

CHAIR MODLIN: Ted, would you agree that, if indeed if I heard your correctly, you would then probably consider the first bullet perhaps to be the most important because that's the one that would most likely lead to an antigen sparing strategy?

Bob?

MEMBER COUCH: Well, you asked Ted a question first, I thought.

MEMBER EICKHOFF: No. I would consider the second bullet the critical one of those three.

MEMBER COUCH: I don't like to create problems with licensing, but I answered this question one time before and I was just sitting here thinking, I guess I'd have to lean that direction still. That when you put an adjuvant in there, let's say you do anything different but an adjuvant is the example we're talking about there, TH1, there are TH2, a mixture is probably going to get you closet; the precedent data does not

include an adjuvant. There's a good bit from '57, unfortunately it's not as high quality as we'd like for the use of adjuvants because there was quite a bit at that time. But if you start then, then I went back in my thinking. I said well now we're changing the vaccine. And when I change the vaccine what am I going to want to see? And it's got to be more than just anti-HA antibody when you change that vaccine, which one would be just anti-HA antibody. And two things would make me happy?

Well, the gold standard is always going to be efficacy. If the efficacy says that you've done something worthwhile; whether it's better, whether it's the same with lower dose or whatever, then that's the gold standard.

Can we get at a gold standard that is less intensive than that? Actually, what constitutes that gold standard is another question; you know, illness, isolation, things

like that. But at any rate, efficacy.

If we get anything less than that, what would I might not be happy with for a change that did not include efficacy? And I can only answer that in saying every immune response that I could measure I would want to know the anti-hemagglutinin, I would want to know it's avidity, I would know the anti-neuraminidase, I'd want to know what happened to the lymphocytes and cell-mediated immunity. And if I really got across the board an improvement in those immune responses, then I don't think I'd require efficacy. But even that's not easy to do.

CHAIR MODLIN: Bruce?

MEMBER GELLIN: You know in some ways it's surprising that this is the first question out of the box, and Seth can sort of hit on this, is that we need to figure out what we want and then we need to define that pretty clearly and then think about the different pathways to get there.

The data that's been generated over the year shows an adjuvant, looks like an attractive and maybe a simpler way to get there.

Clearly the antigen sparing is what got adjuvants into the game initially. I think to me the hidden surprise was the dual benefit of the cross protection.

So I think it goes back to this risk benefit ratio. And the benefit would be to have some demonstration that you've provided some immunologic response such that later on, whether you get another vaccine or you're exposed to another virus, you've already achieved some immunological benefit from it.

An adjuvant is likely to be part of that, but I wouldn't think it's necessarily a part of it. I think there's a definition of what you need and then second is how you're going to get there.

CHAIR MODLIN: Further discussion?

Yes, Norm?

DR. BAYLOR: I just wanted to make a comment.

Bob, I hear all your points. Of course, you recognize that for the pandemic the efficacy is, you know we can't do that. So that's not a consideration, I mean you know pre-licensure.

On your point, Bruce, I mean what do we want. In one sense the "we" has to be the public health. But at the same time we know there are manufacturers, and they're out in the audience and they can speak up, that are developing all types of vaccines for pandemic. And I guess where we're trying to go is we have to have some criteria to evaluate those vaccines, not necessarily what kind of vaccine does the FDA want, it's what type of criteria do the FDA need to evaluate those vaccines that are coming forth. And that's where we're going. That's where we're trying to go. Because we know that all of these,

we're facing these now. This is not something that we're going to face down the road. These are real. This is now.

MEMBER JACKSON: I think also for antigen sparing, it has a great public health implication in terms of population, inoculation during a pandemic. But for the individual, whether your vaccine is antigen sparing or not, is less. I mean you're looking for disease protection.

So I think antigen sparing is important. From a public health perspective I think for the individual perspective, the adjuvant contribution to a clinical benefit may be more important.

MEMBER COUCH: Norman, most of us call it the two animal rule, but I don't want you to necessarily explain that. But you're not going to get that efficacy in the field on H5, hopefully, before we've already used that vaccine. And I'm not an animal model person, but an animal model needs to mimic the human

infection and disease role as much as possible. That animal model needs to be described with that same vaccine, even if it's antigen sparing, for an immune response profile that clearly is the explanation for the immunity and the efficacy in that animal model. And then that's part of the information I'd want to transfer to what I'm looking for in humans to guarantee me the same thing.

Historically that's been quite good. So we'd hope that it doesn't change.

CHAIR MODLIN: Dr. DeBold?

MEMBER DeBOLD: I don't envy the situation you're in because you are clearly having to deal with a fair amount of uncertainty and to some extent theoretical risk especially in the pre-pandemic sort of situation here. But the risk benefit, a piece of this seems crucial from the consumer perspective. Because with adjuvants there are some risk that people will have some reaction, some adverse reactions to the adjuvant itself.

so if there is some way to minimize the potential for individuals to experience adverse reactions that will be real, even though we may be dealing with a theoretical pre-pandemic situation, I think that would be preferable.

CHAIR MODLIN: Those are good points. And I think the intent is that we'll probably discuss that even in a little bit more detail with some of the subsequent questions.

Bruce?

MEMBER GELLIN: Some information that we haven't heard I don't think that may have come up in the meeting that Dr. Golding briefed us about is this very precious resource of one third of the people who actually survived this infection. And it seems to me that there's a lot to be gained from understanding what their immunology looks like right now. And I don't know -- I think this is clearly very difficult data to get,

but I can't think of more important data to begin to have to begin to answer this question. Because here are people whose immune systems should tell a lot about what it meant to be exposed to this virus.

I don't know, Hana, did that come up as far as the data that was there?

DR. GOLDING: I think this is clearly a very, very important point. Because I think a lot can be learned even from the small number of people that have been exposed and survived.

I think Nancy will probably be able to give a little bit more information on the studies that were conducted in poultry workers that Jackie Katz presented. And I'm not sure if there's more data like that from other hot spots of transmission, especially Indonesia.

There is clearly currently a reluctance on the part of some of these countries to share post-exposure sera. On the other hand, the World Health Organization, Dr.

Hadden, did describe the establishment of this Southeast Asia multi-clinical centers new infrastructure that, hopefully, will build trust and wiling to share. And most importantly, to introduce the right assays so these kind of questions, which I consider also of prime importance, will be able to address. Because I think we can learn a lot from the survivors.

In my own personal program on influenza we were able to establish a collaborative effort with the Oxford group in Vietnam. And we are now able to actually analyze the immune responses, all the antibody isotopes recognizes by these individuals. And we find some very interesting -- I think it will really give us some very important information that eventually can be applied to vaccine. But those are five individuals.

So this kind effort, if indeed can be expended to other survivors either through our effort or the CDC and so forth, I think

will provide important information. And as a group we probably should try and encourage it.

CHAIR MODLIN: Bob?

MEMBER DAVIS: Maybe I missed something. But there's probably a lot to be gained from studying people who were exposed and didn't get sick as well, not just survivors. There's probably an order of magnitude, if not more, people who were in the vicinity and one could assume that many of them were exposed and somehow didn't even get sick.

CHAIR MODLIN: Nancy, there have been a number of sera surveys of people with high risk of exposure and it would have included a number of people that have never developed disease as far as we can tell. Isn't that not the case?

MEMBER COX: Yes. There have been a number of sera surveys that have been conducted and more that are underway.

If we go back to the 1997

experience and look at poultry workers in Hong Kong who were exposed to H5/N1, we found sera prevalence of about ten percent in that group. And we were using a Microneut cutoff of 1 to 80 because we had done a lot of calibration of our assay. But we couldn't tell, of course, if those individuals had been exposed or infected to the highly pathogenic H5/N1 or some precursor. Because we only had a single serum that was snapshot in time.

In many of the other studies that have looked at poultry workers who either were wearing PPE or weren't wearing PPE and so on and so forth, we see some real differences. In some studies there were zero people who had antibody among the poultry workers who were involved in calling. And in other studies there were sort of 6 to 9 individuals who were sera positive.

So it's very clear that a lot of people are heavily exposed and never become infected. And I think that while that's very

interesting, that probably has something to do with a genetic factor that may or may not play in to actual pandemic and may or may not play in to an antibody response. So I think we need to kind of tease those things out.

It is very difficult to obtain serum from the survivors of H5/N1. I think the Southeast Asia Clinical Trials Network will have the greatest chance of actually being able to obtain enough serum and large enough amounts of serum, basically, to actually do some of the studies that Hana and others are trying to do.

We find that when we do obtain serum samples for the sera surveys, we get very small amounts of serum. And so by the time we've tested against a couple of different antigens, a clade 2.1 and 2.2 or a 2.3 we've exhausted the serum that we have.

What we can say is that for the few individuals whose serum we have and whose response to the infecting virus was quite

robust, they have a very markedly reduced titer to viruses in another clade. So it shows that for naive individuals their response to H5/N1 is quite strain specific. So that's with natural infection. And I think that if adjuvants really do broaden the immune response, that is a very significant improvement, even over natural infection.

CHAIR MODLIN: Other questions or comments?

Why don't we move on to question 2. Please comment on options to confirm clinical efficacy of a vaccine for pandemic or pre-pandemic indication. We've certainly been talking about this the entire time. I think that probably the problematic words are "confirm clinical efficacy." But I wonder if any have any further thoughts about this?

MEMBER COUCH: You can't confirm clinical efficacy on a pandemic until after it's already occurred or failed. So you're talking before. I guess we're back to --

CHAIR MODLIN: Is there more to this question, Florence, or

DR. HOURN: The new pandemic vaccines that will have adjuvants that have never been approved before or new technologies that we haven't used before can be approved under what we call accelerated approval regulations which allow us to use a surrogate that reasonably likely predicts a clinical benefit. And that surrogate we will be using is the HI immune response. But then the regulations say that the sponsors must conduct studies to confirm the clinical benefit.

So we are now asking you how to help us try to get a better handle on clinical efficacy. In our guidance we had suggested that if manufacturers are pursuing a seasonal vaccine using the same manufacturing process or the same adjuvant, that some of the seasonal efficacy data might be able to be used to confirm the efficacy of pandemic. And we would like your response on that. Is it

useful? Is it not useful? What are pros and cons?

DR. BAYLOR: And, John, let me follow up on that.

CHAIR MODLIN: Certainly, Norm.

DR. BAYLOR: I guess where we're trying to go is we recognized, Bob, that really a true confirmation, we can't do in the absence of pandemic. So how far do we go? I mean, are there options that would reassure us that at least we have something out there we believe is effective?

CHAIR MODLIN: Would it be helpful if it were possible, and I'm not sure that it is, but if it were possible to identify one or a small number of laboratory measures, markers for immune response to one or more doses of vaccine? A measurable HI titer as a measure of sera conversion. I'm kind of struggling right here. But is this --

MEMBER COUCH: Well, I don't know if that'll help you, but I've been there

before. And I need a clarification, Norman, as to what you are talking about with clinical efficacy. We talk about animal models, pandemic you don't get that until after the fact and so forth. If you're talking about a new vaccine now, which I think is what the thrust of your interest is and we're talking about adjuvant in vaccines in here, do you want clinical efficacy before you approve that even though your proposal is to use it in the pandemic, for example? And the question then would be your only opportunity to do that in humans is going to be with the seasonal vaccine.

So when you say I want to see clinical efficacy with a seasonal vaccine, then my question will be the same one I asked earlier. With that clinical efficacy with a seasonal vaccine using the adjuvant, must it be superior to the nonadjuvant vaccine? That's the tough question. You see, if it must be superior, I wouldn't advise many

companies to invest hugely in that. But, you know, they might be lucky and they may have an exceptional adjuvant. But on the other hand, I think it can be shown to be as good as standard vaccine.

DR. HOURN: So in a seasonal adjuvanted vaccine versus a seasonal unadjuvanted vaccine, again to understand what is the clinical benefit of an adjuvant, why are you adding the adjuvant, are there subpopulations that could be explored that there could be a clinical benefit asked of over an unadjuvanted vaccine?

MEMBER COUCH: I'm not asking for that benefit with that question for seasonal influenza. The benefit you expected would be with pandemic, but if you require that you won't get it until after the fact.

DR. BAYLOR: Let me ask you, Bob, I mean in the past we've had to do this in the sense that we based our licensure on the seasonal in the sense that we use the same

manufacturing process and we just exchange that strain. We identified the pandemic strain and we exchanged and we'd used immunogenicity and we really never truly confirmed that. I mean, there were studies done to see how well we did. And that's where we were. And are you kind of saying that's the best we can do? And if it is --

MEMBER COUCH: I don't mind you asking the clinical efficacy for an adjuvanted vaccine. What my concern would be is it should be clearly seen as superior during the seasonal pandemic. It is equivalent to the seasonal vaccine without an adjuvant, would you accept that as having shown clinical efficacy?

The expectation in the pandemic is that it will be better because of the superior immune responses it presumably would show. But if you have to show superiority for seasonal vaccine at the same dose, you could show equivalent, say, at one-quarter of the

dose maybe, something like that. Maybe that would satisfy your requirement for clinical efficacy.

I've got an industry cap on, I guess, with those questions. That's kind of touch.

MEMBER SELF: I guess it seems to me that you know, part of this is that the seasonal flu is a poor animal model for the effective adjuvant in a pandemic vaccine.

MEMBER COUCH: That's been the case so far. There's some candidates out there that companies are hoping will change that perception. But that's where it is right now.

MEMBER SELF: Yes. But that seems to be the problem that I hear with using seasonal vaccine, seasonal flu as the test bed specifically for an adjuvant.

CHAIR MODLIN: I think it's a bad model for any vaccine, adjuvant in it or not. It's new for pandemic flu simply because you're dealing with a very different

population. The difference between a primed and an unprimed population is critical.

Ted?

MEMBER EICKHOFF: The only way you could do is to drop the dose, is to alter the dose, as Bob said.

MEMBER COUCH: But there are two ways to do it. Actually, you can tell I've been here before. There are two ways. One is to drop the dose and then show equivalent with a quarter of the antigen.

MEMBER EICKHOFF: Yes. Right.

MEMBER COUCH: Would that then be the kind of data that the FDA would like to see?

Otherwise, you're talking about doing it in very young, relatively unprimed children. And that would do it also, but that's not an easy way to go either.

CHAIR MODLIN: Bob?

MEMBER DAVIS: Is it just completely off the table to do the real world

experiment of vaccinating people who appear to be at higher risk in Thailand or Vietnam, places where the background rate of this is at least somewhat detectable and really taking a look at what goes on in human beings?

CHAIR MODLIN: I don't know if Nancy or Joe --

MEMBER DAVIS: I mean, I'm sort of asking you to win the lottery and the world series and the super bowl all at once, I know.

MEMBER GELLIN: What question do you want to answer?

MEMBER DAVIS: The question, the ability to prevent invention. This is really a clinical efficacy trial in the field.

CHAIR MODLIN: Bob wants to go live animal markets in Southeast Asia and --

MEMBER DAVIS: Right. So I know very little about the subject. But it seems to me like that perhaps gives us a little bit better information than making inferences based on seasonal flu.

MEMBER COX: Mike, I don't have a lot to say except that WHO has been promised a vaccine for it's H5/N1 stockpile. And there has been discussion about what needs to be need. Advice has been obtained from a variety of experts and so on, and there are different documents on the web. But there have been discussions in some countries that have ongoing outbreaks in birds about immunizing poultry workers on the frontlines. Those trials are very difficult to do. But that would be one way to obtain immunogenicity data, safety data and so on. But it would be extremely difficult.

CHAIR MODLIN: Pamala?

MEMBER McINNES: So if you pull all the pieces apart, you may be able to answer discreet pieces. I'm not sure that you can assemble them into a coherent puzzle again.

So you could look what is the value of the adjuvant, adjuvant X, which you could certainly look at in the seasonal influenza

framework and the variable could be dose concentration of antigen. And you could get as full an immunologic response profile as possible looking at adjuvant together with varying dose concentrations of HA. So that's one piece of information.

If you look at the data that Joe put up about -- I guess it was on slide 12 which showed an H5/N1 less than 5 micrograms with no adjuvant in less than 5 micrograms with adjuvant and you've got 82 percent of people with a four-fold rising antibody and 84 percent with greater than titer of 1 in 40, that's sort of comforting kind of. I mean, that is sort of data that we're used to looking at in the framework of response.

And I presume this is post-second dose, sometime remote post-second dose. What I don't know is what they looked like post-first dose or at baseline. But if you could assume that you have neoantigen with and without the adjuvant that you've now dissected

apart in the framework of seasonal flu and you developed data that looked like this with maybe no rise from zero to one, but certainly from one to two, you got this increasing immune response. I mean, I would be feeling reasonably comfortable that one is then immunologic priming of these subjects. And you would do the safety profile on both the seasonal flu and then on this set of pandemic studies.

I'm not sure you can get a whole lot more than that. Because we can't then move the pandemic HA with the particular adjuvant into a challenge study, although I do know several people I could volunteer for the challenge study. And I'm sure we could all contribute.

I don't know from the workshop -- I just don't know this literature whether there is value from an animal model with challenge that could in fact contribute to rounding out this sense of what you have about these

discreet pieces of the puzzle. But I think that's sort of about the extent of how far I can get in trying to round out this package.

CHAIR MODLIN: Norm?

DR. BAYLOR: Let me throw out your comfort level as far as -- say we just looked at immunogenicity and looked at sera conversion rate and ended it there. I mean, could you give me some feedback on that? Say we just approved these vaccines based on an immune response and looking four-fold rise and sera conversion I mean for a pandemic knowing that there are no definitive confirmatory studies that we could do in the absence of a pandemic.

MEMBER McINNES: I think if there was some information that at sometime remote, a year later for example, I was able to come back, deliver maybe a different H5 and I saw a response, I would feel pretty good about that.

CHAIR MODLIN: I mean, Norm, from a public health standpoint I think there's no

question whatsoever that you're far better off doing that than not doing that. I think that's kind of the simple.

Ted?

MEMBER EICKHOFF: Norm, are you talking about an adjuvanted vaccine?

DR. BAYLOR: Either.

MEMBER EICKHOFF: Either> You may well be in that position eventually.

CHAIR MODLIN: Yes, Bruce?

MEMBER GELLIN: Just for the record, I want to second with Pamala. To me that's something that demonstrates you've had something that you might want to call priming and then at sometime later with a new thing that wasn't the same one that you get some benefit. To me those are the parameters. Obviously, with a little more detail than that. But it seems to me those are the kinds of parameters that we need to have.

CHAIR MODLIN: I think it's unlikely that you're going to get into a

situation where you can demonstrate an immune response and not be able to demonstrate some degree of immunologic memory somewhere down the line. I think that's a very logical sequence and important to do. But I think the first step is more important than the second. But both are important.

Could we put up the next slide, please?

Please discuss the immune response criteria for pre-pandemic indication and relevance to criteria in the pandemic guidance document. That's just what we've been doing.

Please discuss a lower immune response result to initial immunization prime if subsequent immunization results are acceptable.

Please accept immune response characteristics to the subsequent immunization with the same antigen and with a heterologous antigen.

And, again, I think we've already

pretty much gotten into this question in some depth already. I don't know if there's anyone -- does anyone else have something to say about it? Pamala?

MEMBER McINNES: I just wonder if Hana could talk to us about the animal model? Is there some contribution that this in challenge could give us?

DR. GOLDING: So actually Kanta Subbarao and Jackie Katz presented very beautiful data looking at the two major animal models, the mice and the ferrets.

And there's no question that the mice are unique in that not all H5/N1 strains have been adopted to grow in them. And if they do, they don't always lead to lethality. However, there are a lot of reagents available. You can challenge them to some degree with both, especially H5/N1 with both clade 1 and clades 2 so far.

And there was a lot that was learned and Dr. Subbarao was able to use even

passive immunity transferring some antibodies. So a lot could be learned I think both in terms of direct protection, homologous and heterologous protection.

Of course, the distribution of the glycan and the -- are not exactly as in human, and it will be very difficult to use them as a sort of efficacy model, per se. But you can do a lot of preclinical proof of concept studies. You can compare different vaccine, different adjuvant, T-cell mediated versus antibody I think the mice can help us to learn a lot.

The ferret is I think is the crucial issue here. Because ferrets do seems to have a more similar distribution of the receptors, the -- and do seems to have a disease that is maybe similar to human. Also, you don't need to do any adaption of viruses. And they have been used for challenge experiments quite successfully.

It was felt that even with the most

successful vaccine you can't actually reduce the level of replication in the upper respiratory tract in the site of inoculation. But you can, indeed, reduce the level viral replication in the lower, in the lungs. And you can protect from lethality and from other sign of morbidity.

Actually, it was felt that the lethality endpoint was the less robust in terms of dose finding. There was not really a good correlation. There were quite a few cases where the immune parameters measured in the ferret were not predictive of the endpoint if lethality was the end point. You could get protection very easily.

And that is a problem. Because if you not have a response, a BLA or a licensed product and you say, okay, let's take the ferret as our next model, you may be able to show protecting from lethality against multiple strains that may or may not be translated into the human scenarios.

So we don't know enough I think about the ferret model. And, of course, you have the other confounding problems that further are so sensitive to influenza, that almost a very percentage have currently found ferrets or have some preexisting antibodies to seasonable influenza. Which again it very elegantly shows that if they antibodies against some of the seasonal influenza and now you give them an H5 or avian influenza vaccine, you give higher titers.

So all of those become confounding in terms of really mimicking what happened out there in the unprimed population. Nevertheless, it was felt that in parallel to licensure, to the pivotal studies, this type, the preferred in particular can give nice additional data about close protection in the challenge models that you are talking about.

CHAIR MODLIN: Any further discussion on question 3? If not, let's go on to question 4 which is please discuss the size

of pre-licensure safety database for pre-pandemic indication. In your discussion please comment on population preparedness and the role of large sample size throughout a rare serious adverse event at a rate such as 1 in 100,000.

Bob Davis, you might be able to help us out a little bit more with this. My recollection from swine flue era was that even though the observed rate of Guillain Barrè was 1 in 100,000 that also comes close to what the background rate of Guillain Barrè is in the normal population. Actually the attributable risk was something less than that, or was that not the case which gives you further challenge in terms of determining sample size for a adverse event this order of magnitude?

MEMBER DAVIS: This was actually a very challenging issue and one which actually probably needs to be talked about a lot in its own venue.

I think I'm not sure I can answer

this specific question. But what I do know is that I think there have been very specific lessons that we've learned from swine flu where the whole issue kind of got away from the people who are in charge of the vaccine study. And it became an event in the media. And that's a situation that you always want to avoid. And it might take two or three years of planning to create an environment where you avoid those events. And I want to compare that to the -- issue that came up where within 24 hours we were able to get good population based data out there. And we were able to say this is what we know and we're going to be monitoring it every day or every week, and that's what we did. And we sort of gave updates every week. And even though the data wasn't completely reassuring, we were at least able to say this is what we know and it didn't get away from us. And it was able, I think, to inform and reassure the general population.

And I guess to me that brings an

issue that I thought was worth talking about, which is that for these sorts of studies where you're ready to actually do a pre-licensure study, you have to realize that the infrastructure that we currently have, like the Vaccine Safety Data Link, is an observational one. They choose to use vaccines and then we observe the safety of those vaccines in a very large population-based setting. This is going to be almost like an intervention where we will actually request their participation in a very unique type of pre-licensure study, and there's no guarantee that they will to participate. I mean, they might. But no one can make the assumption that they will in fact agree. And so the discussions that have to occur really actually have to start occurring now. We can't wait until there is a vaccine that is in the pre-licensure arena. Because it may take, you know, 12, 24, 36 months to go through the whole issue of getting buy-in,

getting HMO buy-in. I mean this is so unique that you will actually have to walk people through all of these issues that we're grappling with right now.

There are other settings. If the VSD doesn't necessarily work, there's the larger network of 60 to 100 million people that are being recruited or being studied for the GBS. But that's one where we actually have even less inaction with the health plans than we have with the VSDs. So those are going to be tricky issues that are going to be necessary to work through for a pre-licensure.

As I say, I know that this is probably far more than you wanted me to talk about, but I'm almost done.

So that's for the pre-pandemic. And for the pandemic study it's actually different. I think in a pandemic study situation where you're trying to keep a handle on safety and you're worried about things like Guillain Barrè Syndrome, which are almost too

rare study. They are too rare to study in the VSD. I mean, that's why we went and created a brand network of 60 to 100 million people.

For GBS you actually probably want to recruit a series of Sentinel hospitals from around the country and simply do very, very rapid turnaround case control studies as the pandemic is occurring and analyze the data as each new case accrues and be ready to make statements about that. Very similar to what we're doing with the rapid cycle studies with the VSD. And we could talk more about that, but it's a little bit out of this arena.

The one thing I do want to say is that trying to handle on this through some sort of enhanced DEVRS mechanism, which I know is sort of something that's been discussed, I think is exactly the wrong direction that we want to go. You know, that's nonpopulation-based. It's nonepidemiologically sound data. It's completely hypothesis generating and what we're trying to do here is hypothesis

test in a very, vary rapid, very accurate way. And so I would actually just want to put it out there to make the statement I don't think that's the direction we want to go.

So I think that there are issues here having to do with the size. You know, currently we're looking at ACAM 2000 where I think ACAM 2000 is doing intense observation on 15,000 and even less intense but still observational data on 40,000. Something around that area. And Roterex I think is 40,000 plus or minus a bit. So, you know, I think that's an accepted number. Is that correct? I'm not sure. But that's the ballpark we're talking about.

So that's probably where we probably would need to go from some sort of pre-pandemic study. For the pandemic study it's a completely different issue. And that one needs to be sort of discussed from the ground up.

CHAIR MODLIN: It looks like to me

that Norm is asking for an appropriate size for the safety database for pre-licensure study. And I don't think that you're going to be asking manufacturers to enroll hundreds of thousands of people pre-licensure. So the question is what is the adequate size?

We don't know much, and it's actually a very difficult thing to say. Because we don't know anything about even phase 1 and phase 2 studies with respect to risk for various adjuvants. And I think those probably have to inform this question, would be my guess.

Frank?

MEMBER DESTAFANO: Well, yes. I think I agree with -- and as you were implying, that pre-licensure is going to be hard to do a phase 3 trial with a 100,000 people or something like that. But maybe it could be down staged, you know, with a requirement with a large phase 4 study to vaccinate in stages a large group in which you

build in some backbone to get some fairly intensive surveillance.

This is a preparedness model, after all. And the model we have for that would have been the small pox program. There was sort of a registry of vaccinated and it was built in with theirs and other reportees so that you did have your numerators and denominators. And it proved to be successful in identifying the cardiomyopathy and those kinds of things.

So I think maybe a phased approach. I don't know if it's possible to do some provisional licensure given completion of a large well conducted phase 4 study.

And I think, you know, for something as rare as Guillain Barrè Syndrome, 1 per 100,000 for swine flu is the attributable risk. But I think for rare events like that; I don't know Guillain Barrè Syndrome maybe is an a priori hypothesis, but I don't think we know that for these vaccines. And we don't know anything else.

I think there's, with enhanced reporting could be a suitable backbone again for signal detection, which is primarily what you're going to be doing right now with these vaccines that we really don't know what kind of rare adverse events they may have.

CHAIR MODLIN: Dr. Self?

MEMBER SELF: It was said earlier that this is all about a risk benefit calculation, and I think that's exactly right. And what we're not talking about is the benefit and what the odds are of a pandemic over -- or some reasonable horizon. And I think that's the way the structure. And to specify that is going to be required to make any sort of rational decision about what level of risk you need to bound and therefore how big a study you need pre-licensure to define the risk side of that equation.

CHAIR MODLIN: In other words to predict the likelihood of an H5 pandemic?

MEMBER SELF: Well, that's what

we're talking about. That's when this would have some benefit, right?

CHAIR MODLIN: Yes. Ted?

MEMBER EICKHOFF: I'm not sure where our conversation earlier about using adjuvant in seasonal vaccines came out. But it seems to me the issue is relevant to the struggle we seem to be having with this particular question.

Because if the FDA and the manufacturers, we could encourage them to do some trials of the several adjuvants that are out there and seem to be at least somewhat effective in the seasonal vaccine context, that would at least begin to give us a handle on the adjuvant safety issue even though it wouldn't be anywhere near 100,000. Nice if you could 100 people.

CHAIR MODLIN: Bruce?

MEMBER GELLIN: So before I start over, I'll look over the GSK corner so you can start thinking of who you want to bring to the

microphone.

But I think that the question here is that we have -- this is obviously, we're worried about a pandemic which is a global problem. We have global companies, and they're operating in other places than North America. So thanks technology there's a press release today from GSK from Europe that talks about their candidate adjuvant Prepandrix vaccines reaches important EU milestones, regulatory milestones.

So I'd actually like to hear some of the experience that the companies had with the EU with the EMA or I believe that's the right one, to say how has your experience there, how can that inform our discussions here. Because this is about your Prepandrix, which is as it says here is the first candidate Prepandrix influenza vaccine to receive a positive opinion, in capital letters, from the CHMP.

So clearly you've been down this

line. I would think of a similar set of questions both in terms of what you need to demonstrate to say that the pre-pandemic vaccine is providing some kind of benefit, what you're proposing for safety studies. So I'd be curious to know what those conversations are like that lead to a press release today. And for the record, it says "Not for distribution to the U.S. media."

CHAIR MODLIN: You're certainly welcome to respond. Barbara?

MS. HOWEL: Barbara Howel from GSK.

Actually, Bruce, we don't have anyone from the global headquarters here today, so I can't really speak to the discussions with the EMA.

We did see the press release as well while we're sitting in the audience, however.

CHAIR MODLIN: Okay. Bob?

MEMBER COUCH: I've not been involved in any of those discussions as

priority groups. But you could consider, at least as you sit around and think about it, that there is a risk if H5, take that as an example, that's one that came up with a discussion that I was involved in -- if there is a risk of H5 and we say it's still a risk, the risk of being able to adequately handle the pandemic rests with the first responders. So that if we say, okay, we're not pre-pandemic vaccinating that population, we're pre-pandemic considering vaccination for those individuals, health care professionals you know emergency and so forth, who would be required to care for the pandemic when it occurred.

If any of you were around in '68, I wasn't, doing something else, you know it was a disaster.

CHAIR MODLIN: Any other comments or questions?

Dr. DeBold did you want to expand upon your earlier comments now that we're

talking about safety?

MEMBER DeBOLD: I guess I just have a general question about the adjuvants that are being discussed. Because I've heard the term being tossed around a couple of times "novel adjuvants." Are there new things that in the works that we don't know about? And if so, I think I would agree with what I believe you said earlier about trying to test the adjuvant by itself before combining it with a vaccine. And maybe that's what happens anyway, because otherwise it seems to me you're putting two unknowns together and you're not going to be able to tease out necessarily the effect due to the adjuvant versus the vaccine.

CHAIR MODLIN: Norm? Actually, just for clarification, it was not exactly what I was suggesting. But obviously I think what we've already heard from Ted, which is that with these adjuvants the opportunity to study them in the setting of seasonal

influenza would give us an immense amount of information.

Norm, did you want to --

DR. BAYLOR: I'd like to kind of follow up with Ted and also the rest of the Committee as far as do you see the development and sort of, I guess, the development of the adjuvant in seasonal vaccine? So if we're going to use that sort of as a model, do you see applying that? I mean, what's your opinion on applying that to the pandemic? I mean we're talking about a different hemagglutinin. And so what's the comfort level there of applying that, and even the idea of developing the seasonal adjuvanted product and the need for that seasonal adjuvanted product?

CHAIR MODLIN: Ted?

MEMBER EICKHOFF: My comfort level would be pretty good. Because I could see a significant use for an adjuvanted seasonal vaccine if it broaden cross protection. In

other words, we might be able to think seriously about not changing strains quite as often as we have to do now. We might be able to tease out immune response, a better immune response out of some people at least who don't respond well in the immunocompromised category. I don't think an adjuvant is suddenly going to make people respond magically, immunocompromised people respond magically. But there may be subgroups of immunocompromised patients who will do better with an adjuvanted vaccine.

And there may be a couple more examples. I just can't think of them right now.

CHAIR MODLIN: And also, obviously, we're talking about completely different risk benefit ratios. so I think that if you have a fair amount of data that gives some level of confidence with seasonal influenza, I think once you migrate into the very different risk benefit ratio for a pandemic or even a pre-

pandemic vaccine, I think the ability to accept previous data regarding an adjuvant is pretty high. At least in my opinion. I would suspect that the others would agree.

Does that get at your question, Norm?

Any further discussion? Yes, sir.

MR. KENNEY: I'm Rick Kenny from GSK.

We wanted to respond a little bit more to your question. You caught us a little bit off guard.

We clearly -- the AMEA file is handled by a second group. A full discussion of that would require other folks to come to the microphone.

But the database that was used for the approval of that vaccine for the pre-pandemic setting was just in excess of 7,000 adults and elderly subjects. We're not yet into the pediatric trials in any major way. So that's kind of denominator of where we are.

I think one of the biggest lessons that was learned that may be appropriate for this context from that series of studies was that adjuvants enhance the cross protection potential. That if you look at the heterologous protection, that may be the crux of what should be the benefit for a pre-pandemic vaccine. In fact, the mathematical models that have been proposed over the last year to show the possible benefit of a vaccine have really required somewhere around a 30 percent heterologous protection to stop a pandemic.

So what we are trying to move towards proving is the potential for that cross protection using some sort of a readout, some sort of a surrogate.

Does that help.

DR. HOURN: Can you just clarify in terms of the favorable decision? Is it for a use in the inter-pandemic period as we were describing pre-pandemic vaccine or you mean

that to be used during a declared emergency?

MR. KENNY: Well, there's actually two files that were submitted. One is for a pandemic use -- a pandemic vaccine. Europe defines the whole pandemic/pre-pandemic terms a little bit differently.

But both the pre-pandemic vaccine and the pandemic vaccine were recommended for approval.

Whether or not it's actually used by a country in the pre-pandemic setting, I believe is a country-specific decision. But this allows it. And for a lot of countries, it allows the purchase of that vaccine.

MEMBER COUCH: But when you say "pre-pandemic," you're talking about for example now. Start next week if everything was ready for the population recommendations?

MR. KENNY: Their definition -- right. Their definition hinges on making vaccine that's using a strain that's available in the pre-pandemic period. So making vaccine

now, yes, that can be stockpiled or used for first responders, or what have you.

CHAIR MODLIN: Did you want to follow up on that?

MEMBER GELLIN: Right. Just a couple of other things.

We had this discussion about some kind of priming and then something to follow up later. That wasn't part of the discussion in this regulatory pathway in Europe, is that right, about some evidence of a demonstrated boost later on?

MR. KENNY: To my knowledge, the prime boost data was not part of that package.

MEMBER GELLIN: Okay. Thanks.

MR. KENNY: But if I may, in a pre-pandemic period, again if you can show that there is a possibility of a heterologous boost, to me that seems like a very strong argument in favor of allowing a pre-pandemic indication, allowing the possibility of protecting the population; that's the benefit.

MEMBER GELLIN: No, nobody would disagree. I was just wondering what bar you were trying to jump over in Europe and if that was one of the preset bars about cross protection --

MR. KENNY: No.

MEMBER GELLIN: As well as this question about coming in at some point later to demonstrate a subsequent immune boost.

MR. KENNY: And I think that the difference is in the definition of pre-pandemic vaccine. They're seeing it as a vaccine that can be made with today's strains versus the mock pandemic vaccine that has to be made in the future with future strain.

CHAIR MODLIN: Bob?

MEMBER DAVIS: Just a remark that makes me want to qualify a little bit. And that is that, and seasonal vaccines is what I know and I doubt if the H5 is much different, you get heterologous protection because you have measurable heterologous cross reacting

antibody. That's our surrogate for that. And that's a consequence of the magnitude of the homotypically antibody because that determines the extent to which is cross reacts with related drift variance. And I think that must be true for H5 also, but I don't know that. In which case the value of the adjuvant is not producing the cross reacting antibody, if the value of the adjuvant is increasing the antibody response homotypically and that increases the cross reactions.

CHAIR MODLIN: Lisa?

MEMBER JACKSON: Well, Bob, I'm sure you know this literature better than I, but doesn't the recent follow up study the VTU did to the Sanofi-Pasteur vaccine sort of imply that that may not necessarily be the case? Because it seemed like the boost response or the response to the post-one year administered antigen was not necessarily a factor of what dose was given at day zero and the antibody response at that. So it seemed

to raise the possibility that whatever is going on immunologically may not be well identified by the 29 day post HI response necessarily.

MEMBER COUCH: You're talking about John Trainer's H5 data?

MEMBER JACKSON: Well, the Kingswell paper. So they did a follow on that?

MEMBER COUCH: I don't know the H5 data that well.

MEMBER JACKSON: Yes. Yes.

MEMBER COUCH: But the two things that you do with a new antigen that in addition to the magnitude, as you give repeated doses, you actually broaden that response which can be shown to be specifically reactive antibody. So that's another function that might have been counted for something like that.

CHAIR MODLIN: Further discussion?

Norm, do you and Florence want to

have the final word?

DR. BAYLOR: I guess I'll say something.

I think this discussion that we've had this afternoon demonstrates the complexity of this issue, in particular the complexity that the regulators have. I mean because we have to have criteria to evaluate these vaccines. And we will continue to come back as we gather more information, as we see more data as we try to develop a pathway to license these vaccines. But we will be coming back and updating you and asking for more advice.

I think this was a good discussion, but I think the questions are still complex and the answers are not that cut and dry, as you can see.

CHAIR MODLIN: Norm, they obviously are.

We want to thank you I think for probably educating all of us and kind of raising our awareness with respect to the

degree of complexity here. I think there's a general awareness of this, but it's helpful I think for the members of the Committee to be able to get our arms around it.

I would like to thank the members of the Committee for a terrific actually two day meeting. And thank you for your participation. And I look forward to working with you at the next meeting.

We're adjourned.

(Whereupon, at 4:09 p.m. the meeting was adjourned.)