FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS
EVALUATION AND RESEARCH

VACCINES AND RELATED
BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

July 23, 2009

Hilton Hotel
620 Perry Parkway
Gaithersburg, Maryland

"This transcript has not been edited or corrected, but appears as received from the commercial transcribing service. Accordingly the Food and Drug Administration makes no representation as to its accuracy"

Proceedings by:

CASET Associates, Ltd.
Fairfax, Virginia 22030
caset@caset.net

TABLE OF CONTENTS

P R O C E E D I N G S (8:00 a.m.)

Discussion of Clinical Trials to Support Use of Vaccines Against the 2009 H1N1 Influenza Virus

Agenda Item: Call to Order and Opening Remarks

DR. MODLIN: Good morning. My name is John Modlin. I am serving as Chair of VRBPAC. I'd like to call the meeting to order.

Just a couple of quick comments before we start. The venue here is crowded, I understand that. I understand that this is the best we could do at the last minute. There are additional seats out in the hallway here, and I understand also in the hotel lobby, with a feed there. So if it is too uncomfortable or too crowded in here, there are other options.

We have a full agenda today, so I am going to try to move us along as expeditiously as possible. I am going to start by turning the meeting over to Christine Walsh.

Agenda Item: Conflict of Interest Statement

MS. WALSH: Thank you, Dr. Modlin. Good morning. I am Christine Walsh, the designated federal officer for today's meeting of the Vaccines and Related Biological Products Advisory Committee. I would like to welcome all of you to this meeting. Today's sessions will consist of presentations that are open to the public as described in the Federal Register notice of July 8, 2009. I would like to

request that any media inquiries be directed to Miss Pepper Long from the FDA Office of Public Affairs. Pepper, thank you. I would also like to request that everyone please check your cell phones and pagers to make sure they are off or in the silent mode.

I would now like to read into the public record the conflict of interest statement for today's meeting.

The Food and Drug Administration, FDA, is convening the July 23, 2009 meeting of the Vaccines and Related Biological Products Advisory Committee, under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all participants of the committee are special government employees, STEs, or regular federal employees from other agencies, and are subject to the federal conflict of interest laws and regulations.

The following information on the status of this advisory committee's compliance with federal ethics and conflict of interest laws, including but not limited to 18 USC 208 and 712 of the Federal Food Drug and Cosmetic Act are being provided to participants at this meeting and to the public. FDA has determined that all members of this advisory committee are in compliance with federal ethics and conflict of interest laws.

Under 18 USC 208, Congress has authorized FDA to

grant waivers to special government employees and regular government employees who have financial conflicts, when it is determined that the agency's need for a particular individual's service outweighs his or her potential financial conflict of interest. Under 712 of the Food Drug and Cosmetic Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees with potential financial conflicts when necessary to afford the committee their essential expertise.

Related to this discussion of this meeting, members and consultants of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and for the purposes of 18 USC 208, their employees. These interests may include investments, consulting, expert witness testimony, contracts and grants, CREDAs, teaching, speaking, writing, patents and royalties, and also primary employment.

The committee will discuss clinical trials to support use of vaccines against the 2009 H1N1 influenza virus. This is a particular matter of general applicability. Based on the agenda and all financial interests reported by members and consultants, no conflict of interest waivers were issues under 18 USC 208b3 and 712 of the Food Drug and Cosmetic Act.

Dr. Margaret Reynolds is serving as the industry representative, acting on behalf of all related industry, and is employed by GlaxoSmithKline in Washington, D.C.. Industry representatives are not special government employees and do not vote. In addition, there may be regulated industry and outside organization speakers making presentations. These speakers may have financial interests associated with their employer and with other regulated firms.

The FDA asks that in the interest of fairness that they address any current or previous financial involvement with any firms whose products they may wish to comment upon. These individuals were not screened by the FDA for conflict of interest. This conflict of interest statement will be available for review at the registration table. We would like to remind members, consultants and participants 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 relationships that you may have with the sponsor, its product and if known, its competitors.

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

DR. MODLIN: Thank you, Christine. I am going to ask those who are sitting at the table to quickly go around and introduce themselves and their institutional affiliations. We will start with Dr. Jackson.

DR. JACKSON: Lisa Jackson, Group Health Center for Health Studies in Seattle.

DR. MC INNES: Pamela McInnes, National Institutes of Health.

DR. WHARTON: Melinda Wharton, National Center for Immunizations and Respiratory Diseases, Centers for Disease Control and Prevention.

DR. DE STEFANO: Frank DeStefano, Immunization Safety Office, Centers for Disease Control and Prevention.

DR. STAPLETON: Jack Stapleton, the University of Iowa.

DR. LEVANDOWSKI: Roland Levandowski. I don't have any institutional affiliation, but I am an infectious diseases physician working as a volunteer for public health organizations.

DR. GELLIN: Bruce Gellin, National Vaccine Program Office.

DR. EICKHOFF: Ted Eickhoff, University of Colorado.

DR. DEBOLD: Vicky DeBold, National Vaccine Information Center.

DR. ROMERO: Jose Romero, University of Arkansas for Medical Sciences and Arkansas Children's Hospital.

DR. REYNOLDS: Margaret Reynolds, GlaxoSmithKline, industry representative.

DR. SANCHEZ: Pablo Sanchez, University of Texas Southwestern Medical Center, Dallas.

DR. BAYLOR: Norman Baylor, Director of the Office of Vaccines Research and Review at FDA, Center for Biologics.

DR. WEIR: Jerry Weir, Director of the Division of Oral Products in the Office of Vaccines.

DR. SUN: Wellington Sun, Office of Vaccines, CBER.

DR. MODLIN: Thank you. As everyone is aware, we have a single item on the agenda today, one of extraordinary public health importance. It is an urgent issue, that is why we are meeting today.

Norm, I understand that you are going to lead off with the FDA presentation.

Agenda Item: FDA Introduction

DR. BAYLOR: Good morning, everyone. I am going to set the stage for today's meeting by providing a small backdrop and introduction to today's meeting.

In today's meeting we are convening our Vaccines and Related Biological Products Advisory Committee to present FDA's approach to the licensure and availability of vaccines against the pandemic H1N1/2009 virus. We are collaborating

with our government partners, such as the National Institutes of Health, Centers for Disease Control and Prevention, BARDA, which is the Biomedical Advanced Research and Development Authority, the National Vaccine Program Office and other agencies within the Department of Health and Human Services. We have been collaborating with the World Health Organization on this issue as well as other national regulatory authorities and the vaccine industry to insure the licensure of a safe and effective vaccine against pandemic H1N1/2009 influenza virus.

The regulatory pathway to licensure. Over the coming weeks the U.S. government and the vaccine manufacturers will have to make critical decisions. One of these decisions is formulating a vaccine against the pandemic H1N1 influenza virus. There will also have to be recommendations for vaccinations of targeted groups and potentially the entire U.S. population.

As far as recommendations for vaccination, that is not he focus of this meeting. The focus of this meeting is strictly on the licensure or regulatory pathway.

However, due to the rapid spread and uncertainty of the pandemic this fall, FDA has considered regulatory pathways to facilitate licensure. We determined that a monovalent unadjuvanted vaccine against pandemic H1N1/2009 influenza virus can be licensed as a strain change supplement

to existing BLAs. This is consistent with licensure of new seasonal vaccines for influenza. It is consistent with past regulatory actions, and it also facilitates the availability if vaccination is recommended. As we go on through the presentations today, we will expand on these issues and give you background as to some of the rationale in more detail.

The outline of the agenda today will present considerations for manufacturing and testing of vaccines. We will also go a little bit further into the regulatory approach to the clinical evaluation of the vaccines, and an overview of postmarketing safety monitoring and evaluation will also be presented.

CDC will provide an update on the surveillance and epidemiology of this influenza virus. The National Institutes of Health will provide an overview of their proposed clinical studies. BARDA will present an overview of the Department of Health and Human Services role in preparedness and procurement of pandemic H1N1/2009 influenza virus vaccines, and the manufacturers will provide a brief overview of their plans for manufacturing, as well as clinically evaluating vaccines against this virus.

Let me just give you a little backdrop of where we are and the current situation. CDC will expand on this in their talk. We all know that a pandemic was declared by the Director General of the World Health Organization on June

11, 2009. The WHO also stated last week that the 2009 influenza pandemic has spread internationally with unprecedented speed. In past pandemics, influenza viruses have needed more than six months to spread as widely as the new H1N1 virus has spread in less than six weeks. Again, this is a statement from the WHO last week.

This snapshot is already out of date. This is cumulative number of confirmed human cases of pandemic H1N1/2009 reported to the WHO. I show this slide just to show you that most of the world or at least a large part of the world is covered here, noting infections or deaths throughout the world. As of July 16, and I'm sure the CDC will update these, the cases in the United States were over 40,000.

In the Southern Hemisphere they are currently reporting pandemic 2009 influenza virus activity, and this might be a predictor of what we will see in the Northern Hemisphere beginning with our influenza season. A number of reports throughout the media on things that are happening in the Southern Hemisphere. I'm sure we have all heard of anecdotal reports of our friends or family who have been in the Southern Hemisphere, who have reported how things are there.

So looking at our planning considerations, the current situation and expectations, the continued circulation

of this virus, we believe the number of cases will continue to increase, and vaccines will be an important intervention against this virus. It is necessary for preparedness to have an adequate supply of vaccine available.

However, there are uncertainties at this stage. The possibility of a development of an increased virulence of this virus and associated morbidity, especially in children and young adults as we are seeing now, the possibility of widespread antiviral drug resistance, as well as the severity of this 2009 H1N1 influenza pandemic could increase under such an uncertainty, and there could be antigenic drift.

In conclusion, the pandemic 2009 influenza virus is continuing to spread globally, and there are uncertainties about how this virus will behave this fall in the United States during our influenza season. The Food and Drug Administration is committed to insuring the availability of safe and effective vaccines against the pandemic H1N1/2009 influenza virus, in the event that regulations to use the vaccine are made.

As part of the government's efforts in influenza preparedness, the Food and Drug Administration along with other agencies within the Department of Health and Human Services believe that licensure of monovalent, non-adjuvanted vaccines against the influenza H1N1/2009 influenza virus as a strain change is the most expeditious pathway for providing a

safe and effective vaccine to the public. We are also considering the availability of adjuvant vaccines if needed under an emergency use authorization. This is an option. Discussions concerning the recommendations for use and implementation of an immunization program for the vaccine, these are ongoing in other parts of the government, as well as other advisory committees, will take this on, and some discussions have already occurred by some of these groups.

I am going to quickly go through the discussion points, John. Then we are going to present these later on at the end so you can go through them. But just to give you a flavor and to think about these as you are hearing the presentations, then when we get to the discussion.

The first discussion item is, we would like the committee to discuss our approach to licensing a non-adjuvanted pandemic 2009 influenza vaccine via a strain change supplement without new clinical data, and whether this is appropriate. The pandemic H1N1 vaccine would be manufactured by U.S. licensed manufacturers using their currently licensed seasonal influenza vaccine process and the current doses in the current seasonal vaccines.

We would also like the committee to discuss whether recipients of pandemic influenza vaccine should be administered two doses of vaccine at its initiation of the immunization program, if that were to be recommended. We

would also like you to discuss the consideration for immunizing special populations such as children below the age of six months, as well as pregnant women. We are asking you to discuss the use of adjuvant vaccines. We are also asking you to discuss the proposed post-licensure evaluation for safety, identifying any gaps that may have been included in our proposals. We would also like you to comment on approaches to assessing vaccine effectiveness, and consider the potential need for diagnostic methods to distinguish the pandemic 2009 H1N1 strains from the circulating seasonal strains, as well as other influenza-like illnesses.

So those are the discussion points. Now I am going to turn the podium over to CDC. I think Dr. Fiore is up next.

Thank you very much.

DR. MODLIN: Thanks, Norm.

Agenda Item: Epidemiology of Newly Emerged H1N1 Influenza Virus/Strain Selection/Assessment of Vaccine Efficacy: Presentation by Dr. Anthony Fiore

DR. FIORE: Good morning. I am Anthony Fiore from the Influenza Division at CDC. Over the next few minutes I want to provide you with an update on U.S. epidemiology of novel influenza A H1N1, and a little bit about the international picture, and then finally describe the plans for the Advisory Committee on Immunization Practices special

meeting, which is next Wednesday, July 29, in which we will consider groups that might be targeted for vaccination.

First, the usual state by state snapshot of influenza activity in the U.S. This is July 11, week 27. You don't usually see a map like this for July 27. We normally would have no activity and at most, sporadic activity in a few states. In fact, we don't even report these maps over the summer typically. You can see that even though the furor over this illness has died down, there are still many states that are reporting widespread influenza activity, and all of the viruses being isolated at this point, or virtually all, are novel H1N1.

This is data from our Influenza-Like Illness Surveillance Network or ILI Net. This network has a group of over 2,000 physicians that report weekly the percentage of patients that come into their office with acute respiratory illness. In the green line and the blue line here, you see the last two seasons worth of data with a typical winter peak. The red line is this past season. You see that typical winter peak, a fairly mild season by this measure at least. Then you see starting at the of April and early May a bump-up again, which we had not seen in previous seasons. This of course is novel H1N1. The dashed line is the seasonal baseline, so it picked up just above that seasonal baseline, and how has gone down below baselines that we might

see in the winter, but is still above normal activity.

This national picture obscures what you might see if you looked at a regional level. Here is three of the ten HHS regions with the same sort of data depicted. At the top there is New England. You can see they had that same second peak, a bimodal peak there. New Jersey and New York, Region Two, which was particularly hard hit, had a very substantial peak. In fact, it went up above -- on the bottom left, you can see that it went up above the seasonal baseline. In fact, went above what we typically see in the winter. Then this area around here, the Mid-Atlantic region, had a picture that looked more or less like the national picture.

So in terms of confirmed cases, we are just getting weekly reporting now, so I don't have an update on confirmed cases. We will have another update tomorrow. Thus far there are 40,617 laboratory confirmed cases, 4800 roughly hospitalizations, 262 deaths, all of these due to laboratory confirmed influenza. We know that as far as cases go, this substantially underestimates the number of people who are tested. States now are focusing just on doing testing on people with severe illness, particularly those that are hospitalized, because of laboratory capacity issues. So we are only testing some of the people. In fact, a minority of people in most areas who are ill with illness that is compatible with H1N1 are being tested and getting laboratory

confirmed. That is important to keep in mind when you see these data.

Fifty percent are male. The median age looking at all cases is 12. The median age of hospitalized cases is 20. The median age of deceased cases is 37. Again, these counts are affected even more as time goes on by the focus on testing persons at highest risk for complications and those that are hospitalized. In early June we began aggregate confirmed case reporting, which means once a week reporting with states only being required to report cases within a fairly broad age group. I'll show you those age groups in a minute. The specificity of data that we are getting from confirmed cases is less than it was at the beginning of the outbreak. This is by intent. This has always been in the pandemic planning, that we would to go the sorts of surveillance systems that we use for seasonal influenza as the pandemic unfolded and as widespread community transmission took hold.

This slide shows cases, the rate per 100,000 population by age group. These are those age groups I mentioned. You can see here the five to 24-year-old age group. Children and young adults have the highest rate of cases with almost 20,000 cases in this age group, and a rate of 24 per 100,000 population. These age groups, particularly in the younger age groups, where most people do not have a

severe infection that requires them to be tested, you have to keep that in mind when you look at these data. Strikingly, and this will come up again and again in other slides, very few cases and a low rate in the older age groups.

This shows the hospitalization rate per 100,000. In the hospitalization rate you see a somewhat different story. Hospitalization rates are highest in infants and pre-schoolers or to four-year-olds, it is second highest in five to 24-year-olds and is lower in the older age group. As I will show you in a minute with the comparison to seasonal influenza, it is really quite different. We normally see the highest rates of hospitalization in the oldest age groups.

I'll show you a blowup of a couple of sections in this graph, in case you can't see it from the back there. This shows six different age groups in which we measure laboratory confirmed hospitalization rates in our emerging infections program surveillance sites. These are surveillance sites that have been ongoing for many years now. This only shows the spring and the summer of 2009.

Just to orient you to this slide, the Y axis shows the rates. The vaccines are scaled somewhat differently according to age group because of the differences in rates that you typically see. The X axis is time, beginning with late April, week 15. The dashed line is a baseline or an average, I guess benchmark would be the right term, for what

we normally see for a winter season for influenza in these sites by these age groups.

What you can see most strikingly here, I'll show you the blowup in a minute, is that we have had a winter season's worth of hospitalization for five to 17-year-olds over the summer of 2009. This has really only been in about a six to eight week span. On the other hand, and strikingly different from seasonal influenza, for those 65 and older, we are seeing very few hospitalizations.

Here is that blowup of the graph that I wanted to show you, five to 17-year-old school age children with a cumulative hospitalization incidence that approaches or reaches that of the average of the last three influenza winter seasons, seasonal influenza. Eighteen to 49-year-olds are getting there, getting towards the average for a winter season in the summer of 2009.

This is the bar graph that is supposed to bring it home, how different this is from normal seasonal influenza as far as distribution of age groups that are hospitalized. Here in the light blue you see the 2007-8 season. You remember, that was a mild to moderate season. Then as is typical for seasonal influenza, we saw the highest percentage of persons hospitalized in those 65 and older. You can se the tall peak there in light blue. Strikingly different for the pandemic 2009 H1N1. We see hospitalization rates that

are the highest in younger age groups and very low hospitalization rates for those 65 and older.

As far as deaths, these age groups make it somewhat misleading to show it this way, because the age groups are different sizes. The largest number of deaths have occurred among 25 to 49-year-olds. As far as case fatality rate, it is somewhat different. Even though we have had very few cases in those over 65, when persons in those age groups get infected, they do get into trouble, and the case fatality is the highest in that age group. Case fatality rates are quite low in that age group that has the most deaths; it is just the sheer number of cases that is driving the fact that the highest number of deaths are in those younger age groups.

Just to summarize the findings you have seen in those graphs the past few minutes, the distribution of cases and hospitalizations and deaths looks like this. The highest incidence of lab confirmed infections is in school age children. The highest hospitalization rates are in zero to four-year-olds with school age children coming close behind. The hospitalization rates for the time period April to June of 2009 are approaching the cumulative rates that we see for seasonal influenza on average over the past three years among the school age children and 18 to 49-year-old adults. The fewest number of cases, but the highest case fatality ratio is in older adults.

The distribution of cases by age group is very different compared to seasonal influenza. The highest proportion of hospitalized cases are in children and young adults. There are few cases of hospitalized lab confirmed infection in older adults.

I didn't show you these data because it gets a little bit complicated here, but the data thus far indicates that similar to seasonal influenza, those who have been hospitalized often have underlying medical conditions. About 70 percent of cases thus far have had an underlying medical condition of some sort. This could be anything from asthma to pregnancy to COPD or heart disease or whatever. But you could look at that from the other side; 30 percent of those people that had to be hospitalized due to lab confirmed infection with H1N1 were previously healthy.

I wanted to alert you to the fact that the data is going to look somewhat different going forward. WHO on July 16 indicated that for countries like the United States and many other countries in the world, they are experiencing community wide transmission. They can shift now their focus of surveillance activities to going through their established indicators for monitoring seasonal influenza activity. They no longer need to submit regular reports of these individual lab confirmed cases and deaths. That is partly due simply to capacity issues, but it is also due to the fact that as you

focus testing on certain people, those that are most severely ill, those lab confirmed case demographics become not very representative of what is going on with the outbreak.

For newly affected countries, WHO does continue to encourage that the first confirmed cases get aggressive investigation, and countries that are just getting this virus introduced do continue to submit lab confirmed case numbers and descriptive epidemiology of those early cases.

In the United States in the near future you will see this aggregated confirmed case counting ceasing, this lab confirmed case counting ceasing. You will see a continued focus on monitoring those cases that are most severe, those cases that are lab confirmed hospitalized cases and deaths. We will continue our usual influenza monitoring systems. That includes syndromic surveillance that we do through ILI Net and Biosense. The population-based surveillance platforms such as the Emerging Infections Program, which is a population-based system that covers about 14 percent of the United States. Vaccine Safety Datalink and other surveillance sites will be the focus of where we look for influenza. And of course, viral surveillance which Dr. Cox will talk to you about in a minute, will continue.

This is just another version of the map that Dr. Baylor just showed. It indicates that there are many countries now that have lots of cases. The biggest red

splotches indicate 10,000 or more cases, and you can see that countries both in the Northern Hemisphere and in the Southern Hemisphere are now experiencing outbreaks that have gone up over 10,000 cases.

This is an example from Australia, in a box that shows the national data as of the 13th of July. They have 3,912 confirmed cases. The overall assessment was that incidence was increasing in most of Australia, but it was declining in the Victoria region, which is around Melbourne. They had 268 or about seven percent hospitalized, 45.6 percent in the ICU and five deaths. I think you probably could find even more updated data from Australia, but that is just a snapshot.

The graph here is looking at the Victoria area. It is intended to give you a sense over time of what this looks like, what novel H1N1 looks like compared to some of their previous seasons. This looks like about 12 seasons worth of data. This is a somewhat similar system to ILI Net, where providers report incidents of influenza-like illness that come into an office. The most recent time frame no the far right, a peak that extended up past this normal seasonal activity, similar to the way a couple of past seasonal influenza seasons have done, such as the 2007 season for Australia, the 2003 season and the 1997 season. In Victoria you can see a dipping down, and this is the source of

Victoria reporting that incidence was relatively lower in this past couple of weeks compared to what it had been earlier. This is not a map intended to represent all of Australia. This is just to give you a sense of the scale of influenza-like activity with this outbreak as compared to some previous seasons.

Here is a map from PAHO, Pan American Health Organization, just showing countries and states that have had the highest activity. The darker red is where there is the highest activity. There are some areas where we really don't know what is going on through much of the middle part of Central America, for example, but in places like Chile and Argentina where they do have relatively good surveillance systems, it is clear that they are experiencing lots of activity. You read about it in the newspapers.

It is a little bit hard to get a handle on exactly how severe this is. Our people on the ground there are not reporting that health care infrastructures are overwhelmed or anything like that, but this is clearly a brisk flu season, and a lot of it is due to novel H1. They also have other viruses circulating, but a lot of it in more recent weeks has been due to novel H1.

Just a summary that we put together a few days ago to get the overall picture of what is going on in the Southern Hemisphere. Is there any evidence that the

epidemiology has changed? In other words, is distribution of cases or the more severe cases in the Southern Hemisphere different from the U.S.? We don't have that sort of evidence at this point. Are the types of pre-existing conditions that people have who are getting the more severe infections different from the U.S.? No, not as far as we can tell.

Has there been a change in the timing of when the influenza season shows up compared to normal? There is some mixed evidence for that. The data that I showed you for Victoria showed a quite early season in that area, but that has not necessarily been true in all of the Southern Hemisphere countries, which have had a normal uptick of influenza activity. What is different is that most of it has been due to novel H1.

As far as health care impact, we really don't have much evidence to indicate that this is more severe than a moderate flu season might be in the Southern Hemisphere. It is still early. A lot of these countries are just getting their introductions in the past few weeks, and of course hospitalization data and the more severe infection data does tend to lag behind incidence data. So I think we do need to have our folks that are currently stationed there and the ministries of health in those countries actively seek to examine whether things are changing or different compared to what has been seen in the Northern Hemisphere.

As far as transmission, community attack rates, are they different from seasonal influenza? We don't know. There is not the sort of data that comes from these areas that can tell us that at this point. We are actively working with them to generate that sort of data.

The last thing Dr. Baylor asked me to talk about was what the ACIP is up to. On July 29 we are going to have a special meeting in Atlanta. This follows up the extra day of meeting that was done in late June. There was an ACIP meeting in June that was extended for a day to talk about novel H1 issues. Now this is a special one-day meeting that is going to focus entirely on novel H1.

The meeting goals are to review the epidemiology and virology in considerable detail, use that data to provide guidance on which groups should be the focus of vaccination efforts, look at things like supply and implementation issues, in addition to the epidemiologic data, to see whether these groups -- we should go further with certain groups and say that these should be prioritized to get vaccination first. Then finally, provide recommendations in the context of wanting to make sure that the overall vaccination program -- and that includes both the vaccination program that is planned for seasonal influenza and pandemic influenza, to be the most successful.

The things that will be shown at the meeting

include epidemiology and virology updates, a discussion of implementation issues. CDC's plans for communication will be discussed. We will talk about vaccine availability, the formulations available and the time lines, when they might be available. Then we will present the results of the Influenza Vaccine Work Group discussion, which has been meeting by teleconference once or twice a week for the past several months to deal with novel H1, just a summary of the discussions that have gone on to date.

The outcome of this meeting, it is hoped that we will have recommendations for use of novel H1N1 vaccines, with pointing towards age or risk groups that should be targeted for vaccination, and also a discussion of how and when they should be prioritized. You will see those recommendations show up on the CDC web within a few days of the meeting, and then of course there will be the usual publication in the MMWR sometime within a few weeks after that, we hope.

With that, I just want to acknowledge the folks that helped me put this together, Jerry Brizee, our branch chief, Lynn Finlander, the team lead for surveillance, other folks in the surveillance unit. Of course, there are many others at CDC that have been involved in this response, and the source of our data, which is the state and local health departments.

Thanks.

DR. MODLIN: Thanks, Dr. Fiore. Why don't we go ahead with Dr. Cox's presentation?

Agenda Item: Epidemiology of Newly Emerged H1N1 Influenza Virus/Strain Selection/Assessment of Vaccine Efficacy: Presentation by Dr. Nancy Cox

DR. COX: Good morning, everyone. I am going to give what I hope will be a fairly brief update of the virology of this influenza A H1N1 virus.

I just wanted to review briefly the sequence of events that occurred because things have been happening so quickly that one tends to forget exactly when we started out our journey to have immunization available against this virus.

The first U.S. case was identified in California on April 15. It was identified as an un-subtypable virus and was sent to CDC. Because we had had quite a bit of experience working with viruses that had been transmitted from swine to humans, we were able to develop primers and probes to do complete genome sequencing, put the sequences into the database very quickly, develop real-time PCR kits which were dispatched to U.S. labs beginning at the end of April, and then the same kits were distributed internationally -- and you can see the numbers here -- by the middle of June.

We started developing vaccine viruses after we had the second case on April 17. We decided that we needed to move ahead and develop vaccine candidate viruses. That was done, and vaccine candidate viruses were shipped to the manufacturers toward the end of May. So things happened very, very quickly in this response.

A lot of people have talked about the origin of the virus. It has been a little bit confusing. Because some of the issues around the origin of the virus and safety of the vaccine are relevant, I thought I would just give you this brief schematic, to show you that the ultimate origin of all the genes of these viruses that are circulating in swine and in humans, is the bird population of the world, usually the aquatic bird population.

Two genes entered the pig population about 1998 directly from birds. The PB-1 is one which entered the human population in 1968 when the Hong Kong epidemic occurred. Then that gene was transmitted into pigs in about 1998.

The HA, NP and NS genes have their origin in the 1918 pandemic virus. So this is the virus that went into pigs ultimately from the bird reservoir, but went into pigs and people at about the same time in 1918. The H1N1 virus was then subsequently evolved separately in their human host and in their swine host.

The NA and M genes were of avian origin. They were

transmitted to pigs in Europe and Asia in about 1979 and evolved in pigs thereafter. So we have this 2009 H1N1 virus which has a very colorful rainbow of genes. And basically it involved reassortment between two swine viruses, the triple reassortant swine virus that was circulating in the United States and a Eurasian swine virus.

Just to give you a bit more information about what is going on in the swine population in North America, I thought I would present this. It is really quite a complex picture. You have the 1918 Spanish flu H1N1 virus entering pigs and people in 1918, and continuing to evolve. The swine influenza virus was actually isolated before human influenza viruses in 1930.

That H1N1 virus continued to evolve. We began calling that virus the classical swine influenza virus. There have been subsequent introductions from humans to pigs of H3N2 viruses right around the time of the '68 pandemic, and then a bit later. Then in 1997 or '98 we had multiple introductions of viruses that were related to the H3N2 Uhahn (?) strains into pigs. At the same time there was introduction of the avian influenza viruses into pigs that were susceptible to swine, avian and human influenza viruses.

First we had a double reassortant, H3N2 emerge, and then a triple reassortant. This virus had this cassette of genes. This is a slide that is courtesy of Dr. Amy Vincent

who is at USDA and has been involved in a lot of the swine studies along with Chris Olsen and a variety of other people.

This cassette seems to be very permissive in accepting HA and NA genes from a wide variety of other viruses.

Again, to emphasis the importance of surveillance in swine, the H4N6 virus in the swine population, in Canada there was an H3N1 virus that entered the swine population. Human H1N1 viruses entered the swine population in 2003 to 2005, resulting in viruses which had both the human H1 and N1 and the human H1 and N2 surface proteins.

Then notably again, an H2N3 virus entered the swine population in 2006. Fortunately this event appears to not have resulted in establishment of this particular virus in the swine population in North America, but there are gaps in surveillance.

Currently in pigs as far as we know, and surveillance is lacking, I must emphasize, we have H3N2, H1N2, recombinant H1N1, classical H1N1, human H1N1 and the surface glycoproteins are H1N2, all circulating in the pig population.

As I said before, this virus resulted from the reassortment of a North American triple reassortant. You can see the three different colors designating the origin of the genes and the Eurasian swine H1N1 virus. This new virus

obtained the neuraminidase and the M gene from this Eurasian swine virus.

Now, a lot of work has been done by individuals who had been doing a bit of swine influenza surveillance over the past years. They have been digging through their freezers, and a group in Hong Kong at Hong Kong University found that there has been reassortment between these two lineages in Asia. The reason is that we have exported our North American triple reassortant viruses to Asia. We have not detected this virus in North American pigs, but it is quite possible that if the viruses can go in one direction they can also go in the other direction.

So when we look at the sequence data itself, and of course this is a family tree, an evolutionary tree, we have shown here a wide variety of viruses isolated from a number of different continents. The viruses shown in red are potential or vaccine candidate viruses, some of which have been sent to vaccine manufacturers who they are working with, others of which are being sent at the moment.

You can see that there is a very distant relationship of these new viruses from the A/New Jersey/8/76 H1N1 virus. So these viruses have evolved considerably. This is the neuraminidase gene; I apologize, I must have got these slides out of order.

We have a lot of homogeneity among the sequences of

these viruses. If we were to compare this to seasonal H1N1 viruses, we would see a lot more longer branches out here. We would not see the viruses so close to the backbone. I think the HA slide has disappeared from my slide deck, but the HA genes show a very similar relationship with all of the pandemic H1N1 viruses being very close to the backbone of the tree.

To put this into context, I just wanted to show the amount of difference between the swine New Jersey/76 virus and the California/7/2009 virus. This is the virus which is our reference at the moment. If we look at the number of nucleotide differences in the HA, we see that there are about 184 or 11 percent of the nucleotides in the HA are different. For the amino acid differences we have about 44, and that is an eight percent difference.

Putting that into context, we can look at -- for the NA we have about 282 differences or 20 percent differences in nucleotides, 82 amino acid differences and 18 percent difference in the amino acid homology.

Putting that into context with the H3N2 virus, we would have to go all the way back to A/Victoria/3/1975 as compared to the current H3N2 vaccine strain A/Brisbane/10/2007. You can see that for the neuraminidase we have an even greater percentage of nucleotide and amino acid differences than we do between these two key H3N2

viruses. So there is really a lot of diversity that was seen between the swine New Jersey virus and the California strain.

I will show you three hemagglutination inhibition reaction tables. Just suffice it to say they are extremely similar to each other. The tables are in their content. I know that many of you won't be able to see the details from the back of the room, so I will just try to go through this.

Most of you are accustomed to looking at these tables. The homologous titers for the virus and the reference for antiserum are shown in the diagonal, highlighted in red. Here we have the swine Iowa virus and its respective antiserum, and you can see that by and large that antiserum doesn't cover these viruses very well, the test antigens. Likewise, the swine New Jersey/76 virus, this is a human isolate, doesn't cover these viruses, the novel H1N1 viruses, very well at all.

We have a number of swine origin that were isolated from humans shown here. There is quite a bit of cross reactivity that we are seeing. Then starting in this column we have the California/7, the Mexico/4108, the New York/18 and Texas/15 reference viruses. There is a lot of homogeneity. In fact, you just can't pick out viruses that are really different from each other with respect to their reactions with a wide number of ferret antisera.

Here we have viruses isolated from fatal cases.

There are no differences either in the nucleotide or amino acid sequences that we can discern that would distinguish viruses isolated from fatal cases and from milder cases. We have a number of MDCK and egg pairs, and there are no differences that we can discern between the egg and MDCK cell isolates. Then we have a number of viruses from Mexico, El Salvador, Guatemala, Auckland and England, and we just see much of the same.

Here is a table that was generated at the WHO collaborating center in London. You see a similar picture. They have a bit more cross reactive A/New Jersey/76 antiserum here that tends to cross react with the 2009 viruses a bit better. But if you look at all of these antisera generated to the new 2009 viruses, they cover all of these viruses from France, Cyprus, Algeria, Singapore, Qatar, Mauritius, very well.

Then I will just show you one more HI table generated by a WHO collaborating center in Tokyo. Once again, with Japanese viruses added here and quite a large number of Japanese viruses tested here, so we have ferret sera to these viruses, and they are looking at the viruses that are circulating in Japan. These are June isolates. You can see that they are all very much the same.

So we have received a lot of viruses from many different countries, and there have been a lot of viruses

that have been sequenced in total or in part. We have over 850 viruses that have been analyzed by sequencing or antigenic data.

We were of course very interested to find out if these viruses were resistant to the two classes of antiviral drugs. All of them are resistant to the M2 blockers, and all of the ones that we have tested at CDC are sensitive to Zanamivir and Oseltamivir. However, we understand that there are approximately five Oseltamivir resistant viruses that have been documented so far. The only one where the individual was not either treated or prophylaxed is the traveler from the U.S. who arrived in Hong Kong and was ill on arrival and tested there.

There was a lot of discussion initially about whether vaccination with seasonal H1N1 viruses would provide some boosting in antibody to this novel H1 virus that emerged. So Jackie Katz and her group had been working very carefully to look at both hemagglutination inhibition titers and micro neutralization titers. It turns out that the micro neutralization titers, the test is more sensitive to picking up antibodies to these viruses.

This just shows you one of many test series that her group has done. These were individuals who are young, they are six months to nine years of age. They had been given the New Caledonia/99 strain in the vaccine. So we are

looking at the response to the New Caledonia virus and the California virus. Then we had a serum panel where the individuals had been given the Solomon Island/2006 H1N1 strain. These were five to nine-year-olds.

It doesn't matter what your age group or which antigen was in the vaccine. What you see is that you have very low titers to the California virus prior to vaccination and after vaccination. However, there is a nice robust response to the homologous vaccine virus, so you have an eight-fold increase in post vaccination titer compared to the pre vaccination titer. In this panel a 14-fold increase, in this panel a 57-fold increase, and in this panel twofold increases. This was looking at live attenuated influenza vaccine, but if you look in detail, you do not see an increase. You have a pre vaccination titer of five and a post vaccination of six. So no matter what seasonal vaccine is given to pediatric populations, you do not see a boost.

Likewise when you look at adult populations, you do not see the boosting effect. So for the Solomon Islands you see a 12-fold increase, for the California/4 twofold, for the Brisbane/58 19-fold, for the California/4 only twofold, and no increase here.

What we can say is that less than -- this is combining a lot of data from a number of different serum panels, and having some stratification by age. We can say

that less than four percent of individuals born during or after 1980 exhibited pre-existing cross reactive neutralizing antibody titers of one to 40 or greater to the pandemic virus, whereas 34 percent of individuals born prior to 1950 had titers of one to 80 or greater.

Vaccination with recent seasonal trivalent influenza vaccines resulted in a greater than fourfold increase in cross reactive antibody to the pandemic virus and only two percent of children aged six to nine years of age, in 12 to 22 percent of adults aged 18 to 64 years of age, and less than five percent in adults aged 60 years or greater.

Seasonal trivalent influenza vaccine with adjuvant induced similar cross reactive antibody responses. That is to say, no significant increases in cross reacting antibody were observed to the pandemic H1N1 viruses, whether you had adjuvanted vaccine or not.

In conclusion, all of the 2009 pandemic H1N1 viruses that have been examined in laboratories around the world are antigenically similar to the A/California/7/2009 reference virus. There is really minor genetic variability in all of the genes of the viruses isolated around the world. So far there is no evidence of reassortment between the pandemic H1N1 viruses and seasonal influenza viruses or the avian H5N1 viruses that are still infecting people in certain countries of the world.

All of the viruses are resistant to the M2 blockers, by and large are sensitive to the neuraminidase inhibitors, but Oseltamivir resistance has been documented in five instances, perhaps six, according to an e-mail I saw this morning, and four of the five developed a resistant virus after treatment or prophylaxis.

Vaccination with contemporary seasonal influenza vaccines with or without adjuvant induces little or no cross reactive antibody to the 2009 pandemic H1N1 virus in any age group. Individuals under 30 years of age are serologically naive, and a proportion of older adults appear to have pre-existing cross reactive antibody. This is consistent with the epidemiologic evidence that Tony presented previously, so we believe that what is being tested in the laboratory as cross reactive antibody is protective. However there are individuals over the age of 60 who do become infected, and as Tony pointed out, those infections while rare can be serious.

So basically the genetic antigenic characterization of viruses, the serologic assays and some animal model data that we have developed, and our epidemiologic assessments are all critical components for our public health risk assessment. There has been substantial consistency between laboratory and epidemiologic results, and there have been some studies that are done that I won't talk about today that suggest that the novel H1 viruses may not be fully adapted to

humans yet. So we are watching very carefully for changes in the genome, changes in epidemiology and so on.

We are looking as I mentioned for changes in antigenic characteristics and transmission characteristics and severity of disease and antiviral resistance, and for the intensity of influenza surveillance.

There is a very limited understanding of the diversity of influenza viruses in pigs globally. This is a major gap in our pandemic preparedness. We are working together very closely with USDA to initiate more comprehensive surveillance in swine populations in the United States, and insuring virus sharing is of utmost importance for pandemic preparedness. So we need to have sharing of viruses across the sectors, just as we as humans share our viruses with pigs and pigs share their influenza viruses with us.

I will close with acknowledgements, to the state and local public health departments, to WHO's Global Influenza Surveillance Network and to all of the influenza division staff who have worked so hard on this response as well as the entire response team at CDC.

Thank you.

DR. MODLIN: Thank you, Dr. Cox. Christine, I am told that Dr. Fiore had a follow-up presentation, is that correct?

MS. WALSH: Yes.

DR. MODLIN: So why don't we take that, and then we will open it up to questions if that is all right.

DR. FIORE: Hello, again. This presentation is probably more relevant to some of the discussions that will occur this afternoon. Also, I should acknowledge David Shay, who created the basis of this presentation and presented it at the ACIP meeting this past June 26. We just had a couple of updates.

The premise of the talk is to describe our plans to assess the effectiveness of both seasonal and pandemic influenza vaccines over the next year.

Beginning with some background and assumptions, vaccines purchased by the government, that we could have 50 million doses or more of monovalent vaccine against novel H1 by 15 October. I guess we will hear more about supply issues later today. We will have a regular seasonal influenza vaccine campaign in addition to this pandemic vaccine program, and two doses will be required.

The information requirements for our vaccine effectiveness studies are probably pretty obvious, but I have listed them out here. Is illness prevented, does effectiveness vary according to whether you receive one or two doses, does it vary by age, the presence or absence of underlying illness or the type of vaccine that was given,

does it vary by outcome. We have certainly seen that with seasonal influenza vaccines, instances particularly in drift years where effectiveness against illness might be somewhat lower than one would like. However, protection against things like more severe outcomes like hospitalization remains quite high, and we are looking at that also.

For some of these outcomes, a rapid vaccine effectiveness assessment would be optimal if it can be done. Also, the overarching concern and what policy makers want to know is whether the absolute vaccine benefits are comparable or exceed the risks that might be present from any potential adverse events.

CDC prefers to use lab confirmed outcomes in their vaccine effectiveness studies. These include the validity and the comparability of vaccine effectiveness estimates across other studies. As we know, sensitivity and particularly specificity of some of the clinical outcomes, like influenza-like illness or acute respiratory illness is fairly low, and the specificity varies by group, with older age groups having less specificity with a typical ILI type definition. The specificity can even vary over the course of an outbreak, and that is why we look for laboratory confirmed outcomes as the way that we measure vaccine effectiveness.

We will need to estimate both for novel H1 and for seasonal influenza. That is another reason that you need the

laboratory confirmed outcomes. The plan is to leverage the sorts of platforms that have been developed as part of pandemic preparedness over the past five seasons, to give a vaccine effectiveness estimate for both seasonal vaccines and for the pandemic vaccine.

We have four different areas where we are doing vaccine effectiveness studies. The one that we are most excited about and the one that is probably the most useful in the short term is vaccine effectiveness against RT PCR confirmed medically attended influenza. That means the person came in with an illness and had an RT PCR diagnosis of influenza in our community based sites, Marshfield, Wisconsin, Michigan, Rochester and Vanderbilt. The team refers to this as MMRV, realizing that acronym was already taken.

The vaccine effectiveness for prevention of hospitalization is as diagnosed by provider ordered clinically available tests is what is done in the ten emerging infections program sites. I mentioned in the earlier talk that these sites encompass about 14 percent of the U.S. population with population-based surveillance. This is fairly different, I will describe the methods in a minute, but fairly different from the MMRV studies, because of the fact that the providers made the decision about doing the testing.

Of course, we are also looking at early assessments of vaccine effectiveness among groups that might get vaccine early, in particular health care workers and others that are in high priority for receipt of vaccine. Finally, we have been already looking at vaccine effectiveness assessments by screening method, meaning that we retrospectively go back, look at cases to see whether they were vaccinated. That was done in the early stages of this to see whether seasonal vaccine looked like it had any evidence of protection against novel H1N1; it doesn't.

The community assessments, the MMRV that I referred to, cases are people that come in for medical care, they have an acute respiratory illness. They are enrolled in the study immediately if they consent. They are tested with RT PCR. Those that test positive are cases, those that test negative are the comparison group, the controls. The vaccination data is collected at time of enrollment from the cases themselves, but there is also a record review step to try to confirm that. There is also use of registries when available.

The system was developed over the past couple of years. The idea is to make an interim and a final vaccine effective estimate each season. We did succeed with an interim vaccine effectiveness assessment in 2007-2008. You recall that was published in April, and showed some evidence of effectiveness of the 2007-9 vaccine against that drifted

H3 strain. We will use similar methods to assess vaccine effectiveness for both seasonal and the pandemic vaccines in this coming year.

The EIP studies as I mentioned are somewhat different. Patients get hospitalized at one of the EIP sites, in hospitals in one of the EIP sites. Their clinician decides on their own whether they are to be tested for influenza retrospectively. We go back and look and see who was tested and who was positive. In this coming year we will try to get a closer link between the actual testing and the time that the cases are identified and try to confirm all those cases with RT PCR methods.

Controls are persons who are age and community matched, but who are not hospitalized with an acute respiratory infection up to the date of admission of the corresponding case. The cases and controls are interviewed. The medical records are looked at. This method has been used to look at effectiveness against lab confirmed hospitalizations among young children over a three-season span, and we will be looking at older adults. We began looking at older adults in the 2008-2009 season; those results aren't available yet.

This large catchment area is a real strength of the EIP system. It allows us to look at more severe outcomes like hospitalization that a smaller system that encompasses a

population group would not be able to do. While hospitalizations while common in the global scheme of things are small enough that it would be hard to capture them in anything but a very large surveillance system, capture them in numbers enough to allow an assessment.

We are in negotiations to look at vaccine effectiveness among those who received vaccines first. Health care workers would be one group. We also have longstanding collaborative efforts with the Department of Defense. Of course, Department of Defense personnel, at least some of them, are likely to get vaccine in the early going. Those methods are pretty well worked out and have been used over the past several seasons, and presented here at VRBPAC, as I recall, for effectiveness among deployed personnel.

We are looking at special studies among those at particular risks, looking at ways that we can get a vaccine effectiveness against pregnant women and newborns, pregnant women who are vaccinated and the newborns born to those vaccinated women.

In summary, we have a variety of different methods available to us. We will be monitoring for novel H1 infections at those four community vaccine effectiveness sites. Normally all these vaccine effectiveness studies wrap up shop in April. Of course, there was a lot of scrambling

when the novel H1 hit to get these going again, and they did get going again. In fact, in some instances never stopped from the season. We went right on through the spring and summer and will continue on as long as they are needed.

We have a number of challenges in trying to assess rapidly vaccine effectiveness. Probably the biggest one was that we could have lots and lots of different viruses circulating in this upcoming season in novel H1. We will have our usual players and potentially variants amongst those viruses.

Also, there will be many vaccines in play here. When you count up all the seasonal vaccines and all the pandemic vaccines that we are talking about, maybe a dozen or more different vaccines that are out there, it will be quite a job to try to determine who has gotten what.

David expresses his thanks to other members of his team and others that have helped with these efforts over the past several years, and will be helping in this coming influenza season.

Agenda Item: Questions/Clarifications

DR. MODLIN: Thank you, Dr. Fiore. Let's open this up for questions for both Dr. Cox and for Dr. Fiore from the members.

DR. JACKSON: Tony, did you get a chance to look at whether there appears to be any influence of getting last

year's seasonal flu on the occurrence of novel H1 cases in the sentinel sites, the MMRV sites?

DR. FIORE: No, there has not been vaccine effectiveness. In fact, it is pretty much zero, I think it is one percent or something like that, for getting a seasonal vaccine during 2008-9, and then protection against novel H1 in the spring and summer of 2009. We have not seen that. That has also been confirmed in some of the other sites around the world that have looked at this.

DR. JACKSON: Assuming that other vaccine supply is limited and/or only certain groups are targeted, has there been any discussion either in the MMRV sites or elsewhere conducting a placebo control trial or perhaps a crossover trial whereby some people get placebo first and are observed, and later get the real vaccine, or some more controlled experimental approach in addition to the observational methodology?

DR. FIORE: We don't have that planned at the moment, and I probably would need to put you in touch with David Shay to see where those discussions -- if they occurred, where they led and what ended up stopping them. But those plans aren't in place at the moment.

DR. MC INNES: For the case rate by age group and the hospitalization by age group, you showed zero to four as one of your ranges. Do you have data to show that further

broken down, so zero to six months of age, some sense of what is happening in really young infants compared to infants, toddlers, young children?

DR. FIORE: We have that data for the early parts of the outbreak back when we were getting still line listing types of reporting, when the specific ages were reported for each case. Now that we have gotten the aggregate reporting, that data becomes more difficult to get, because the states report, we had X number of people ages zero to four.

The place where we might get that is in our emerging infections programs sites. There are probably not enough cases to make much of it at this point. The limited data that I have seen for specifically thinking about zero to four-year-olds showed roughly the same sort of incidence across the zero to four group, and that is a little bit different from seasonal flu, where you see the highest incidence in younger than six months in particular and also among those younger than one year.

There are relatively few cases in that group, enough so that I don't know that I can make much of rates, nowhere near the numbers that we get over many seasons for seasonal flu. The other thing to keep in mind with that age group is that children that age, both for seasonal flu and for novel flu get hospitalized because people are worried about them sometimes, and it is a sepsis workup or something

like that. A lot of those hospitalizations are quite brief for that age group. We certainly have seen severe infections, but the criteria for getting hospitalized are a little different.

DR. STAPLETON: At the other end of the spectrum then, you say 30 percent of those hospitalized had no predisposing conditions. Could you look at the older people and see what percentage of those people are hospitalized and not have predisposing conditions?

DR. FIORE: Nearly all of those over 65 had a predisposing condition, yes. The persons who are thought to be previously healthy, that 30 percent, very much occur in that younger age group, school age children, younger adults.

DR. LEVANDOWSKI: I have got a couple of questions, one I think you will probably be able to answer easily, and one that there may not be a response to.

You didn't mention, and I think you probably would have told us if it were true, whether there have been any kind of outbreaks in nursing home situations or assisted living or any of those types of things in elderly. That is one question. Maybe I will just let you respond to that if you would.

DR. FIORE: We have not seen that at all. No nursing home outbreaks that we have heard of.

DR. LEVANDOWSKI: Then the other question you may

not be able to respond to relates to how does this experience with H1N1 compare to what happened in 1977 when the H1N1 Russian flu established itself worldwide in human populations? That strain of course was very closely related to what had been the human H1N1 influenza viruses from the 1950s and before, but can we draw any kind of parallels or comparisons from the experience as to what happened back in 1977 and subsequently to what is going on now in terms of this penetration into younger age groups and not so much in the elderly? Because that seemed to be true at that time also.

DR. FIORE: I don't know. I am turning to Nancy to see if she has that.

DR. COX: Yes. In 1977 the susceptible population was under 20 years of age. So you did see large outbreaks in all kinds of settings where younger people congregate, and schools. There were school closings, the university closed and so on. But you didn't have young adults being infected to any great extent, certainly not to the extent that we are seeing here.

Although our surveillance systems were not as good, we really had more of a coincidence of the circulation of that particular virus, the '77 virus, during our winter season and not late spring-summer. But it did predominate in the younger age groups, while H3N2 continued to circulate in

the age groups that were not susceptible to the new H1N1 virus in '77.

In terms of severity, I think we really didn't have such sensitive surveillance systems as we have now. But there really didn't seem to be the same extent of severity in people with underlying health conditions in the younger age groups. But it would be hard to do a direct comparison because our surveillance is so different now.

DR. GELLIN: Two for Nancy and two for Tony, to elaborate on things that you said.

For Nancy. If you talk a little bit more about the adjuvant and the lack of cross reactivity you saw here, and parallels with what we know now with what we would know of similar studies with H1N1.

Secondly, from your perspective, how would you translate the comment, it is not fully adapted to humans, and what that leaves us with?

DR. COX: For your second question, it may not be fully adapted to humans. For those studies we used a ferret model. A ferret model is a very good model, but perhaps not a perfect model. What we saw has some parallels in what we are seeing in terms of community transmission. What we saw is that basically, transmission from ferrets in one cage to ferrets in an adjacent cage was less efficient than for seasonal flu.

We worked with a lot of different seasonal influenza viruses, with H5N1 viruses, which aren't transmitted at all. We used at least three different pandemic H1N1 viruses in these transmission studies. Instead of having three out of three ferrets infected for each of the viruses that we tried, we only had two out of three ferrets infected in adjacent cages, and the infections tended to occur quite a bit later than they do for seasonal flu.

So it indicated to us that with all the experience that we have had looking at viruses in this ferret model, that this novel H1N1 may not be fully adapted to human transmission, because the seasonal human influenza viruses are so consistent in the way they transmit in ferrets.

So what we will be looking for are specific amino acids that we know have increased transmission or replication in humans, and for any evidence of new changes that might occur simultaneously with larger community outbreaks and so on. So we will be again keeping the laboratory findings and the epidemiology linked very closely.

Now I have forgotten your first question.

DR. GELLIN: We have learned a lot about adjuvants and cross reactivity with H1N1. How would you contrast what you are seeing so far with what you have done with that?

DR. COX: As we all know, when adjuvants have been used with the H1N1 pre pandemic vaccines, we have seen both a

higher level of antibody and a more cross reactive pattern of antibody.

For example, if an individual is given a vaccine that included a clade 1 virus, and you had adjuvant in the vaccine, you got broader cross protection and a higher level of antibody. Those H1N1 viruses are much more closely related to each other than the seasonal H1N1 and the pandemic H1N1.

So I think the reason that we are not seeing that boost is because of the antigenic distance between these viruses. If we were to do antigenic cartography and make a nice picture, we would see a much greater distance between the viruses. I think that is what probably accounts for it.

DR. GELLIN: The epi and transmissibility studies, you mentioned about Southern Hemisphere. Could you comment about ongoing analysis of what we saw here in the spring and summer, and how some of those studies might be revealing about transmissibility?

Then on the vaccine effectiveness, you may have mentioned this but I may have missed it, how will you be able to sort out people who may have been infected this past spring who then are enrolled in the study? Is there a way to screen those people so they don't contaminate your analysis?

DR. FIORE: The second question first. There isn't really a way to screen them. I have seen bias toward the

null contaminate the analysis. There will be people who are previously infected and immune. I guess it will depend on how they sort themselves out according to vaccinated or unvaccinated. But it is something we are going to be stuck with.

As far as other studies that have been done in the spring and the summer, the results are forthcoming in the ones that are underway in the Southern Hemisphere now.

Transmissibility has been assessed in a couple of different ways. There have been a couple of different field studies that have looked at transmissibility to household members, where close contacts with people were confirmed cases. In those studies we see similar results, or at least that are consistent with results that Dr. Cox just mentioned with the ferrets. While there is a good bit of household transmission to the susceptibles, depending on the study it can be anywhere from five to 25 percent or so, it is not outside of the bounds of what one might expect to see for influenza viruses. It is not 70 percent or something like that.

Other studies that are underway include studies that look at -- some of the studies have included components, going back to the studies I just mentioned, where we have gone and collected acute, and now we will be collecting convalescent blood specimens from those groups, to see

whether people, even if they didn't have a symptomatic infection, might have had some evidence of development of antibodies indicating subclinical infection.

We are also doing periodic surveys in both the emerging infections area programs sites and also nationally through the behavioral and risk factor surveillance system, asking people periodically over the course of time, did you have an influenza-like illness, is the question. That will give us some sense of the level of community illness.

Those sorts of studies that were done in New York City during the peak of their problems, maybe a month or so ago, indicated that in the neighborhood of seven or eight percent of people were reporting that they had an influenza-like illness within the previous couple of weeks. Of course, we don't know how many of those illnesses were due to novel H1. They are not lab confirmed illnesses. There is some degree of other causes of respiratory illness that are occurring there, but it gives you some sense of the community attack rate.

Hopefully knowing there are caveats about not knowing about who really has influenza, if you follow it over the course of time, we might get some trend sorts of data.

DR. MODLIN: Do you have another question, Bruce? Anyone else from this side? Vicky?

DR. DEBOLD: I am trying to get a handle on what

people are most afraid of. If I am getting this correctly, we are most afraid that this virus could mutate in a way that could result in substantially greater levels of hospitalization and fatalities. Are you seeing any evidence at this point of substantial mutation? Is there something that you are seeing?

DR. COX: No, we are not seeing any changes in the viruses that indicate that they are more virulent. We looked initially for known virulence markers for other influenza viruses, and they are absent in this particular H1N1 virus.

We are continuing to monitor very carefully, but we haven't seen anything that we believe is significant. As the viruses continue to spread among humans, we do expect to see greater diversity over time, but we have seen very homogeneous sequences compared to seasonal flu, as I mentioned. It is actually quite surprising that we haven't seen more antigenic variation or genetic variation to this point.

DR. MODLIN: Anyone else? Ted, did you have a comment?

DR. EICKHOFF: Two comments. No questions, but two comments. First I would like to commend the folks from CDC for being as on top of things as you obviously are.

Second, a comment back to Roland about the experience in 1977. Gordon Mickeljohn and I had post

surveillance at Lowry Air Force Base at that time, and I recall that episode quite well, because there was a very sharp outbreak of influenza, of Russian flu, in Air Force recruits, who were about 18, 19 years old. It just went through them literally like wildfire. From beginning to end, the whole outbreak took about four weeks and it was over.

There was in the community a lot of school absenteeism. There was very little workplace absenteeism, reflecting what Nancy said. It was really a very unusual kind of outbreak in its severity, not mortality, morbidity. There was no excess mortality in the country at that point, but a very sharp morbidity spike.

DR. MODLIN: Maybe I have one final question. Both your surveillance data and your serological data so far suggest that there is virtually no immunity to this virus in anyone under 30. In persons over 30 you are beginning to see some evidence of immunity . Certainly attack rates are lower, and you have some antibody that is being detected.

How do you explain this based on the fact that we have all been exposed to H1N1 viruses now, going back at least 30 years? The virus that reappeared in 1977 appears to be very similar to that that was circulating before 1957. I am having a hard time seeing how this spectrum of immunity has developed based on knowledge of what we have been exposed to in the past.

DR. COX: Thanks. That is a question that we have asked ourselves a lot. Our working hypothesis is that the viruses that circulated prior to -- during the 1930s and '40s had some common epitopes with this. So there were H1N1 viruses that were circulating. We had the Weiss 43 and the FM-147 viruses, which Ted will remember very well as classical H1N1 viruses that have been used often in the laboratory.

So what we are going to do to explore this hypothesis is to look at what kind of antibody exists in different age cohorts to see if there is cross reactive antibody to these older viruses, and if that could account in part for what we are seeing. We will look at the cross reactivity between a whole variety of the different antisera that we have developed to both swine influenza virus and swine origin influenza viruses in humans to see what that cross reactive antibody looks like, if it is there.

DR. MODLIN: Thank you very much. I certainly appreciate it. Let's move on. Dr. Jerry Weir is going to be giving us an update on manufacturing considerations.

Agenda Item: Manufacturing Considerations

DR. WEIR: Thank you. I am going to make a few very general and brief comments about some manufacturing considerations for the pandemic H1N1 2009 influenza vaccine. Most of my comments will apply to inactivated vaccines, but

I think you will also hear from the manufacturers later and you might hear a few more specific comments about manufacturing concerns and considerations.

A few minutes ago you saw a time line of the emergence of the virus in the spring of 2009. Shortly after that as the virus emerged there was a consensus that a recommendation needed to be made for what would be included in a vaccine for this virus if it continued to evolve. On May 26 the World Health Organization released a recommendation for the development of vaccine against pandemic H1N1/2009 virus.

Now, of note, U.S. public health agencies were represented in this body. That included both CDC and CBER. The statement that was released in late May was that the majority of the novel influenza A/H1N1 isolates are antigenically and genetically related to A/California/7/2009 H1N1 virus.

Should vaccines be prepared against the novel influenza A virus, it is therefore recommended that vaccines contain the following: An A/California/7/2009-like virus. You just saw data presented a couple of minutes ago that indicated that very little has changed since this recommendation. In fact, most of the isolates continue to be very similar and homogeneous and related to California/7.

In vaccine development for influenza viruses, it is

crucial that a reference strain be developed that is antigenically related to what has been recommended, but also suitable for manufacturing. Currently as of this week there are several available reference strains manufacturers can use. They include a couple of classical reassortants shown on the first line, one made by the New York Medical College, one made by CSL in Australia. There are also several reverse genetics or molecular biology derived reassortants. These include reassortants made by the CDC, by NIBSC in the United Kingdom, and one made here at CBER.

There was ferret safety testing done early in the epidemic to show that these reassortants were attenuated relative to wild type. In fact, ferret safety testing was done as I have shown here for X179A, IVR-153, RG-15 and NIBRG-121. All of these tests were completed and show that the reassortants were attenuated relative to wild type. There was a biocontainment committee hosted by the WHO that recommended that similar type reassortants would not need to undergo the same sort of ferret testing, as long as they were made in a similar fashion using similar donor strains.

I noted that reassortants for live attenuated viruses are produced by individual manufacturers. All of the reference strains listed here and all of the ones that are under development as additional reference strains are California/7/2009-like, and from a regulatory point of view,

both classical and reverse genetic reassortants are acceptable for vaccine production.

Now, as the reassortants were produced, a lot of development work went into determining how suitable they were for manufacture. At the present time, the development work has indicated that the existing reference strains that I mentioned on the previous slide have an expected yield of around 30 percent of a typical H1N1 seasonal vaccine strain. This has obvious implications, and the potential reduction in the current global vaccine production capacity estimates.

Manufacturers have expressed a desire and a need to the World Health Organization and our collaborating centers for better yielding vaccine strains. In fact, there are some additional reassortants that are in the process of being developed. Some of these use other wild type strains for the hemagglutinin neuraminidase. I listed a couple of examples, A/England/195/2009, A/New York/18/2009. Again, all of these reference strains are also A/California/7-like and would be suitable for vaccine manufacture.

I note a caveat here. At the present time there is no expectation that significantly better yields would result from the reassortants that are in process. That is simply based on the fact that wild type virus grew poorly and all the reassortants to date seem to grow poorly.

On the other hand, if a higher yielding strain is

found, additional clinical trials are not likely to be needed. That is based on the fact that these reassortants would also be a A/California/7-like.

One of the key manufacturing concerns especially for inactivated vaccines is the production and availability of potency reagents. Without going into the gory details of the development of potency reagents, I will just tell you that the potency of inactivated influenza vaccines is determined, are calculated in micrograms per dose of hemagglutinin, and that is determined by a single radioimmune diffusion assay. But it is standardized among the manufacturers using reagents supplied by regulatory agencies.

There are two components to the potency reagents. One is a reference antiserum and one is a reference antigen to which an HA value is assigned. The reference antisera is strain specific and the production of that antisera begins when a new HA can be prepared and used to immunize animals. High titer antisera of course usually requires multiple injections. The pandemic H1N1/2009 HA for injection into animals has been very difficult to isolate. The reference antigen is an inactivated whole virus preparation in which an HA value is determined by the collaborating WHO essential reference laboratories. These are four, CBER, NIBSE in the U.K., TGA in Australia and NIID. Production of a reference antigen is at an industrial scale and requires manufacturers

to be in production using a candidate vaccine reference strain.

This slide shows what we know today about the time lines for the availability of pandemic potency reagents for inactivated vaccines. At the present time we have reference antisera available from the NIBSC in the U.K. That has been distributed to the other WHO essential reference laboratories earlier this month. There was a reference antigen that was produced and distributed by TGA in Australia. This was also sent to the other collaborating ECLs earlier this month. Right now, calibration and assignment of the antigen values for the initial reference antigen is ongoing. The target date is still later this month. When that is available, that material can be used to evaluate clinical trial vaccines.

The reference antigen for U.S. manufacturers, we are still targeting the end of the month. What we will do in this case is, when another preparation of reference antigen is made available, it will be bridged to the first reference antigen by SRID in house with a small set of collaborating laboratories. The key here is that we don't go through the entire process of shipping it around the world to all four ECLs and starting the process from scratch. So it is a much faster process.

The final bullet. Preparation of reference antisera for U.S. manufacturers is underway. We are

currently evaluating specificity antisera and trying to optimize this.

Now, as far as the availability of potency reagents for inactivated vaccine. Due to the urgency of the pandemic situation, formulation of the vaccine for clinical trials is needed before these potency reagents are available and reagents are calibrated. We are taking a flexible approach to allow the use of alternative methods. I gave you an example of HPLC for potency determination of initial vaccine lots that can be used in clinical trials. Our plans are that manufacturers will test all vaccine lots by SRID, the traditional assay. When reference reagents become available, vaccine lots will undergo the complete usual testing and lot release procedures that we employ for all seasonal influenza vaccines.

So in summary, the emergence of the pandemic H1N1/2009 influenza virus has presented numerous challenges for vaccine manufacturing. As I said, you may hear some more of these when the manufacturers talk. Some of these challenges were expected and they were expected because we have been through an extensive pandemic preparedness planning for the last several years. These included things like the planned switchover and scale-up of manufacturing. The development of reference strains and reagents as well as things I didn't mention such as bio containment procedures

necessary when a new virus emerges.

As always, there is the unexpected. There were some challenges that have been unique to this particular H1N1 virus. These included the low yields that we have seen after the reassortants and even the difficulty in the isolating of HA for antisera production. But nonetheless, I would like to close and note that we have had an extraordinary interaction and cooperation among the manufacturers, public health agencies and national regulatory authorities to address these difficulties.

DR. MODLIN: Thank you, Dr. Weir. Why don't we go on to Dr. Sun's presentation and then we will open this up for questions for both Dr. Sun and Dr. Weir.

Agenda Item: FDA Regulatory Approaches and Activities to Support Use of H1N1 Vaccine

DR. SUN: Good morning. What I would like to do is discuss with you the ongoing work at CBER OERR in response to the H1N1/2009 pandemic.

In my 15 minutes I will describe the thinking that went into choosing the best regulatory pathway, describe the clinical trial design that we believe will address the key issues, and to introduce how emergency use authorization may play a role in the response to this pandemic.

You have heard that this virus is a new triple human-swine-avian reassortant, and that there is sustained

transmission outside of the normal flu season. There seems to be low antibody levels and higher attack rate among children and adolescents. That cross reactive antibody in the older age groups suggests that perhaps the older population may be primed, and the recent seasonal vaccines are probably unlikely to afford protection.

Fortunately in 2009 we do have multiple vaccines that are options that are available from several manufacturers. By way of a little review, the currently licensed U.S. influenza vaccines, we have a combination of inactivated as well as live attenuated. Note that not all the vaccines that are licensed have indications for the pediatric age group. That may be important later on in our discussions.

From a regulatory perspective, these are the available pathways for the use of a pandemic flu vaccine. Which alternative you choose is a function of the experience with the manufacturing process, the available clinical experience, as well as public health exigency.

Let's take the example of the seasonal flu vaccines. Annually they are licensed through a strain change supplement. For the inactivated vaccines, the submission is an application submitted under the existing license, accompanied with chemistry, manufacturing and control data. These usually include the passage history of the vaccine

viruses as well as hemagglutinin analysis and labeling information. For the live attenuated licensed vaccine, similarly it is under an existing license along with its CMC data. But there we do have limited safety data as part of the submission for the supplement.

This is the key decision. Dr. Baylor referred to it in his introduction. CBER will license the monovalent pandemic H1N1 vaccine made by licensed processes as a supplement to the seasonal vaccine license. Thus, manufacturers will submit a supplement to their seasonal influenza biologics license for the pandemic H1N1/2009 vaccine, analogous to the seasonal strain change supplement.

Licensure by the strain change supplement without new clinical data at the time of license relies on non-clinical as well as CNC information. The clinical data in the biologic licensing application for seasonal influenza vaccines, and this would include post-marketing experience from years past, for example. The age range, dose and dose regimen for the pandemic H1N1/2009 vaccine will be the same as for each of the licensed seasonal vaccines.

The vaccines will be formulated at 15 micrograms per dose of the hemagglutinin for the inactivated and about six to seven logs of fluorescent focusing units for the live attenuated. Note that this is applicable to the non-adjuvanted vaccines only when manufactured by license egg-

based manufacturing process.

Our rationales for this approach are listed here. In case of urgent public health need, this pathway we believe provides the most direct regulatory pathway to licensure. There are historical data that suggest that vaccines containing 15 micrograms of H1N1 antigen as well as the six to seven logs of the live attenuated would be immunogenic. The complete data from proposed clinical trials of inactivated monovalent H1N1 vaccines and post dose two of the live attenuated will be submitted post license. Modifications can be made as indicated by data from these post licensure clinical trials.

This approach was also taken in 1986 when a drifted H1N1 appeared in the March to May time frame. This was the 1986 H1N1 Taiwan strain. In this particular example, there was also an effort because of the appearance of this virus that promoted development of a monovalent supplemental vaccine to the seasonal for that year.

The H1N1/Taiwan represented a new antigenic variant of the H1N1 at that time. The monovalent H1N1/Taiwan vaccine was licensed and considered a strain change. The H1N1/Taiwan strain in '86 was licensed as a supplemental vaccine to each of the manufacturer's license application for seasonal trivalence without new clinical data.

We recognized very early on that we will need a

vaccine that can be deployed in case of a second wave of pandemic early fall, and that we need to be prepared for the implications for population that mostly is probably immunogenically naive to this virus. Time is not on our side.

So we actively engaged the licensed manufacturers moving forward. There was fair agreement that this vaccine probably should also be a monovalent supplemental vaccine. The clinical trials should be designed to inform dose, dosing regimen and safety.

We communicated a common design to the licensed manufacturers. These clinical trials are randomized double blind control dose ranging studies. Two doses should be given at an interval of 21 days. There should also be, especially in the earlier trials, to look at immunogenecity after the first dose, so we can get the earliest possible information. The age range from six months and above with different strata.

We recommended that adult and pediatric studies be conducted concordantly. Also for those manufacturers with adjuvants we recommend evaluating the vaccines comparing unadjuvanted with the adjuvanted.

The target should be for the earliest possible start of these clinical trials. We also recommended that these clinical trials be conducted under U.S. IND.

This is a summary slide of the clinical trial basic design. It really seeks to answer some of the clinical questions. One, is the standard dose for seasonal sufficiently immunogenic? Two, which age groups will require two doses? Three, is the adjuvant really dose sparing?

The limited sample size which you see here, about 100 per arm, will provide descriptive statistics and represent the minimum required for precise estimation of proportion of seroconversion. It is a balance between the alacrity with which we can conduct these trials versus getting sufficient information to make decisions.

The end points for these clinical trials are primarily immunogenecity, 21 days post vaccination, the proportion of sero negatives with HAI greater than one to 40, the proportion of positives with 24-fold rise in HAI antibody. We wanted to look also at GMTs and some other exploratory end points such as the day 14 immunogenecity after vaccination, and also looking at microneutralization titers.

Other end points. On safety, solicited local and systemic events in seven days and onset of unsolicited SAEs, new onset medical conditions and follow-up from six to 12 months. For those with adjuvants we recommend a 12-month follow-up.

Next I would like to give a brief description of

the emergency use authorization. This is a special pathway for medical products to be used before they are approved. Under the Section 564 of the Federal Food Drug and Cosmetic Act, the emergency use can be authorized if there is a declaration of a national emergency by the Health and Human Services Secretary. This was done on the 25th of April, which preceded the declaration of the pandemic.

Two, the FDA Commission in consultation with the Directors of NIH and CDC, have to determine that there is a serious life threatening condition of disease, that based on scientific evidence, the product may be effective, that the known and potential benefit outweighs the risks, and that no adequate approved or available alternative exists.

The possible scenarios for the use of the pandemic H1N1 vaccine under EUA would include for example vaccines with adjuvants, which would be an unimproved product. It would also include use of approved vaccines for unapproved age. This would be an example of unapproved use of an approved product.

To summarize. The 2009 H1N1 pandemic is a declared national emergency. The severity of the ongoing disease in the U.S. so far seems comparable to seasonal, but the course and severity of the pandemic in the fall are unpredictable. We have to plan for the worst.

The unadjuvanted, inactivated and live attenuated

manufacture using the licensed egg-based process have a proven track record of safety and effectiveness with the current formulations. The licensure of a supplemental monovalent pandemic H1N1 vaccine as a strain change is consistent with our previous regulatory actions.

A strain change BLA supplement formulated at 15 micrograms pe dose of the hemagglutinin and ten to the seventh for the live attenuated will allow for the earliest availability of licensed vaccines. Clinical trial design is for developing early immunogenecity data to inform dose and schedule modifications if necessary.

The regulatory pathways have been developed for all vaccine options in case of a population immunization program. Lastly, we will need post-marketing surveillance and safety assessments of vaccine effectiveness.

So this is really our bottom line. The desired outcome for us is to facilitate options and flexibilities for the policy makers.

I would like lastly to acknowledge the large H1N1 team within the Office of Vaccines, and there are probably other individuals, but these are within the Office of Vaccines, and they have all been great contributors to this effort.

Thank you for your attention.

DR. MODLIN: Thank you, Dr. Sun. I know we are

running late, but both Dr. Weir's presentation and Dr. Sun's presentation are really at the heart of why we are here today. So I think probably it would be a good idea to take some questions and comments now before we go on to the NIH presentation.

DR. RENNELS: I have a question. Maybe, John, it is better for the discussion this afternoon, but the question is, does the severity, the clinical severity of the current pandemic disease at this point, does it fall under the category of serious and life threatening?

DR. WEIR: Who are you asking that question?

DR. RENNELS: Well, I guess to Dr. Sun, since he was the one discussing when an EUA could go into --

DR. SUN: At many levels a decision is probably made, at a policy level but also on a medical basis. I think a disease that causes widespread morbidity and mortality in some populations would be considered a serious condition. That is my view.

DR. MODLIN: Peggy, could I have a go at that? Well, let's leave it until this afternoon. I think it is an excellent question.

DR. RENNELS: Yes, I think so.

DR. MODLIN: But an important one. We will definitely revisit that.

DR. DEBOLD: In the trials were you are discussing

using adjuvanted vaccines, is alum and traditional alum based adjuvants being considered? If not, why not?

DR. SUN: The current U.S. licensed vaccines, there are no alum in those vaccines. I know that the adjuvants that are being considered include alum, at least in the U.S. There have been other manufacturers who have tried alum with their flu vaccines.

DR. MODLIN: Vicky, in brief, studies with avian influenza, H5N1, there those that have been supplemented with alum have not been very successful. It is proven it is not a very successful immunogen so far, so I think just based on that recent experience there has not been a lot of enthusiasm for moving into alum as an adjuvant for the current vaccine. I don't know if anyone else wants to address that. But Phil is nodding his head. I think that is the basic problem.

DR. ROMERO: In your fourth slide you reviewed the currently licensed vaccines in the United States. Based on what we heard regarding the 70 percent reduction in the yield of these current strains. Do the producers of vaccines that would be available for children and in particular those vaccines for kids greater than six months of age, do they think they can meet the demand for the vaccine here?

DR. SUN: I think that is a question that probably we will go over later on when Robin speaks, so I am going to defer that question on the slides in Dr. Robinson's talk.

DR. DE STEFANO: You said that the vaccine may be approved before maybe all of the clinical trials data are in, and that changes could be made later from the evidence. How does that work? What is the timing? Any modifications being made before the vaccine is actually distributed for use?

DR. SUN: I think I heard how these modifications after the clinical trials may be made?

DR. DE STEFANO: Yes. I think you said that -- as I understood it, the vaccine may be approved before you have complete data in from the clinical trials. Then there is the possibility to make modifications later. Is that correct?

DR. SUN: I think the current recommendation would be to use the same dose as the seasonal obviously, going forward. But if we were to find for example in these clinical trials that it deviates substantially in terms of immunogenecity from what we expect, then I think there will have to be a recommendation made, for example, instead of one dose, maybe two doses.

DR. DE STEFANO: My question is, is it feasible to do that within the time frame, to make changes?

DR. SUN: I think that it is certainly feasible to increase the number of doses. I can't speak to how difficult it would be later in the season, how you would change formulations to have higher antigen content. But I think that is certainly still possible.

DR. MODLIN: Norm, did you want to add to that?

DR. BAYLOR: Just a couple of comments on that, Frank. What we are trying to do is make the vaccine available. As I said in my introduction, as far as recommendations to use the vaccine, that is a different discussion.

But also, there are many uncertainties, as I presented in my introduction. This is one of those uncertainties. We go with the knowledge we have. We know that a 15-microgram dose of hemagglutination for an H1N1 virus has worked in the past. So we are basing it on what we know. But there is that uncertainty that the data could show that there needs to be modifications made.

I think all of the government, the manufacturers, will have to determine. Those discussions are going on now, what will be the contingencies if this doesn't work. So again we are trying to do what we can based on what we know at this time. But there may have to be adjustments made as we move forward.

DR. MODLIN: Roland, did you have a question?

DR. LEVANDOWSKI: More of a comment. It relates to your question earlier as well, in terms of one of the slides in this last presentation, talking about cross reactive antibodies. Although it seems pretty clear that the current vaccines don't produce antibodies, or that people who have

not been exposed to the right strains don't have antibodies that cross react with these newer H1N1 viruses, I'm not sure that the absence of antibody means no priming.

I think that if you look at the other studies with H1N1 vaccines, and also with H5N1 vaccines, it is clear, there seems to be a principle that there can be individuals who don't have antibody that you can detect initially that respond very well to one dose of vaccine.

So I mention that. It is probably something that we will discuss later on a lot more.

Also, in terms of the clinical trial design, I note that we are now looking at day zero and day 21 for the dose interval for the two doses. That is reasonable. It is something that is done in Europe and elsewhere. The only concern I would express about that, even at this early time, is that if there is a need for individuals to get both the trivalent seasonal vaccine and the supplemental vaccine if they are given at different intervals, it may cause some confusion.

That is in relation to what was brought up about the Taiwan/186 supplemental vaccine previously. A big problem was that it was late, but an even bigger problem was that there was a lot of confusion about what to do with that vaccine, who should get it, and that communication piece for administration of a vaccine like this I think is going to be

extremely critical. It is apart from the licensing considerations that we are talking about here, but it does relate to it, since it is going to be part of the package insert; use the vaccine this way. It will need to be carefully considered at all levels, I think, in terms of how to make sure that there is smooth operation for delivery of all of these vaccines.

DR. EICKHOFF: Just a quick question for any of the FDA folks at the table who would care to respond. Supposing the clinical trials suggest that we ought to be thinking in terms of 30 micrograms per dose rather than 15. Can that adjustment be made within the -- can that be done under the same license? This is not even a strain change, just a dose change.

DR. BAYLOR: That's a good question. If we look at the trivalent, the TIV, that vaccine has 45 micrograms of hemagglutinin in it. So we would go with the strain change. I think the regulatory parameters will allow us to use a strain change looking at a 30-microgram.

Again, this is a supplement to the licensed application, and supplements to licensed applications include changes to that application. You raise that level to a biologics license application where there are significant changes or due product, what we would determine as a new product. This would be a change. Until this change could be

-- whether it is 15 or 30 microgram or 45 microgram, this change is a supplement. It is a change to that current application. So the 30 micrograms, those are included, that dose is included.

DR. EICKHOFF: So we could theoretically go up to 45 micrograms?

DR. BAYLOR: From a licensing perspective, yes. As far as from a scientific perspective and a practical perspective, that would need to be discussed. Again, how practical would that be? That is something that we can discuss later on today in some of the discussion points. But again, to answer your specific question, we could do the 30 micrograms under a supplement.

DR. JACKSON: A question for Jerry. For those of us who are not so familiar with that end of the process for vaccine manufacture, could you summarize what you think the main implications of the issues with the potency reagents are? What do you think will happen? When will they be available, how long does it take to do whatever is done with them?

DR. WEIR: I gave you the best guess on time lines. It obviously changes every week. I do think that they will be available at least in limited supply within the next few weeks. But if you note, I also pointed out that we are taking a pretty flexible approach to letting the trials

proceed using alternative methods. I think we have a reasonable plan in place such that everything can be back calculated into what really goes into the trials and a dose finding range from the trials will generate the information that we need.

So at this point in time, I am still optimistic that it will all work out with the reagents.

DR. JACKSON: When you say trials, are you talking about pre-release testing?

DR. WEIR: The trials will start before we have the actual SRID reagents available. So that means manufacturers will formulate based using a method that traditionally they have not used.

What we are asking them to do is, when those reagents become available, hopefully within the next few weeks, we are asking them to go back, assay what went into the trials. My guess is that they willing get a different number than what they think they put in, simply because the techniques will be different. But we have asked them to first of all be conservative in their estimates and how they calculate using their alternative method. I think every one of the manufacturers is set up so a dose range will cover several ranges. So what I think will happen is that they will get an immune response related to the dose they think they put in, an then they will get one related to an immune

response to the newly calculated numbers when the reagents are available.

I think we will get enough information like that to be confident that we have an immune response that is sufficient to a particular microgram of HA that was put in.

Did I complicate it too much?

DR. JACKSON: When you say trials, are you talking about human trials?

DR. WEIR: Yes.

DR. JACKSON: So vaccine will be released to start evaluating prior to the usual stages that are done before a vaccine is released, as far as --

DR. WEIR: I'm sorry, say that again?

DR. JACKSON: I'm not sure, when you say trials, are you talking about vaccine --

DR. WEIR: Clinical trials.

DR. JACKSON: Clinical trials of human volunteers.

DR. WEIR: Yes, the ones that we are proposing to start within the next few weeks.

DR. MODLIN: Thank you. We are running behind. I think we can make up a little bit later on, but I am going to suggest that we take our break now. Let's make certain we are back at 10:35 on the dot. Thanks.

(Brief recess.)

DR. MODLIN: Before we start with Dr. Lambert's

presentation, I believe, Norm, you had a couple of clarifying comments that you wanted to make before we get started.

DR. BAYLOR: Yes. I wanted to clarify some potential confusion over the lot release reagents, referring to your question, Lisa.

As far as the lot release reagents, lot release reagents are prepared to test the potency of the vaccine. Those reagents are in the process of being prepared, and normal process of lot release will occur when the vaccine is ready. So our normal lot release determining the potency of the vaccine.

In our discussion earlier when Dr. Weir presented, the alternative methods we are going to use for determining the potency of the vaccines that are going into the clinical trials, because those lot release reagents are not quite ready yet. Then there will be a recalibration to the data that we obtained from the potency of the lots in the clinical trials. So that is what we are trying to do.

I hope that is clear now. But again, the alternative procedures are being used to determine the potency of the lots that are going into the clinical trials. When these vaccines are released for distribution, they will be released as we normally do. Potency will be determined by the SRID as we normally do every year for our seasonal influenza vaccine.

DR. MODLIN: Thanks, Norm. Let's go on. Our next presenter will be Dr. Linda Lambert from NIH, who will be giving us an overview of the clinical studies that NIH is planning. Dr. Lambert.

Agenda Item: Overview of Clinical Studies by NIAID/NIH

DR. LAMBERT: Thank you. We would like to thank the organizers for the opportunity to present to you an overview of the studies that the National Institutes of Health will propose to conduct.

The outline of this presentation is an overview of the initial five clinical protocols, a brief update on our clinical trial infrastructure, and then a study that we started in June in response to H1N1 virus emerging, looking at generating safety and immunogenicity data in pregnant women.

The initial response to the H1N1 outbreak from one of the activities that we were involved in related to vaccine related issues were in depth and regular discussions with FDA, NIAID, HHS including BARDA.

As you have heard from Dr. Wellington Sun, the FDA took the lead on licensure discussions with the companies, HHS through BARDA on the U.S. H1N1 vaccine supply, and in particular the U.S. stockpile and the clinical trial material that will be used in the NIH trials that I will be giving you

an overview of. NIAID was tasked to identify options for U.S. government clinical trial support and also to assess and adjust, if needed, our clinical trial capacity.

In the process of having those discussions as well as discussions and presentations in front of other groups, there were areas that were identified where NIAID could possibly help support this effort. The options that we put on the table were, if it was necessary, the NIH could get involved in conducting trials that would support licensure of products or the emergency use authorization of these products, possibly the evaluation of these products in special populations, to generate data that we have articulated as maybe helping informing policy or real world scenarios or gap areas.

Some of the areas that we identified in that category include accelerating the availability of data from one versus two doses in different aged populations. Clearly that continues to be an emphasis of having safety and immunogenicity data as rapidly as possible. The administration of H1N1 vaccines with seasonal influenza vaccines. There were some data that were presented at a WHO meeting suggesting that receipt of TIV vaccine prior to H5H1 vaccine blunted the H5N1 vaccine responses. Studies looking at different dosing intervals, the use of different adjuvanted products, and then mixing stockpiled vaccine with

adjuvants from different companies. So those were the identified areas.

What I am going to do now is tell you -- and these studies that I am going to present in the next few slides are the first five studies that the NIH is poised to conduct. But we certainly appreciate that there is ongoing discussions at this committee meeting, at ACIP and elsewhere to identify, are there additional areas that we need to address and consider.

Briefly, these five protocols in our discussions with HHS and with FDA. The data that the NIH is helping to generate at this time is not intended to support licensure. It is intended to be as complementary as possible to what the companies are planning to do in their own trials.

So as a brief overview, we are proposing studies looking at one versus two doses of unadjuvanted vaccine from CSL in healthy adults, and from Sanofi Pasteur in healthy adults and children, and then the co- versus sequential administration of TIV and H1N1 vaccine in adults and also in children. I am just going to briefly give you some more detail on each of these studies.

The units that will be conducting these trials, as many of you are familiar with, are NIAID vaccine and treatment evaluation units. They were first awarded in the 1960s. They have served the government as a ready source for

the conduct of clinical research. In fiscal year 2008 there were eight new awards that were made, and now we have got a series of subcontract organizations that increase that capacity. They bring with them a broad range of capabilities for different clinical trials of different candidate vaccines, different drugs, as well as the ability to do targeted surveillance and burden of disease studies. While the bread and butter of these units is clearly healthy adult populations, they also provide access to special populations such as the immunocompromised and pregnant women.

This slide is an overview of where those units are. It is Group Health Cooperative in Seattle, the Children's Hospital Medical Center in Cincinnati, the University of Maryland in Baltimore, Emory University in Atlanta, Vanderbilt University in Nashville, St. Louis University in St. Louis, Baylor College of Medicine in Houston, and the University of Iowa in Iowa City.

The protocols that we chose to move forward with first are the one versus two dose studies of an H1N1 vaccine in healthy populations. Again, the goal of these studies was to generate as quickly as possible data looking at safety as well as the immunogenecity of the vaccines.

The subjects in this study will receive two doses of vaccine, either 15 or 30 micrograms of the vaccine given 21 days apart. For the healthy adult study we are proposing

to conduct separate protocols, one with Sanofi Pasteur and one with the CSL vaccine in the different age ranges, adults 18 to 64 and older adults 65 and older. A pediatric trial and a separate protocol is proposed looking the Sanofi Pasteur vaccine in children in three different age stratum, so 100 per dose group in each of those age stratum, two doses, either 15 or 30 micrograms. The end points are safety and immunogenicity, adverse events and SAEs six months following the second dose, four-fold rises in proportion with antibody titers one to 40 or greater by HAI, 21 and 42 days after immunization.

What we built into this study to feed into the concept of the rapid availability of immunogenicity data were additional blood draws eight to ten days after each dose of the vaccine. We also expect, as we did with the initial H5N1 trials that the NIH conducted, we expect to look at a subset of vaccinated subjects. So we don't expect to enroll the 100 per group before we start looking at the blood samples at days eight to ten, day 21, post dose one and 21 days post each dose.

The lead PIs for this study from our VTUs are Dr. Pat Winukur and Dr. Karen Kotloff.

The second set of protocols that we are planning to is the co- or sequential administration of an H1N1 vaccine with the 2009-2010 formulation of the trivalent inactivated

vaccine. The goal is to look at the safety and immunogenicity of those vaccines The H1N1 vaccine, the study design is set to look at the H1N1 vaccine given before, after or co-administered at the same time with the TIV vaccine. Two doses. We propose to use the 15 microgram Sanofi Pasteur H1N1 vaccine. The administrations, whether you are getting H1, HI TIV or TIV H1, H1 or other combinations in co-administration. The doses are 21 days apart.

The study is proposed, one protocol looking at adults 18 to 64 and 64 years of age and older, and in primed children. Those are children over the age of nine and above and children who have received two doses of TIV in a previous year. The three age stratum for the previous protocol I described are the same here.

And studies in unprimed children, so children who are under nine years of age or who have not previously received two doses of TIV. We are finalizing that protocol and plan to conduct that study as well.

Similarly, the end points are safety and immunogenicity of the vaccine, adverse events six months after the second dose, and the same output for the immunogenicity analyses. The lead PI for these series of studies is Dr. Sharon Frey at our St. Louis VTEU.

The third concept which is in development is the

concept that we in close collaboration with others and an ongoing effort from the Department of Health and Human Services, as part of the pandemic preparedness efforts for H5N1. This has now carried over to H1N1. A significant part of the strategy is to assess the safety and immunogenicity of mixing stockpiled vaccine antigens and an adjuvant from different manufacturers.

We are developing a study to evaluate the CSL and Sanofi Pasteur H1N1 vaccines, mixed prior to administration with GSK's ASO3 study. That is again in close collaboration of study design with DHHS, who has the contracts in place for the procurement of the vaccines.

The protocol currently is designed as 3.75 micrograms of ASO3, 3.75 micrograms of the vaccine given with ASO3 and seven and a half and 15 micrograms of the antigen with and without ASO3. Two doses, 21 days apart.

The status of this project is that we are on track to submit an IND containing the protocol for the Sanofi Pasteur ASO3 combination study within the next week, and the CSL ASO3 study is to follow. The lead PIs for this series of trials is Dr. Lisa Jackson from Seattle Group Health and Dr. Kathryn Edwards from Vanderbilt.

I thought I would also tell you where we are with other studies, and also end with a study we started in June. We are interested in taking feedback from FDA colleagues,

HHS colleagues and CDC ACIP, I presume from this group as well, for additional H1N1 vaccine studies that the U.S. government believes are high priority. One of those that is in development right now is a protocol that we are developing to look at the safety and immunogenicity of H1N1 vaccines in pregnant women.

To end, one of the responses to H1N1 that we undertook was a trial that was initiated on June 11 in our VTEUs with participation from a lot of their subcontract sites, enrolling second and third trimester women with a single dose of the 2008-2009 TIV vaccines from two different manufacturers. The end points are antibody responses. As of yesterday there were 41 women enrolled. The PI for this trial is Shitel Patel at Baylor.

We were planning a follow-on study prior to the emergence of H1N1 to look at the 2009-2010 TIV formulations from the four licensed U.S. manufacturers. That was scheduled to start this fall. So depending on capacity and the need to get the H1N1 protocol moving along, that study may happen or may be deferred.

So with that, I will end, and acknowledge there is a significant amount of efforts underway from a large number of sources. Certainly our colleagues at DHHS. The H1N1 vaccines for the NIH trials are being developed and provided to us from HHS under contracts. Colleagues at CDC, FDA, the

vaccine manufacturers, and then the large number of individuals who work with us directly at the NIAID, our investigators and our different contractors for data coordination in our assay laboratories. I think certainly our independent safety committee members who met yesterday as a matter of fact on these protocols, and my colleagues at NIAID in my division.

Thank you.

DR. MODLIN: Thanks, Dr. Lambert. Let me ask if there are one or two quick questions for Dr. Lambert.

Maybe I could ask one. In terms of special populations, you and your colleagues in the VTEUs and elsewhere, is there any consideration of doing special studies in infants under six months of age? I'm sure that has been under discussion. I would just be curious as to how far along you are with those discussions.

DR. LAMBERT: You are absolutely right, that is a discussion that we have had since early May. At this point we can say that we have a protocol that is in house that is being reviewed internally. I believe we are close to identifying an investigator who would conduct that study if we need to do it.

So from our perspective, we are looking for feedback. That is a complicated issue. We have done a study with inactivated influenza vaccine with the 2004-2005 and the

2005-2006 formulations in a small number of infants under six months of age, so there is some published safety and immunogenicity data in that age group. So our perspective is that we are preparing that protocol, should we need to do that trial.

DR. DEBOLD: Who is going to be enrolled in the mixing and matching vaccines trial? What are the populations?

DR. LAMBERT: The study that I described includes healthy adults who are 18 years of age to 64 years of age, and elderly who are 65 years of age and older. That is the study design that will be going to the FDA within the week.

DR. MODLIN: Dr. Lambert, thank you very much. Let's go on to the next presentation, which is from BARDA, Dr. Robin Robinson.

Agenda Item: Overview of DHHS Procurement of H1N1 Influenza Vaccines and Adjuvants

DR. ROBINSON: Good morning, and thank you for the opportunity to talk to you about our vaccine strategy. What I will over the next few moments talk to you about is not only the strategy that was developed several years ago and how that has built the foundation as we have gone into the H1N1 vaccine planning and execution of that plan, but where are we as a result of doing the plan relative to the manufacturing of the product, and what are our expectations

going forward as of about 12 midnight last night.

Through a number of different events, November 2005 the national strategy for pandemic influenza was given birth, primarily from much of what happened with H5N1, some of the natural disasters such as Hurricane Katrina, and the poor immunogenicity of H1N1 vaccine that was seen in some of the NIH clinical studies. You get really alarmed as the capacity of products manufacturing for vaccines worldwide in the U.S. would be very, very limited if we had to go to war with an H1N1 virus. Then the HHS pandemic plans came out, and the implementation plan came out in May 2006, across the government, and even at those state and local levels where who would be doing what.

For this audience, there are two goals that have been our stalwarts going forward. The first one is that we wanted to establish a dynamic pre-pandemic influenza vaccine stockpile that would be available for the critical workforce of about 20 million people.

To this event, we have already passed it, so there is no pre-pandemic vaccine, or if the virus does change, then everything we will be making right now would be the pre-pandemic vaccine. But more importantly, we would be able to provide a pandemic vaccine for all citizens that wanted it within six months of a pandemic declaration. So two doses were needed and 600 million doses, a very lofty and

aggressive goal. We put together a five-year plan to be able to accomplish that.

One of the ways we did that was an integrated pandemic influenza product portfolio approach, with the vaccines for advanced development of cell based, antigen sparing, which gave us new adjuvants, and next generation recombinant vaccines, stockpile acquisitions for H1N1, and most importantly, an infrastructure building with retrofitting existing facilities, building new cell based facilities, which we would not be able to do right now if we hadn't provided a secure year-round egg supply for the vaccine manufacturers for the licensed products.

The H1N1 vaccine stockpile. Over the last five-year effort, about 22.5 million doses at 90 micrograms if we provided it with an adjuvant 7.5 micrograms, and that number would rise up to 268 million.

I put this intentionally in here, not to say that we have practice of doing this, but the H1N1 virus is still out there, it is still moving, and it is still causing deaths. So we shouldn't forget it.

This is an old slide, for planning purposes, when we would have a production capability to address 600 million with and without adjuvants. By 2011 with egg-based domestically here in the U.S. those manufacturers, we would be able to get 300 million courses that we would need, or 600

million doses. But what you see with the adjuvants, if they were adjuvant sparing, by 2009 we would be able to do that.

That is what we thought going forward, all the way up until about March of this year. That changed. The strategy we had would be very similar to what you would do with any emerging influenza virus that had pandemic potential. You would always be looking at the epidemiology of the virus, but vaccine development immediately would start. So that decision was made and it started with CDC, starting with the reference strain generation and going out to FDA and other laboratories. Then the clinical studies to follow on that would be manufacturing of the clinical investigational lots. But simultaneously looking at vaccine manufacture in the big red area there, and which I will be talking a little bit more about.

As Jerry Weir talked about the potency reagents, they had to begin as soon as possible. Then next will be the making of the commercial bulk vaccine antigen, and also the adjuvant. Why the adjuvant? Why now, even though we know it would have to be used under EUA? Because we wanted to give ourselves the greatest flexibility and the most choices, if the disease severity changed from what it is right now, or that the circulating virus antigenicity would be different from the strains that we have in our vaccines, and other reasons. So you couldn't wait until later on.

Then you have to go get the ancillary supplies. You can't wait around to buy the syringes and needles that you need in October; it will have to be done now. That is all part of the planning.

Then planning for the formulation sometime later in the fall, based on the clinical studies that are ongoing that Linda talked about earlier. Doing that, if the decision were made, we would then provide the U.S. government and the Department the ability to make some choices to go forward with an administration program. But you can't go forward with the program unless you do the planning. The CDC is moving forward with the states and locals on immunization planning, in anticipation that the U.S. government will do a vaccine program for this fall, which is why we are here.

In addition to the national strategy, the playbook has gone as we anticipated, but two notable exceptions. The first exception is that the H1N1 virus was not one that we had chosen. So the whole concept of pre-pandemic vaccines was out the window.

Secondly, the logistics of doing some of the more bureaucratic things have been more cumbersome than one would have anticipated, we have learned that. So I bring that up so it is part of your planning going forward.

But the approach that we had was that we had many on and off ramps, such that at any point we could stop and

say we don't need any more vaccine or we need to continue with it. Our overtures with the manufacturers were not only with contracts, but with letters of intent, so giving them an idea of overall, what did we want from them, being able to provide contracts with options that we would only buy so much at a time.

It has already been talked about, the licensure and the EUA issues for these vaccines. But again, the scenario sensitive issues are disease severity and the antigenicity of the virus. So as we go forward, key decision issues, and these are certainly not an exclusive list, but the prioritization of the vaccine for Sanofi Pasteur, the vaccine type which I will talk about in a moment, thimerosal preservative in or out of the vaccines and for what populations, whether or not we use the oil and water adjuvants, and then post immunization adverse events safety monitoring.

What would be the vaccine products going forward? If the disease and the virus moves as it has done through the summer, then we could have a standard vaccine that was U.S. licensed, and what would those look like. We see the multi-dose vial presentation from four of the manufacturers for the inactivated vaccine, and also prefilled syringes for single dose. Those prefilled syringes could be thimerosal free or trace thimerosal, and the sprayers from MedImmune for the

live attenuated vaccine.

If we go to a scenario in which adjuvants would be needed, then we could have a standard vaccine available early on and then as data became available from clinical studies to support A, the antigen sparing effects of the adjuvants and two, that provided the necessary cross reactivity that might be needed, then we would see the adjuvant from Novartis come as a preformulated product, as one vial, multi-dose, and then from a combo back from GSK could be combined with their own antigen, with Sanofi Pasteur's antigen and the CSL antigen, which the NIH talked about in the mix and match study. So you would take the adjuvant out of the vial, then put it into the vial with the antigen, shake it up, and then start removing your doses, not too different from what is done with diluent now.

These projections as we go forward would be if it continues on. This is based on our estimations that we thought from our H1N1 experiences that the manufacturer would probably get a low or poor yield. That has been borne out. That is exactly what has happened, as we are right now. Hopefully with optimizations in the new strains it may improve.

Secondly, this is at 15 micrograms HA per dose for the vaccine. The third is that this was without interference of the manufacturers for their seasonal influenza vaccine

manufacturing, including their field finish of the product.

So as we go forward, we would see about 160 million doses being available for the U.S. from the five manufacturers that we have contracted. Then each month about 80 million going forward. If you start looking at the calculations and the goal that I presented earlier, where would that six month milestone be? It would be December. We would not be at the 600 million mark, but that is where we would be. As we go into March, then we would get closer to that 600 million mark. So with the way that we are having to utilize the vaccine from all over the world, from manufacturers from Australia, from the U.K., from Canada and then also from the U.S., being able to provide about nine months.

If we were to provide adjuvant, then the data would be available such that it could probably come out in November. So we would have 160 million as licensed vaccine of the adjuvant alone formulation, and about 160 million for November-December, and then January. Then we are getting a little bit closer to the six month with the adjuvant.

Of course, this is all subject to change, if we see differences in yield, but also if we have other difficulties in the manufacturing process.

How much have we actually bought, so to speak, cash on the barrel, for the U.S. so far? We have bought

approximately 195 million doses of H1N1 vaccine. We keep this as bulk product until we know exactly how it should be formulated, so we do have that flexibility at this point. Secondly, the adjuvants we bought are 120 million doses.

Will we buy more? Right now we have bought most of the capacity that was available to us through September 30. We will be looking as we go forward with some changing events if they do occur through August to make further decisions to buy more vaccine and adjuvant.

How would the vaccine be distributed? This would be an effort led primarily by CDC. BARDA will be handing off with the five manufacturers the product from their fill finish manufacturing sites to a single entity McKesson, which is a wholesale distributor that has quite a bit of experience with seasonal influenza vaccine, and the vaccine would be at a number of different sites from there, and then go from McKesson, which uses the VINBIP (?) program that CDC has established for the vaccine for children. That vaccine has a central allotment and ordering system with the states. So that allows the states to interface with CDC to be able to get the vaccine out to them.

So it would go to state health departments, other entities within the states in a public way, but also private providers. So being able to go anywhere from 40,000 to 90,000 sites and about 30,000 parcels a day, would be what we

are looking at. Then of course is 300 million the right number or is it less than that. I think what you are saying in many countries including us is there is a number less than that. But certainly what will be talked about next week would be the target populations that would receive a limited supply of the vaccine going first.

I leave you with the thought that where we are right now is the egg-based vaccines. It could be for certain situations or EUA we might have to use cell based vaccine, maybe one or two manufacturers that may be far enough along that they consider that. But whether or not we use adjuvants, that is the pathogenicity which we can watch and maybe predict a little bit, antigenicity which we can watch and maybe predict. But when we only can look at what has happened previously, but it depends on whose crystal ball you have. Then where would that vaccine be delivered in that peak or pre-peak or afterwards.

I'll stop there. Thanks.

DR. MODLIN: Thank you. Questions for Dr. Robinson?

Agenda Item: Questions/Clarifications

DR. GELLIN: Robin, there is a lot of confusion, speculation and misinformation about doses, availability, timing, time lines. It would be helpful for everyone -- that is the slide I want you to look at, to look at that and put

that in the context of what we heard this morning about the yields and the virus, and what this means for potential availability of finished vaccine that would be available for an immunization program.

DR. ROBINSON: Thanks, Bruce. The 30 percent of normal yield for H1N1 human viruses for vaccine manufacturing is a number that is not too far from what we had projected to begin with. In the manufacturing terms you hear number of doses per egg. So we had pegged 1.4 doses per egg. So we are hearing anywhere between 1.3, 1.4, a little above that, a little below that. So we are right here. If for some reason it goes below that, then these numbers all start falling and they start shifting to the right as to being available later.

So that is the ground truth of where things are right now for the inactivated. MedImmune will probably talk a little bit this morning about their experiences with the amount of vaccine doses that they are receiving from their production. It is greater than anticipated, so we are procuring vaccine, not only the inactivated but also the live attenuated.

Usually one of the questions we have had recently is, what do we have vaccine earlier than October. If the vaccine were licensed and the decision were made to go forward and we needed to go earlier, say in September, we probably would not be able to go much earlier than the middle

of September. There are several reasons. One is, when the manufacturers will have their formulation and fill plants available, coming off of seasonal influenza vaccine manufacturing to be available for H1N1 vaccine. So that is the consideration. We really don't want to interfere with that unless there is absolutely no other way we can do it.

Secondly, there will be less. As we go into production in September there are more production plants going at full capacity as we go into late August, into September. So you will see the numbers would go up. So the amount that we would have there would be much less than the 80 million per month that you see in November-December. It would probably be in the order of 30 to 40 million.

DR. EICKHOFF: Given that 30 percent yield estimate, at what point does the whistle get blown and we decide yes, we need an adjuvant vaccine?

DR. ROBINSON: This is the real crux of the matter, one of the hardest decisions that we have in front of us going forward. As Bruce has indicated, this is one of the reasons not only for this advisory board but others. We are posing that question to you, what do you think of some of the factors into that. So do we have a decision tree laid out, what the decisions, how would we make the decisions? Yes. Who would make the decision? I think that is pretty clear, who those people would be.

The part that we have not reconciled and we are working on right now is how we are quantitating the amount of risk and the benefit there. So that is a key issue that we have got to grapple with over the next 30 days, basically.

Are we going to have any more data from the severity or the virus being changed? Possibly. If it clearly does that, then I think it pushes us towards that. If it doesn't, then it becomes, can we have enough vaccine for the targeted populations and what will be the demand going forward.

We have planned all along with H1N1 and other pre-pandemic exercises for the worst case. This is not the worst case right now. So it is much more difficult to make in the gray zone area that we are in right now. So your question is very cogent.

DR. RENNELS: A quick one. Who will make the decision?

DR. ROBINSON: Ultimately it will be a decision by the HHS Secretary and input from the advisory councils and others at the White House level.

DR. DEBOLD: I was reassured to hear Dr. Cox say that the virus has been antigenically fairly stable. If the virus stays on that trajectory and we don't observe significant mutation, what is the plan?

DR. ROBINSON: If the virus doesn't change and we

don't see a change in severity at this point, then this would be scenario A.

DR. DEBOLD: So we would go ahead with plans to begin vaccination even if the virus stays as it is?

DR. ROBINSON: It is likely to. The summit that was two weeks ago, the Secretary talked to the state and local health officials. She gave indication that we are moving in that direction right now.

DR. MODLIN: How long does it take the manufacturers of the process to go from bulk antigen quantities to having vaccine available to the end user, let's say to the state?

DR. ROBINSON: We are going to break that down just a little bit. The formulation and fill finish is for a process of days. Then the QC testing is several weeks. There is one test that takes two weeks, and you can't change that. Then the review and QA release of the product. So we give that about four weeks. That really can't be expedited too much more than that. Then getting it to the distributor and out to the states after that. So we are probably talking about another seven to ten days.

DR. MODLIN: So we are talking four to six weeks, would be an estimate there.

DR. ROBINSON: That's right.

DR. MODLIN: Any other questions or comments? Dr.

Robinson, thank you very much. I'm sorry, Bruce.

DR. GELLIN: Robin talked about the decision maker, but there are a lot of inputs to this decision. There are a number of different federal advisory committees, and each has a piece of this. I think among the recommendations that come is from advisory committees like this, that would feed into a decision.

So here we are going to be discussing different regulatory pathways for different formulations. Those are the kind of things that will fold into this decision as well. Next week ACIP will weigh in. There are other advisory committees that you may have heard of. The National Defense Science Board made some recommendations on vaccine, especially on potential vaccine availability separate from when you might use it, but have vaccine potentially available. The National Vaccine Advisory Committee has a particular focus on overseeing the vaccine safety monitoring system and some financing issues.

So I think that is the spectrum in the existing federal advisory infrastructure that the Secretary is going to be looking towards in addition to all the other places where she will get advice.

DR. MODLIN: Thank you for that comment. Let's go on. The next presenter is Dr. Hector Izurieta from the FDA, who will be telling us about the postmarketing safety

monitoring. It is very apropos to Bruce's last comment.

Agenda Item: Post Marketing Safety Monitoring During An Influenza Pandemic/Post Marketing Collection of Effectiveness Data

DR. IZURIETA: I am going to discuss preparedness to monitor safety of the pandemic H1N1 vaccine. This is a collaborative work. I will mention a short number of many who have helped here.

There are a number of potential issues, and you have discussed most of them. I will not delay on that. This is a new vaccine strain, monovalent vaccine expected. There could be a potential for use of novel adjuvants. We are not going to discuss this at this point, but that is a possibility. Large numbers of vaccinees are expected in different age groups. We expect most age and race groups represented among vaccinees, and a relatively rapid vaccine administration if things go as expected.

There will be, and there is already high public attention and expectation for safety surveillance. That has very good things. It strengthens our capacity. There is an expected increase in reporting of temporarily associated events regardless of causal association to vaccination compared to even seasonal vaccine, meaning if something happens to somebody after vaccination the vaccine will be accused, whether the vaccine is guilty or not. That is

something that we have to elucidate, and it is not going to be easy or simple.

We have made significant improvements in a relatively short time. As Nancy Cox has presented, the first U.S. case occurred in April, and the evolution of our surveillance efforts have been magnificent as we take into account the short time we have had to prepare. We have made improvements already in passive surveillance systems, the adverse events reporting system mainly, including data mining, availability of personnel and the timeliness of analysis.

We have enhanced surveillance for pre-specified adverse events, identified based on prelicensure safety data, published literature, post licensure safety data with seasonal or other influenza vaccines, and the available international data on pandemic 2009 vaccines, based on our interactions which are stronger and stronger, with international and other partners.

For this movable situation, we need adoptable tool box to do surveillance. Our strategy is to do enhanced more timely pharmaco vigilance for signal detection identifying suspects, basically, signal strengthening and verification, meaning there will be many, many reports of things that could be or not associated with vaccination. We have to confirm whether there is an association, verify whether that

association is or is not significant, and then go into confirmation of that association. For rare adverse events that is increasingly difficult and means increasing time.

We have increased communication and collaboration among U.S. agencies as I will show, and also international. In regards to methods we are trying to use similar comparable methods so different databases can work together on case definitions, even specific outcomes of interest, and we are making very significant efforts in sharing of preliminary safety surveillance under the leadership of our civil director and others.

There are efforts for signal validation and confirmation of potential associations interchangeable, meaning that if a database in Europe finds something we will try to verify that in databases here, and vice versa. So these collaborations have potential.

I will try to very briefly summarize what our tool box is now. Please understand that this is evolving as we speak. More collaborations, more work is being done today and tomorrow.

The Vaccine Adverse Event Reporting System, for those who don't know it very well, has a number of strengths. Near real time reporting, rare or unexpected adverse events are often reported, and there is lot surveillance and we do data mining, so we mine data finding strange and unusual

signals. The population is nationwide. It is passive surveillance. It depends on who wants to report. Manufacturers are obligated to report nonetheless, but this is not a probability sample of the population. That is why we call it signal detection. There is under reporting and even consistency and completeness of reporting. There is known denominators, who is reporting, who is not, among the vaccinees. There are no standard controls. There are a number of reporting biases that many of you already know. The report could be and we expect will be stimulated given the attention given to H1N1. There are potential increases of report, and we of course need and we are obtaining medical offices for review. We are improving data mining and the signal verification. They will serve VAERS' expected analysis, meaning how many cases have you observed in the databases, how many we could expect given the size of the population vaccinated.

There are other systems that have been used. The Veterans Administration for instance has electronic data on vaccinees and among the health personnel, 300,000 or more. They will try to capture the proportion of vaccinees seeking health care in the VA system. This is not 100 percent sample, but they are planning similar efforts for the whole population of the VA as well.

We have a number of tools for what is the most

difficult task, which are the strengthening, the verification and the confirmation of those numerous signals that will come to us. One of them is the oldest system in our tool box, which is the Vaccine Safety Datalink, organized and managed by the Centers for Disease Control with some little assistance from us. Frank DeStefano, who is here, is one of the first people who worked on these databases. Others at CDC and in other institutions also are represented here at the table from other VSD centers.

It is near real time. It is a very experienced group. They have more than nine million members. Most ages are represented with a large proportion of children, and there are of course issues regarding ascertainment of vaccination, depending on how the vaccine distribution works. The HMOs and the managed care organizations that make part of this system will or will not have the necessary data available to know who is vaccinated and who is not, and therefore be able to data mine who among those cases has been or not vaccinated.

That is an issue that I will repeat and repeat until everybody gets bored with me on this. We need to know who is vaccinated and who is not among the people who have and not outcomes.

The Medicare system works with substantial help from Jeff Gelman and others and others. FDA has worked since

2002 on this, and since 2006 we have pilot tested this system. It is also a near real time surveillance system. It is one of the largest databases in the world, complex, and it is a claims based system. So 38 million members among the elderly. We need to know among this system who is vaccinated. The claim for vaccinees has to get to Medicare for Medicare to know who was vaccinated, and then we can put our system in place. The system is in place, whether we can make it work well.

The Department of Defense collaboration. There are some of our collaborators present here. It is a very strong system. They are expected to be among those who receive vaccinations at the beginning of the distribution system. Approximately 1.3 million active duty personnel, probably 200,000, 300,000 more are vital civil servants, among those who will be vaccinated at the beginning. Very strong database, access to medical records and a strong collaboration between FDA, CDC and the Department of Defense to provide safety data on this population.

New collaborations with the Indian Health Service, which have more than one million members, electronic databases. We will need Indian Health Service to have data on who is vaccinated and who is not in order for the electronic medical record system to be used for surveillance of adverse events. So we need to increase their capability,

but there is a strong willingness to collaborate, and this is an important minority population.

The Vaccine Safety Datalink as I said is sponsored by CDC. It is focusing on timely identification and rapid assessment. Nine million individuals, sequential and analytical methods to be used meaning near to the time in which the event occurs. As time goes, as vaccinees increase, as cases increase, we will monitor whether the cases that occur go or not beyond an expected threshold. Let's call it an alarm ring to see whether we should do more aggressive data verification, more traditional cohort case controls, et cetera.

There will be appropriate comparison groups. As I said, there is a lot of experience there. Also, it requires a great vaccination information link to the outcomes.

Other CDC tools; Emerging infectious program for special studies, collaborations with the American Academy of Neurology for reporting of Guillain-Barre syndrome, similar to a system that is being implemented in Canada as we speak, field investigations. CDC has a large capacity for field investigations with EAS officers. And the collaboration of the CISA, Clinical Immunization Safety Assessment group, for verification of cases.

The FDA-CMS collaboration. As I said, thanks for all the assistance from CMS since 2002. We started this work

to develop the capability for electronic safety monitoring using Medicare data. The pilot project which took place in 2006, which is exemplified here, shows that we can receive weekly data from Medicare and analyze the vaccines. As you can see in the first graph, the accrual of vaccinees allowing for a small delay in claims, and as their accrual in vaccinees grows, the accrual of number of GBS cases among vaccinees will be shown.

In the second graph in blue, you can see that we had around October the first case of this sentinel disease, in this case GBS, among the first 325,000 vaccinees. So the first signal appears to be a positive signal because very few vaccinees have yet been accounted for. But as the surveillance progressed in time, the signal stabilizes. In this pilot study we see the signal stabilizing at the rate which is as expected. So there is no alarm here, there is no positive signal. This is a negative study, but in any system, even in a system that has 38 million population, we really need to let the system work. Time has to do its work for us to know whether there is or not a problem.

The Department of Defense collaboration. This is a very busy graph, but I will try to walk through it very, very quickly, just for you to have a feeling for what we are doing with the Department of Defense.

We have on the left pre-specified adverse events,

which are adverse events that we think will need surveillance regardless of whether we find or not signals. We are basing it in prior history or influenza or other vaccines.

On the right is a larger group of adverse events that we think need surveillance. To this list we can incorporate new adverse events as people report through the passive surveillance system and others. So on the left-hand side we will add with respect to retrospective cohorts to estimate background rates. We are doing that right now this week with the Department of Defense collaboration. Then we will do listing of cases, vaccine dose statistics and check for positive signals, then to enhance surveillance using what we call rapid cycle analysis using max BRT, which is a method developed by Martin Colder from Harvard and others. and check for positive signals. These will be in coordination with the Vaccine Safety Datalink project, so specifically for this purpose of rapid analysis, the Department of Defense system will be part in a certain way of the VSDL system, which has a huge experience in this.

Also, we will use other surveillance tools, data mining for specified and non-specified adverse events. If a signal is detected for any event, we move it to the rapid cycle analysis or directly to the self control, case control or cohort study. So it is a little complex in appearance, but it is going to work.

There are a number of considerations as I said already regarding vaccine administration. I would like to repeat that again. Distribution and administration of vaccines are likely to vary by state, by city and by county, and the usefulness for safety surveillance will also vary. The more consistent the distribution, the better accountability of who is vaccinated and who is not in each system, the better surveillance we can work with.

There needs to be linkage of vaccination data. We call it exposure to outcome data, the disease, the medically attended event. This is essential for the capacity and the timeliness for detection and evaluation of safety signals.

In summary, this pandemic preparedness has done good things for us. It has enhanced our capacity for timely signal detection, verification and confirmation, and these gains can be applied for pandemic vaccine and for any other vaccine surveillance.

We have strengthened our collaboration and communication, not only among government agencies in this short time, and also internationally. This also has potential for improving vaccine adverse event surveillance for many other vaccines.

There is of course variability in data quality and in timeliness in the different systems. We have to acknowledge and recognize that. The timely availability of

conclusive post-utilization safety data does remain a challenge, given the following: Expected rapid vaccination period, questions regarding vaccine distribution and recording, as I have repeated several times so far, and the rarity of expected adverse events.

We have a population that expects us to provide safe vaccines and we are working for that. But the more rare the disease, the more time, the more data you need to know whether there is or not a problem.

I would like to acknowledge all the collaborators from the different institutions, including CBER, the Department of Defense, CMS, Senior Health Service, and particularly CDC.

Thanks.

DR. MODLIN: Thank you, Dr. Izurieta. Are there questions or comments?

Agenda Item: Questions/Clarifications

DR. RENNELS: One comment. It really is impressive how the safety surveillance has evolved over a brief period of time. But there is one partner that I see missing, and that is industry. The manufacturers feel very strongly that they need to be involved in safety evaluation of their products.

DR. IZURIETA: This presentation was focused on the government work and the international collaborations between

us and WHO and other regulatory agencies. That is how we have focused. But we do acknowledge the collaboration of industry, both in the clinical trials and in post-licensure. More specific discussions are ongoing regarding where else they could contribute to.

But they have been active, and we consider them partners in this effort. They have done their share and we expect more from them. But this presentation is not focused on their particular. I don't know if somebody else from FDA wants to comment besides that.

DR. MODLIN: I guess not.

DR. EICKHOFF: Do you or perhaps someone from CDC have any estimates of the capacity of the health care community broadly defined, physicians' offices, clinics, non-traditional sites of all kinds, to actually deliver vaccine into people on a per day or per week basis?

DR. IZURIETA: That could be CDC. Melinda?

DR. WHARTON: I don't know, Ted, that I have a specific answer to your question, but even when the ACIP was considering the expansion of seasonal immunization to children throughout school age, the whole issue of capacity of the traditional immunization system to provide that we really have a lot of concerns about, and feeling that just in terms of routine seasonal influenza, to add all that immunization onto what the health care system was doing was

going to be enormously difficult.

Our assumption was that it would be implemented gradually over time. The capacity would improve. We would find ways to be efficient. I don't think at this point any of us have -- we don't know what the recommendations are going to be in terms of which populations will be targets of any immunization recommendations. We also don't know of the targeted populations how many of them are actually going to seek immunization.

So I don't know how many people will end up being vaccinated of whatever groups are targeted, regardless of what capacity issues we may have.

DR. MODLIN: Other questions or comments? Dr. Izurieta, thank you very much. We certainly appreciate it. It is nice to hear these plans and the fact that they have been and are increasingly well developed.

Speaking of manufacturers, the next item on the agenda will be for some brief comments from each. Dr. Tsai, I presume you are presenting from Novartis.

Agenda Item: Manufacturers Comments on Development, Clinical Trials and Timeliness for Pandemic H1N1 Vaccine

DR. TSAI: Thank you, and good morning. To provide a context for understanding our clinical trial program, I will first describe Novartis' portfolio of licensed and

candidate influenza vaccines, highlighting our oil and water emulsion adjuvant 59, and adjuvanted H1N1 vaccines that we have manufactured on egg and cell platforms.

In describing our H1N1 vaccine trials,I will focus on those using the U.S. licensed Fluvirin based candidates. I will mention briefly trials for products to be distributed in Europe. I will conclude by summarizing our supply time lines.

This is our influenza vaccine portfolio, which includes non-adjuvanted seasonal vaccines, adjuvanted vaccines, and those made on cells. The platform is being used to produce H1N1 vaccines are shown in the black font.

Fluvirin is our U.S. licensed sub-unit vaccine, but we have also produced H1N1 antigen on that platform for the U.S. stockpile. The next line down, we also have another TIV licensed outside the U.S. called Agrippal, which is under U.S. FDA review.

When we add MF59 to that vaccine, the result is an adjuvanted vaccine called Fluad, that is licensed in Europe and indicated for adults over 65. We have used that same process to make an adjuvanted H1N1 vaccine which is called Aflinof,(?) and that is also in development in the U.S. and in Europe. This vaccine has been studied extensively in clinical trials in 10,000 subjects, and that has allowed us to license a pandemic vaccine in Europe under the mockup

procedure. That placeholder, which is called Focetria, now has been invoked to license the H1N1 vaccine.

Lastly, we have cell culture derived seasonal vaccine licensed in Europe as Optiflu, and we have also studied an H5N1 derived vaccine produced on that platform, and an H1N1 vaccine also will be made using that process.

We have not used emulsion adjuvants in the U.S. However, we have considerable experience with MF59 in Europe, where it has been a component of the seasonal vaccine Fluad, with more than 45 million doses distributed. In addition, we have safety data on 33,000 subjects in controlled clinical trials, that include 3,000 six to 36-month-old children who have received Fluad in an ongoing efficacy field trial. We have seen no safety signals in either the clinical trial database or in the pharmacovigilence database.

MF59 leads to higher and broader antibody responses in the seasonal vaccine to drifted heterovariant strains and in H5N1 vaccine to the majority of viral sub-clades. And importantly, MF59 allows for antigen dose sparing.

As you have heard, children and young adults are at greater risk for illness due to the new H1N1 virus. So I will highlight some clinical trials in those age groups that show how MF59 can augment the immune response.

On the right are results of a trial of the adjuvanted H1N1 vaccine containing seven and a half

micrograms of antigen in children six to 35 months of age on the left-hand bar, three to eight years old in the middle and adolescents nine to 17 years. The dotted line near the X axis shows the European regulatory expectations for two and a half fold increase in antibody titer between the pre- and post-vaccination samples. After two doses, the toddlers exhibited 129-fold increase, children 117-fold increase, and adolescents a 67-fold increase, leading to GMT HI titers of 688, 585 and 344.

So with HHS support, we have also made a cell culture derived H5N1 vaccine. This trial looked at antibody responses in healthy young adults, given two doses. We varied both antigen and adjuvant concentrations. The antigen concentrations are shown on the X axis, ranging from 3.75 micrograms to 15 micrograms, and the adjuvant doses in the colored bars ranging from none to 100 percent of the usual dose of MF59 in the licensed vaccine.

The difference in responses to the unadjuvanted vaccine shown in the white bars compared to all of the adjuvanted formulation shown in the colored bars is self evident. All of the adjuvanted formulations led to a significantly greater proportion of subjects achieving HI titers of 40 or higher.

So responses to 3.75 or 7.5 micrograms of antigen combined with half of the usual dose of MF59 were non-

inferior to those of the 15 microgram dose combined with the full complement of MF59. So this study shows the potential for both antigen and adjuvant dose sparing.

The MF59 clinical database is comprised of more than 33,000 subjects, the majority of whom have received influenza vaccines, in the red. Just under half were adults over 65. More than 10,000 were younger adults 18 to 64 years of age, and 3,000 were children. Many of these trials were done under U.S. IND.

A pooled analysis of 94 trials with a median duration of follow-up of six months found no increased risk for severe adverse events, the new onset of chronic diseases or autoimmune disorders. This analysis has been submitted to CBER.

Both the pediatric Fluad study and all of our H5N1 pandemic studies have been under the oversight of independent data safety monitoring committees, and none of the trials have been interrupted for safety signals.

Finally, we are in the last year of a large scale observational study that will provide additional safety data.

So against this background, I will now describe our clinical trial program, starting with studies based on the Fluvirin candidate.

This slide provides an overview of the studies. They will in parallel study children down to three years of

age and adults including seniors who receive both unadjuvanted and adjuvant formulations. Safety will be monitored for a year and will include clinical laboratory determinations.

The primary immunogenecity end points will be based on HI responses that we will also explore for their kinetics. Then additional trials including post-marketing safety assessments are under discussion.

Importantly, we are conducting a pilot study that has been designed to provide results as quickly as possible to inform the formulation decision. That study will be followed afterwards by the pivotal registration study.

The design of the pilot study is shown here. Adults and children will receive either 15 micrograms of unadjuvanted antigen or seven and a half micrograms of adjuvanted with MF59, and varying doses will be administered. Varying schedules are planned. So the 15 micrograms of antigen will be delivered either in doses three weeks apart or in two doses on the same day in opposite arms for a total of 30 micrograms. The seven and a half micrograms of adjuvanted antigen will be delivered either in two doses one week apart, three weeks apart or on the same day in two injections in opposite arms.

The first study visit is scheduled on or about August 17 and the first serological result after dose one is

expected in mid-September, after dose two in late September, and the final study report should be available in mid-November.

The pivotal registration studies are shown here. Adults and children will receive varying doses of antigen or adjuvant, the adjuvant doses ranging from seven and a half to 30 micrograms and the adjuvant doses from none to 75 percent to 100 percent of the usual dose of MF59. The first subject visit for this trial is scheduled for about August 27. The preliminary serological result after dose one should be available in late October for adults, and in early November for children, and after dose two in early November for adults and mid-November for children, and the final study reports in December.

I mentioned that we have H1N1 vaccines to be distributed in Europe. Time doesn't permit me to describe those trials, but you should be aware that we are also conducting a pilot study of the MDCK cell derived vaccine under an investigator initiated structure at the University of Lester. Varying doses of antigen and adjuvant will be studied in various schedules, and the first subject visit was scheduled for today. We should have results for that study in mid-September.

That concludes my description of the clinical trials. I will move on now to describe our product supply

time line.

Novartis has committed its Liverpool site, where we manufacture Fluvirin to produce the pandemic U.S. vaccine supply through the end of the year. Bulk production has commenced already, and our goal is to produce 90 million 15 microgram bulk doses by the end of November, based upon yields.

Fill finish production will proceed upon the government formulation decision, and the first finish doses should be available four to six weeks after that decision. Antigen production yields as you have heard are below levels expected for seasonal strains, and we are continuing to work to optimize that process by evaluating alternate strains and reassortants, and by other means.

Thank you.

DR. MODLIN: Thank you, Dr. Tsai. I think in the interest of time we will hold questions, if we might, and move on to the next presentation, which will be from Sanofi Pasteur.

DR. GURUNATHAN: Good afternoon. My name is Sanjay Gurunathan. I head the Clinical Development Group at Sanofi Pasteur. It is my pleasure today to speak to VRBPAC and update VRBPAC on our plans to license a safe and effective H1N1 vaccine.

We have heard through various presentations this

morning the status of the current H1N1 epidemic, framing for us the urgency to develop a vaccine as soon as possible. Sanofi Pasteur has been working very closely with various public health agencies to address this urgent public health need to provide as much vaccine as soon as possible to the U.S. public and other countries.

We have worked very closely with the FDA to develop a plan which I will be describing in a few minutes to you. But the key driver behind the plan is to generate clinical data as soon as possible so that important public health decisions can be made on formulation, which would then trigger vaccine production and supply.

So how are we doing this? We will be conducting studies looking at safety and immunogenicity, studying various doses across a range of age spectrums, across all the age spectrums actually. Pediatric and adult and elderly studies will be conducted concurrently.

We will be looking at a -- what we are proposing is a two-dose schedule with vaccinations given three weeks apart. An interim analysis will be planned after each dose for both safety and immunogenicity to provide expedient clinical data. We will also be studying both adjuvanted and non-adjuvanted formulations.

Just to give you a little more detail and an overview on the clinical plan, we have developed this plan in

close collaboration with the FDA. As I said before, the key driver of the plan is to get clinical data as soon as possible, so that rapid decisions can be made on formulation dosage and schedule selection, so that vaccine production can start, which will enable vaccine supply. We will be looking both at safety parameters and immunogenicity parameters as part of our assessments in all these studies. The studies are sized to assess immunogenicity against performance criteria that the FDA has provided to all the manufacturers.

In terms of the development plan overview, we plan to conduct three clinical trials, two in adults and elderly and one n the pediatric population. We plan to study two types of vaccine candidates, a non-adjuvanted formulation and an adjuvanted formulation. The adjuvant we are proposing to use is going to be an oil and water emulsion, which is very similar to the other oil and water emulsions used and studied by some of the other manufacturers.

We will be studying dose ranging studies in our clinical trials. For the unadjuvanted formulation we are going to study 7.5 microgram, 15 microgram and 30 microgram per dose, and for the adjuvant formulation we will be studying 3.75 and 7.5 microgram per dose.

We have phase I data already from approximately 1,000 subjects using our adjuvant. It is the H5N1 vaccine candidate, which has shown the vaccine to be safe, at least

based on 1,000 subjects we have, and also confirmed for us the dose bearing capacity of these adjuvants.

The table gives you an overview of the proposed overall database for our program. The databases will be approximately 2,000 subjects. The first column gives you the size of the database for the unadjuvanted vaccine program, and the second column gives you the size of the database for the adjuvanted vaccine program.

For the unadjuvanted vaccine program, the size per age strata is described in this slide. For subjects more than 65 years of age, the database size will be approximately 300 for the non-adjuvanted formulation, 500 between 18 and 64 years of age, 200 between three to nine years of age, and 200 between six to 35 months of age. Keep in mind that the flu zone process is licensed up to six months of age.

For the adjuvanted program, the database size is approximately 500, and in consultation with the FDA we have included a placebo arm in our studies, and the database size is listed in this slide.

This slide highlights our key current clinical time lines. Of the non-adjuvanted program, which includes two studies done concurrently, both in adults and elderly in one study and in children in the other study. We project the study start to be in the first week in August. Day 21 immunogenecity data, which is three weeks after the first

vaccination, to be in early October, and day 42 immunogenecity data, which is three weeks after the second vaccination, by the end of October.

For the adjuvanted program, we propose a study in adults and elderly. The study start is proposed to be in mid-August. The day 21 immunogenecity data to be distribution by the end of October and day 42 immunogenecity data available by mid-November.

I want to highlight two points in this slide. There is a week differential between the unadjuvanted and the adjuvanted program. This is because in consultation with the FDA, we are doing some safety prescreening labs for the adjuvanted program -- that accounts for some of the delay -- and also in an agreement with the FDA we will be looking at the safety data from the adult cohort before we embark on pediatric studies.

It would be remiss of me not to mention some manufacturing considerations that drive both the clinical time lines and also ultimately availability of vaccine. This morning we had a discussion already on the calibrated reagents, and so I won't get into too much detail. I guess there will be more discussion this afternoon. If we were to wait for calibrated reagents to start our clinical trials, the trials would begin mid-September. In order to expedite the start of the clinical trials so that clinical data can be

available as soon as possible, we have proposed to formulate based on HPLC, as was discussed this morning. That would enable the start date to be pushed from mid-September to early August. Given our history of flu manufacturing and our experience with the HPLC assay, we feel comfort in that we can predict the antigen content with reasonable accuracy.

To give you how to translate these time lines into some perspective, the saving in time lines could translate into vaccine being available as early as December, as opposed to say early 2010 if we were to go with a later start of our clinical trials.

Some additional considerations include, which has already been discussed extensively this morning, low yields for H1N1. We are continuing to work to optimize RCs to try and improve our yields. Every public health authority has emphatically stated that securing doses for the seasonal vaccine production is an important public health priority. As the largest manufacturer of flu vaccines in the United States, it is certainly an important manufacturing consideration for us.

We are working with the FDA to gain approval of additional filling lines, in addition to the one that was already approved in May 2009 this year. Gaining these approvals would greatly enhance our ability to supply vaccine.

Just a brief comment on vaccine availability. Some of these discussions already have taken place through various presentations this morning. Four key decisions are needed to drive vaccine availability.

We need to make a rapid decision to decide -- informed decision to decide on formulation targets. The options are listed on this slide. We can either base it on the first available clinical data which would be available in October or subsequent milestones that would come late October, early November. Or a public health authority could request to formulate prior to availability of clinical data.

We need approval of labeling and packaging components. We need to get some concurrence with CBER on release strategy, and we need an HHS task order for formulation filling and packaging.

Normally, if all these decisions are made today, which they cannot be, it would take approximately six weeks after these decisions of vaccine availability. Just to translate that into time lines, if the decision was made today, the soonest vaccine would be available would be mid-September.

I will close with my last slide. Sanofi Pasteur has a long history to respond to public health urgencies. We remain committed to do so. Our large scale production of vaccine lots was initiated on 22nd June 2009. As I showed

you, clinical trials will begin in early August with results as early as in October. As I showed in the previous slide, four critical decisions are needed that would drive the availability of first doses.

We have been working very closely and appreciate the collaboration we have had to date with various public health agencies, including the WHO and HHS. I believe our plan provides the best balance between securing the doses for the seasonal influenza vaccine and at the same time providing an expedient plan for provision of H1N1 vaccine.

Thank you, and I'll stop here.

DR. MODLIN: Thank you very much. Again in the interest of time, I think we will go on to the next presentation, which will be from CSL.

DR. BENNET: Thank you very much for giving us the opportunity to present here today. I am Joanne Bennet. I am Head of Regulatory Affairs from CSL in Australia. What we would like to do is give you an overview of our seasonal vaccine Afluria, our plans around novel H1N1 vaccine manufacturing supply, and an overview of the clinical trial program.

In terms of our vaccine that is currently licensed in the U.S., we have an indication for adults aged over 18 years, and we are currently undertaking post-licensure commitment studies to obtain a full license and to extend

that indication into the pediatric population.

In terms of our experience with the vaccine, although we are new to marketing in the U.S., we have actually got 40 years of experience with manufacturing this vaccine. Since 2004 we sought registration in Europe. We had 25 million doses of vaccine. Now in the last five years we have extended that to 17 million doses. The vaccine is licensed in 27 countries worldwide.

I guess I probably should say for some of you who may not know us, our key skill is in the manufacture of biological products. We are possibly better known in the U.S. through supply of our plasma products, through our CSL Bering company, which is headquartered in Pennsylvania. Our vaccine though is manufactured in Australia. We are the only Southern Hemisphere manufacturer of influenza virus vaccine, and we sell the vaccine through our CSL Biotherapies arm in the U.S.

The vaccine is a traditional egg derived vaccine. It is a split virion inactivated vaccine. We have two presentations licensed here in the U.S. We have a thimerosal free prefilled syringe which is made from a totally thimerosal free manufacturing process, and we have a multi-dose vial presentation.

As I stated previously, adjuvant manufacture is made solely at CSL in Australia. However, we do have some

fill and finish capability in Australia. The product for the U.S. is currently filled and finished in our facility in Marburg in Germany.

We do have a licensed supplement that is pending approval with the FDA for a filled and finished site located in Kankakee, which is south of Chicago in Illinois.

In terms of where we are for our seasonal influenza vaccine, we are on track to make our U.S. commitments this year. Where we are with our H1N1 vaccine, we have commenced manufacture on the 20th of June this year. Although we worked on developing one of the seed lot strains ourselves, because of when we did our head to head comparison, we selected the New York Medical Center strain so it is not the CSL seed strain in our vaccine.

This is an overview of our planning calendar. We were able to complete our antigen manufacture for Northern Hemisphere by early June, and we were able to take the opportunity to initiate manufacture of our H1N1 antigen. We can carry that through until about October.

At the moment, until the WHO makes some decision about what they will do for the Southern Hemisphere season, we need to plan to initiate Southern Hemisphere vaccine manufacture again in time for supply early next year.

In terms of formulation, we have almost completed the formulation of our Northern Hemisphere seasonal vaccine.

We are poised to be able to commence formulation of our H1N1 vaccine early next week, if the Australian government deems it is something that they wanted.

In terms of our clinical trials, we have two clinical programs. We are contracted by priority order to supply the Australian government in the event of the pandemic, and they have placed an order with us. So therefore we have a clinical trial program to support supply of the vaccine in Australia, and we also have a clinical trial program that we have worked with the FDA to meet the needs of the U.S. population.

The two programs are complementary and overlapping. The U.S. program of course is executed under our BARDA HHS contract, and we have our IND filed with the FDA. We do appreciate the dialogue that we have had with the agency to date in terms of working towards the design of the program. What we are proposing to do is use our thimerosal free formulation for our pediatric trials.

This gives you a perspective of our U.S. trials. We have got two populations, the adults and older adults. Overall we will have these studies in 1300 participants. They will be placebo control studies, and we are exploring 7.5, 15 and 30 microgram of antigen. In our pediatric program with the thimerosal free product, we are exploring 7.5 and 15 microgram with HA versus placebo.

To give you a perspective of what we are doing in Australia, we are doing the study in Australia in what we call our younger adult age cohort. However, what we have done is, we have wanted to split the analysis so that we could understand what the antibody response is in those participants who may have had prior exposure to other pandemic H1N1 vaccines, which is why we are splitting the cohorts equally here.

In Australia we are only exploring two doses, 15 and 30 micrograms. We are also exploring the same doses in the pediatric population.

This is the format of the studies that we are doing here in the U.S., where we have got a small number of placebos versus 200 in all of the test treatment groups for the adult populations and 100 in each of the treatment groups of our pediatric populations.

The clinical trial end points have been explained both by FDA and the prior speakers. I think what is notable though is what we are planning to do from a safety perspective. We are undertaking monthly assessments to six months, so that this will facilitate timely safety signal detection, especially for those unexpected SIAs or adverse events of special interest such as Guillain-Barre syndrome or vasculitis, anything that may have been recorded and possibly associated with an influenza or other vaccine. We are also

monitoring for new onset chronic illness. We are also undertaking an interim review of immunogenicity and safety data after doses one and two.

It was interesting to arrive in the U.S. yesterday and to find that we had had press. We had coverage for the initiation of this study with the first participants vaccinated in Australia on the 22nd of July. We are planning to, once we have reviewed the post dose one safety data, we should be able to initiate our pediatric study. That is also concurrent with our plans for initiating the study in the U.S., which will be undertaken concurrently. Our first interim review of post dose one data, safety and immunogenicity, will occur in September, and our final post dose two data across the programs is due in about December.

In summary, we have commenced manufacture at our H1N1 antigen. The clinical trials have commenced in Australia. Initial data will be shared with the FDA in September. Although these studies aren't being conducted under an IND, we have submitted those protocols to the IND, because we believe it is important to facilitate an understanding of the vaccine dose selection across the globe.

We filed our IND with FDA. Our U.S. clinical trials are on track to commence in mid-August. Our vaccine will be thimerosal free in the pediatric trials, and we are also supplying the vaccine to NIAID for the additional

trials.

Thank you for your time.

DR. MODLIN: Thank you. The next presentation will be from MedImmune.

DR. MALLORY: Good afternoon. My name is Raburn Mallory. I would like to thank you for this opportunity to present MedImmune's H1N1 development activities to the VRBPAC.

I am going to talk a little bit about our H1N1 vaccine, then touch briefly on our clinical studies and when we think we will get data available from those studies, and then talk about the progress we have made in manufacturing and the good yields that we have seen with our vaccine.

MedImmune's H1N1 vaccine is a live attenuated vaccine. At least initially this will be delivered intranasally using a prefilled single dose AccuSpray device. This is the device that is licensed for our seasonal vaccine. Each dose contains 0.2 mls of vaccine delivered intranasally. The dose that we will be looking at is ten to the seventh FFU, fluorescent focus units. This dose has been selected based on multiple clinical efficacy studies. The potency of the dose for the clinical trials will be established using our standard methods.

We know that for our live seasonal vaccine FluMist that it replicates intranasally and generates a broad immune

response including cellular, humoral, mucosal responses. We have seen high levels of efficacy in multiple studies, even though we have not seen HAI as a correlate of protection.

I would like to move now and talk a little bit about the design and conduct of our clinical studies to evaluate our new H1N1 vaccine. These studies are based on our annual strain change procedure. On an annual basis when we want to incorporate a new strain into FluMist, we conduct a safety study in adults. We have done this over the previous seven years.

For our H1N1 vaccine we will be conducting two studies. We will be conducting the adult studies in adults 18 to 49 years of age. In addition we will be conducting a pediatric study in children two to 17 years of age.

For dose schedule, we will be evaluating the two-dose schedule delivered one month apart, and subjects will have immunogenicity drawn after both doses. Subjects will be randomized four to one vaccine to placebo, and they will additionally be randomized one to one to have their blood drawn at either day 14 or day 28 after the first dose. This is in an effort to get early immunogenicity data available both to CBER and to the public health community.

The objectives are to demonstrate that the new strain, the H1N1 strain, is attenuated. We will be looking at fever rates in both vaccine and placebo recipients. We

will be looking at solicited symptoms and adverse events for safety, and as I mentioned we will be looking at immunogenicity after both doses f the vaccine.

What I am presenting here is the timing of the clinical data availability. We have gone out on a little bit of a limb and actually given you dates when we think the data is available. I am going to point to the star at the bottom of this slide, that caveat. This says that the data will be available in the best case scenario where we have our first subject in on August 17, and that we don't run into any unexpected problems with recruitment or conduct or analysis of the studies.

We are going to be submitting data to CBER on multiple occasions so that they can see both safety and immunogenicity data as we get it. The first submission that we will be making is day eight safety data. This will be available on the eighth of September for our adult study. Data from the pediatric studies for all of these submissions comes about a week later, because we anticipate that enrollment will take a little bit longer for the pediatric study.

The next submission that we make to the FDA will be day 15 immunogenicity data after dose one. This is the effort to provide early immunogenicity data from the studies for review.

The third submission occurs around the middle of October for both studies, and includes the full immunogenicity data that we have gathered after dose one as well as some preliminary safety data that we gather after dose two of the vaccine. Then our final submission is day 29 immunogenicity data that should occur around the beginning of November for both studies.

I want to switch track a little bit here now and talk about the manufacturing progress that we have made for our vaccine, and some of the regulatory milestones that we have upcoming.

We generated a 6:2 reassortant vaccine virus using reverse genetics on the 11th of May about three weeks after CDC announced the first human cases. We evaluated 23 separate variants and we selected a master virus for commercial production on the 25th of June.

In contrast to what you have heard from some of the inactivated manufacturers, our yields have been very good with this master virus seed, and approximate those yields that we see with our normal seasonal strains. Based on internal testing, our master virus seed appears to be antigenically similar to the CDC recommended strain. We began commercial manufacture with our master virus seed on the third of July, 2009.

Some of the key regulatory milestones that we have

upcoming that we are working with CBER with is submission of the strain change supplement as they have outlined, which will be followed by review and release of the H1N1 lots. Then we have review and approval for a second high speed filling line in October that will be necessary for us to meet our commitments to the U.S. government vaccine availability.

What I am showing here is timing of vaccine availability. This is filled doses in our AccuSpray container, and bulk doses. What I mean by vaccine availability is vaccine that has been internally QC'd and released by MedImmune. This is not tied to CBER approval; this is just when it will be internally released at MedImmune.

What the graph shows is the cumulative number of doses that we project to have available by month, both for our filled doses and our bulk doses. These numbers are based on projections from the potency that we have seen with an initial three lots that we have produced so far.

The green bars show the projected number of filled doses that we should have available by month, and the blue bars represent the bulk doses. I think you can see that given the very good yields that we have seen with our manufacturing process, that at this point our capacity to produce bulk doses exceeds our capacity to fill them.

I would like to note that if our yields had been

similar to the inactivated manufacturers, i.e., we had gotten about 30 percent of our seasonal yield, the sprayer and bulk doses would have been much more closely matched. We are currently working with CBER, BARDA and other groups to define a path forward to fill our vaccine into an alternative delivery device.

I would like to end by thanking BARDA for their support of our H1N1 development efforts.

Thank you.

DR. MODLIN: Thank you, Dr. Mallory. The final presentation will be from GSK.

DR. INNES: Good afternoon. I am Bruce Innes. I lead GSK's Global Influenza Development Team. In the next few minutes I would like to do three things. I want to describe the adjuvanted H1N1 vaccine that GSK will produce, summarize the data supporting its expected favorable risk-benefit profile, and then outline the planned clinical trials that we expect will yield data able to inform a decision regarding that vaccine's use sometime between September and November of this year.

But first, I would like to review why GSK is proposing to respond to the H1N1 pandemic with a new vaccine formulation. In 2006, the Department of Health and Human Services issued an RFP for development of an antigen sparing pandemic vaccine because contemporary influenza vaccine

approaches to pandemic preparedness, particularly with respect to H1N1, were considered to be inadequate.

GSK was awarded a development contract based on early clinical data suggesting that its novel adjuvanted flu vaccine offered both remarkable antigen sparing and highly effective immunization. For the past three years, GSK has met monthly with representatives from the Department of Health and Human Services, who have supported and monitored our development activities.

GSK has now developed an adjuvanted pandemic vaccine, which based on results from the H5N1 subtype as a worst-case scenario is antigen sparing, highly immunogenic and offers cross clade protection in ferrets. We believe that this vaccine candidate represents an important alternative approach to prevention and control of pandemic influenza, particularly when there may be limited volumes of vaccine available in time to implement preemptive vaccination.

The adjuvant system which we refer to as ASO3 is an alpha tocopherol based emulsion containing two oils naturally occurring in humans and polysorbate 80 as a surfactant. The product is monovalent. It is formulated at 3.75 micrograms of hemagglutinin per dose. It is presented in separate ten dose vials of antigen and adjuvant which are to be missed prior to injection. The standard schedule is two doses 21

days apart.

Antigen is produced both in our Dresden and Quebec facilities. They use slightly different processes. As you see on the slide, GSK's Dresden manufactured H5N1 vaccine was approved last year in the European Union, Australia, Singapore, Malaysia and Hong Kong. An H1N1 version of this vaccine has the potential to be rapidly licensed in September-October in the European Union, based on the submission of limited data under the mockup procedure.

GSK has developed its Quebec manufactured adjuvanted H5N1 vaccine for use in North America, including the United States, and has planned to submit a license application for this product this year. The application will include data on 3500 adults from 18 to 93 years of age, and an integrated summary of safety on approximately 12,000 adults who have completed studies with the Quebec or Dresden version of the vaccine. We believe these adjuvanted H5N1 data strongly support the use of adjuvanted H1N1 vaccine under an emergency use authorization.

Here are the HI antibody data which show that GSK's adjuvanted H5 vaccine manufactured by either the Dresden or Quebec processes are immunogenetically equivalent. You can see that more than 90 percent of adjuvanted vaccine recipients seroconverted after two doses with geometric mean hemagglutination inhibiting titers approaching 500. These

response rates reflect the effects of ASO3 as the vaccine without adjuvant was very poorly immunogenic.

I want you to note that the responses to a single dose are modest. A second booster dose is required when subjects are naive to a subtype.

These immuno equivalence results are important for two reasons. They support the relevance of data generated with the Dresden vaccine, which will be available for trials this fall, one month earlier than the Quebec vaccine, to predict responses to the Quebec vaccine which will be supplied to the U.S. government. But they also support the feasibility of using ASO3 with split virion antigens produced by other U.S. licensed manufacturers such as Sanofi Pasteur or CSL, to achieve antigen sparing with strong immunogenecity.

The adjuvanted H5 vaccine is highly immunogenic in all age groups, in all age groups. Seroconversion rates by age, children three years and above, more than 95 percent; adults 18 to 64, more than 90 percent; elderly adults, more than 70 percent. This level of immunogenecity is superior to that achieved with unadjuvanted seasonal vaccines administered to primed individuals, superior immunogenecity has the potential to afford superior protection.

Here is the evidence that immunization with the adjuvanted H5 vaccine can be cross protective. In ferrets,

administered a range of doses of the adjuvanted vaccine or control vaccine on days zero and 21, and challenged intratracheally with an antigenically different virus. Four weeks later, all the controls died. They received plain antigen at 15 micrograms twice, or only adjuvant, but 22 or 23 animals who received the adjuvanted vaccine survived. Moreover, the adjuvanted vaccine reduced the amount of virus in lung tissue when the animals were sacrificed five days after challenge, at least 3,000 fold compared to controls.

As mechanisms of protection against influenza A virus are thought to be similar regardless of subtype. Given the relevance of ferret protection data to humans, we believe this experiment illustrates strongly the increased protection that might be expected against severe human disease by the adjuvanted H1 vaccine when compared to a conventional inactivated influenza vaccine.

Now, influenza vaccines containing ASO3, their new products. GSK has made substantial efforts prelicensure to evaluate their safety. We have compiled an integrated summary of safety and submitted it to CBER, comprising six months safety data from adults in eight completed trials of H1N1 with ASO3, manufactured in either Quebec or Dresden.

Here you see the occurrence of spontaneously reported adverse events. Rates of medically attended and serious adverse events over six months were comparable

between the vaccine and control groups. The very small difference between the occurrence of all unsolicited adverse events is due to increased reports of reactogenicity at the injection site during days immediately following the vaccination, but these events were predominantly mild and self limited. There was no escalation with the second dose, and compliance in receiving the second dose was more than 95 percent.

GSK has an extensive development program for ASO3 adjuvanted pandemic and seasonal vaccines in all of our currently active and planned trials for these types of vaccines.

There is now active surveillance for potentially immune mediated diseases. Moreover, to insure that our development programs are able to accurately define safety risks we have adopted a policy of balanced randomization between active and control vaccine in phase III studies.

As new data are generated, and that is happening continuously, they are shared with regulatory authorities around the world. For instance, since September of 2008 GSK has been following a cohort of 40,000 subjects vaccinated with adjuvanted seasonal vaccine or conventional influenza vaccine. Just last month, the independent data monitoring committee for this trial met to review safety outcomes in the cohort during their first six months of follow-up.

The IDMC identified no safety signals, and they recommended that GSK continue the protocol as planned, including the administration of a second annual dose of the seasonal vaccine in September to October. To date, the totality of safety data available to GSK continues to support a favorable risk-benefit profile for ASO3 adjuvanted influenza vaccines.

All that I have told you so far has been to place in context our planned clinical development of H1N1 vaccine with ASO3. Let me briefly summarize our plans that are designed to evaluate first the Dresden product, which will be available first, and then the Quebec product to support an emergency use authorization.

There will be 15 trials of D or Q H1 vaccine. They will be done in the United States and Canada or in Europe. They will involve approximately 4,000 adults and 1,800 children as recipients of the adjuvanted vaccine candidate. Most will be IND studies. They will be randomized and blinded trials using a plain antigen control. The trials are designed to confirm the benefit of adjuvant in regards to sparing antigen use, providing superior immunogenecity that is also cross reactive against interference and enabling immunization of naive subjects in one visit using two injections simultaneously.

We will look for interference between seasonal

vaccine and the pandemic vaccine when these products are given either sequentially or concurrently, and we will assess whether the addition to adjuvant to the vaccine can overcome this type of interference, which has been seen previously. We will confirm the equivalent immunogenecity between the Dresden and Quebec products. The safety database will rapidly grow to more than 4500 subjects exposed to two doses by December.

This is a road map of the early studies, showing the estimated study starts and when post dose two data will become available, as shown by the red inverted triangles. The studies in orange are non-IND, they are done in Europe. Those in blue are IND studies, they are done in the United States and in Canada. The smaller EU studies all include interim analyses to provide real time pilot information regarding responses to a single dose of vaccine.

The earliest comparative data for a two dose vaccination schedule in adults using adjuvanted or conventional vaccine formulated using HPLC is anticipated in late September for dose one and three weeks later in October for dose two. But the same study using vaccine formulated with conventional SRID testing is expected to confirm these results only in early November. The earliest pediatric data will come in late December.

CBER has informed us that unadjuvanted H1N1 vaccine

can be approved as a strain change to a licensed product if a manufacturer commits to generate clinical data post licensure. On this slide, Study 005 in blue, is the trial that GSK proposes to use to fulfill such a postlicensure commitment.

In closing, we will manufacture an adjuvanted vaccine. Based on data from our experience with the related H5 vaccine we think this product is likely to be highly immunogenic for all ages, antigen sparing, and that means time sparing. It should offer cross reactivity against draft viruses, and we anticipate that it will be well tolerated with a favorable risk-benefit balance. But this is a new approach. It can only be used under emergency use authorization.

Pilot adult data, adjuvanted versus no adjuvant, may come by mid-October from either a GSK conducted study of HPLC formulated product or an NIH conducted study of the Sanofi Pasteur antigen mixed with ASO3.

Depending on the timing of requests from the Department of Health and Human Services, GSK can deliver ASO3 for use with Sanofi Pasteur antigen beginning at the end of August. We can deliver our own vaccine with ASO3 starting in mid-October.

Thank you.

DR. MODLIN: Thank you, Dr. Innes. I would like to

thank you and all the other vaccine manufacturers for very helpful informative presentations. I wish we had time for discussion and questions, but we just do not. But again, thank you very much. I think this will very much help us with our discussions this afternoon.

We will break for lunch. I would like to have everybody back at 1:30 in your chairs. If anyone does wish to speak during the public comment period, if they would see Christine during lunch. See you at 1:30.

(The meeting recessed for lunch at 12:35 p.m., to reconvene at 1:35 p.m.)

A F T E R N O O N S E S S I O N (1:35 p.m.)

Agenda Item: Open Public Hearing

DR. MODLIN: The next item on the agenda will be our open public hearing session. We have several members of the public who have asked to speak.

Before doing so, I need to read the following

statement. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To insure 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, 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 in a company or in a group that is likely to be impacted by the topic at this meeting.

For example, the financial information may include the company's or the 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 any such 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.

Let me add my own admonition. I hope that each of our public speakers will try to limit themselves to five minutes or less in the interests of time, because in addition to their comments, we have a number of other important issues that we need to get to.

The first speaker will be Susan Chu, M.D. from Ready Moms Alliance. Dr. Chu.

DR. CHU: Thank you, Chairman, for giving me this opportunity. I have first of all a declaration of conflict of interest. I have no conflicts of interest. I have no connection with industry.

We are a small grass roots parent-based organization, nonprofit, to help families prepare for pandemic flu. I have two questions in relation to these vaccines, both related to safety int he use of the vaccine in a pandemic. One is that since we are going to be vaccinating people while the virus is circulating, have the committee given any thought, or anyone given any thought to what happens to people who get vaccinated but then get infected then or soon after, particularly in the case of adjuvanted vaccines. Adjuvants as far as I understand work very non-specifically, which means they could stimulate a whole lot of other reactions that we are not sure of.

So is there a case for doing at least some animal studies or trials to see what happens if you vaccinate someone or a mouse or whatever, and then have them be exposed and see whether their clinical disease is different? My concern has to do with cytokine storm and all that.

The second question that I have has to do with Guillain-Barre syndrome, where the 1976 vaccine appeared to

be more strongly correlated with it than ordinary flu vaccines. There was a study last year that suggested that it may have to do with the hemagglutinin being a molecular mimic for the gangliocyte in the nervous system.

So the question that I have again has to do with the trials that we are going to do. Excuse me, I'm slightly out of breath because I have a bit of asthma. The question that I have is, if Guillain-Barre syndrome was a risk in 1976, whether this virus having similar origins in HA may have a similar level of risk, and whether we are doing studies in animals for example to at least determine whether the data on anti-gangliocyte antibodies would be replicated, particularly in the case of adjuvanted vaccines.

Thank you.

DR. MODLIN: Thank you, Dr. Chu. Just in terms of response to both of your questions, one, I would remind you that of course we with seasonal influenza continue to vaccinate with seasonal influenza vaccine throughout the flu season, so there are many, many people who are vaccinated and subsequently exposed to flu viruses. Hopefully the most common response is that they have some degree of protection. I don't know if anyone has any information to suggest that there is any adverse outcomes from that sequence of events, if any of the other committee members are aware of any information.

Secondly, I'm not certain that there is an animal model for Guillain-Barre syndrome. I have not heard of one. We don't have an enterologist unfortunately on our panel today, but if there is anybody that has any information about that, I'm afraid that all of our experience with Guillain-Barre has been with the human model. We will do the best we can with making certain that we do our best for surveillance for Guillain-Barre syndrome and try to apply our best epidemiologic methods to the study of Guillain-Barre.

Did anyone else want to respond to Dr. Chu? Our next speaker will be Jennifer Lo. Ms. Lo.

MS. LO: I have no conflict of interest and I am not funded by any industry to come here today. As a matter of fact, I was not planning on making a comment, but after hearing the speakers this morning, I would like to make a few comments if possible.

First of all, I want to make a comment on the stability of the virus. The lead vaccine strain, California/07, differs from most of the novel H1N1 currently in circulation by a few amino acids in the hemagglutinin protein. Yet these changes appear to make the virus more human adapted, because the changed amino acid in the current H1N1 in circulation are viewed as more human-like.

So is it a concern that the California/-7 H1N1 vaccine to be made is based on a less human adaptive virus

and is yet expected to be effective against a more human adaptive virus now in circulation?

The second comment is on the low yield on the virus made in eggs. The two aspartic acids near the receptor binding sites have been studied and are considered very important for the virus binding to the host and transmissibility. When reassortment was made in eggs to produce a seed virus for vaccine production, it is noted that there is a change in the amino acid next to one of the aspartic acids. Could this be respiratory for the low yield of the virus made in eggs?

The third comment also is on the GBS adverse side effect. The sampling size, I am concerned it is too small, considering the frequency of GBS is about one to 100,000 at best, and sometimes maybe only one in a million. But the sampling size that I have heard this morning is only maybe about 100 per arm. In some of the industries that they are doing, probably at most it is like about a few thousand.

DR. MODLIN: Maybe just very briefly, I don't think we can answer your first question until we begin the clinical trials. We just don't know how immunogenic the vaccine is going to be until we start to put it into people.

Secondly, I'm not aware of any information that a few amino acid changes are likely to affect the yield. I don't think we know the answer to that. Dr. Cox, I don't

know if you have any information about that, or any thoughts, I should say.

DR. COX: With respect to the change near the receptor binding pocket that appears in the vaccine strain, we believe that that is an egg adapted change, and that particular change is responsible for better growth in eggs, not lower growth in eggs.

DR. MODLIN: Your third question again, had to do with Guillain-Barre syndrome. Obviously that is a complication that has an extraordinarily low incidence that we are not going to pick up with the size of the safety trials that are planned now. I think we all have to acknowledge that. We just won't know anything about that until we begin to do post-licensure studies.

The next speaker will be Dr. Paul Mendelman.

DR. MENDELMAN: Thank you. I am very conflicted. I am an advocate and passionate about vaccines. That is why I am conflicted because I believe it prevents illness and disease.

I formally worked for Merck Vaccines, Avron Vaccines, MedImmune Vaccines. I did the clinical development for phase III for the live attenuated FluMist vaccine. I have no relationship now with those companies. I am the Chief Medical Officer of a company in Bozeman, Montana called LigoCyte Pharmaceuticals.

In 1995, Brian Murphy, at a Pooks Hill Marriott, at a pandemic planning meeting said, the cold adapted vaccine is a perfect vaccine to prevent a pandemic. Maybe Brian was right. I think it is important to point out that the live attenuated vaccine is a self adjuvanted vaccine. It is alive, it is attenuated. It has got receptors that go to the respiratory epithelium, just torpedoes right in. You get daughter cells replication. It is all about antigen presentation. There is NA, there is HA, there is structural proteins. It is a beautiful thing.

In 1996-98, we did a phase III pivotal efficacy trial. In that study we did it with the VTUs; they did a great awesome job. We did it at ten sites, and eight of the sites gave two doses, and two of the sites gave a single dose. There was matched strains in '96-97. It was 93 percent efficacious after two doses, and it was 89 percent efficacious after a single dose.

So I think the committee should consider one dose of live attenuated as being almost as high, certainly there is no difference between 93 and 89 percent. It may be well enough. These were in children 15 to 71 months that are naive to influenza.

In the second year it was 89 percent efficacious against a mismatched H1N1 A/Sydney. I think we all remember A/Sydney. That was 89 percent against a mismatched strain.

This committee voted for safety of FluMist up to 64 years of age based on the pivotal effectiveness trial we conducted in adults 18 to 64, 4500 adults. It was as effective in those over 38 as under 38; 38 was the median age, that was the robust analysis.

Now that 2000 showed up, those of us that are over 50 became elderly, because the CDC sid you are. In the post hoc analysis of the 600 50 to 64-year-olds, 400 vaccinees versus the 200 randomized placebos, all the end points were higher for the vaccinees. They were not statistically significant based on 400 versus 200.

So I noticed that in the emergency planning that in addition to approvals, one can change the age group. So if FluMist is safe up to 64 years of age, I would like to be one of those 200 million people that get a single dose of monovalent novel H1N1, according to licensure.

The last thing I would like to say is that the work on FluMist was an amazing nine years of working with the FDA and the NIH, and really a wonderful, wonderful time. I am glad to have been able to participate.

One thing I would like to ask is that the TIV manufacturers who are going to make monovalent H1N1, if they could please extend their dating for their vaccine and make that part of the supplement to the licensure. I wanted to run placebo control trials after the flu season, TIV versus

FluMist versus placebo. I could not get a single TIV manufacturer to extend the dating so we could run that trial, including our partner at the time, which was Wyeth.

So I think everything I have heard today is best case, and there is going to be slippage. We are going to be ready for the 010-011 season by everything we are doing today. But we are not going to be ready in time for 09-010. So let's get the vaccine out there and let's vaccinate people year round until we have got all the people vaccinated that need to be vaccinated and protected. I will yield all of my FluMist doses for myself to my three young adult children for them to get it.

Thank you.

DR. MODLIN: Thank you, Dr. Mendelman. The last speaker who signed up is Miss. Barbara Fisher.

MS. FISHER: I am co-founder and president of the National Vaccine Information Center, which is a nonprofit vaccine safety and advocacy organization founded in 1982. I have no conflicts of interest.

First, I would like to say as a former member of this committee, I hope that the committee members get an opportunity to question the vaccine manufacturers who presented this morning. I don't know if there is time, but I think that that would be appropriate.

I will make it a very short statement. Although

there was a preempted declaration of a national public health emergency on April 26 which allows the accelerated development of H1N1 swine flu vaccines using unlicensed oil and water adjuvants under the emergency use authorization, as Dr. Cox indicated this morning, there is no signal that the novel H1N1 virus is mutating to cause more severe complications or excess mortality that surpasses that of influenza circulating in most years.

The National Vaccine Information Center does not support the fast tracking of unlicensed adjuvants under a EUA for flu vaccines that are going to be given to millions of children, especially when there are no published biological mechanism studies identifying which children may be at high risk for developing immune mediated brain and immune system dysfunction after use of adjuvanted flu vaccines.

The FDA needs to know more, and parents deserve to know more about oil and water adjuvants before agreeing to get their children vaccinated, especially the millions of parents who have children who are already suffering from chronic inflammation and brain and immune system dysfunction.

DR. MODLIN: Thank you. I assume that there is no one else who wishes to speak? If not, we will go on to the next item on the agenda, which will be our discussion items. I understand that Dr. Sun is presenting each of the six discussion items.

Agenda Item: Presentation of Issues to be Discussed

DR. SUN: We would like to pose these questions to the committee for your discussion. I will just go through all of them first, will that be okay?

Please discuss whether FDA's approach to licensing non-adjuvanted pandemic H1N1 influenza vaccines virus strains and supplement without new clinical data is appropriate, with the clinical data to be submitted postlicensure. The pandemic H1N1/2009 vaccine would be manufactured by U.S. licensed manufacturers using their currently licensed seasonal flu vaccine process at the current doses shown.

Two. Please discuss whether the recipients of the pandemic H1N1/2000 influenza vaccine should be administered in two doses of vaccines at the initiation of the program.

Three. Please discuss considerations for immunizing special populations such as children below the age of six months and pregnant women.

Please discuss considerations for use of adjuvanted vaccines.

Five. Please discuss the proposed postlicensure educations for safety. Please identify any gaps that may not have been included in our proposal.

Lastly, please comment on approaches to assessing vaccine effectiveness. Consider the potential need for

diagnostic methods to distinguish pandemic H1N1 from seasonal strains, and other strains causing influenza-like illnesses.

Thank you.

Agenda Item: Committee Discussion

DR. MODLIN: Dr. Sun, thank you. Let's go ahead and open up the discussion for this first question. In some respects we are being asked to discuss a process that already is well in motion. I am not exactly certain what Norm's response would be if we suggested that this is not appropriate. But nonetheless it is a critically important question, because we are in a -- I won't say unprecedented situation by any means, but we find ourselves in an unusual situation, and I'll leave it at that.

I don't know exactly how to start this discussion. I am looking around for anyone who has anything that they want to say.

I guess I'll start out. I think this is an entirely appropriate way of proceeding. As a matter of fact, one that to me seems both necessary and appropriate and prudent and responsive to the public health's best interest, considering that schools are going to be opening in less than a month. Even though we can't absolutely predict what the behavior of this pandemic is going to be, we all acknowledge that we all at least believe that there is good reason to believe that we will see H1N1 influenza early this season.

It will be widespread and the attack rates will be high.

Unlike seasonal influenza, we are dealing with a situation where even though it may not appear to be any more virulent than seasonal flu is, we need to keep in mind that we have a population that is virtually 100 percent susceptible. So from a population standpoint, even a virus that is of average virulence is going to cause substantially more morbidity and mortality just on that basis alone. I think we have to recognize that.

Bruce, did you have your hand up?

DR. GELLIN: I think it would be worthwhile -- this is going to be to Norman. We have had presentations in the past from the EMEA. I wonder if you could give us a quick contrast, because we have heard from the manufacturers how different things are going on in Europe, if you could outline the similarities and differences. My sense is that it is called something different, but there are more similarities than differences. If you could do a quick side by side of how this would play in Europe vis-a-vis the licensure versus data that may or may not follow.

DR. BAYLOR: Sure. As many of you know, in Europe they are using the mock dossier. The mock dossier is an application where some of the criteria are set up that they would use to evaluate in this case an influenza vaccine. As you saw in some of the slides from the manufacturers, some of

the products have been approved. The H1N1 would be approved with data to come after approval.

So it is very similar to what we are doing. I think our process is somewhat different, in that you recall that the EAME is looking at -- they make recommendations where we actually license these products. So they will make a recommendation, and that recommendation is generally accepted by the member states. With the structure of our government, the FDA will make the decision to license a product for the entire country.

So I don't think the processes of the mock dossier and what we are doing are that different. But again, I think we need to step back and look at what we are presenting. We are presenting this on the basis of what we have experience with, and the fact that we have licensed the seasonal influenza based on a strain change, so a very similar situation.

We also have decades of experience with H1N1, so that is the basis for why we believe that this follows our normal procedures, procedures that we have used before. So it is not really steering away from something we would do normally for the seasonal vaccine.

DR. MODLIN: Norm, do you want to comment on -- this is a general comment about how much flexibility the agency will have to adapt and to change based on information

as it comes in? It sounds to me like we are not going to have any clinical data whatsoever, at least until mid to late September at the earliest. Clearly the need may change as the pandemic matures. But how much flexibility does the agency have? How much data are you going to need to make important decisions? Data coming back from one manufacturer, or do you think we should wait and be more conservative to see what you hear from three or four other manufacturers? Do you want to give us a general idea of what your thinking is about this?

DR. BAYLOR: Again, as we said this morning, the licensure process, that is a different pathway than recommending a vaccine for immunization. So we are strictly speaking of the regulatory pathway.

So if we license this vaccine as a strain change, we do have the flexibility. When the data comes in from the trials, we will evaluate that data and we can make decisions as far as changing the package insert, because we are going to have to have a package insert for this product, and we are going to have to modify the package insert. So we can modify the package insert. We can put whatever data we obtain from these clinical trials that will go into the package insert.

But what are the triggers, and it is not really an FDA decision, what are the triggers that would dictate using this vaccine or how this vaccine would be used. In other

words, if a recommendation was made that two doses need to be used, or the recommendation that the vaccine would be used prior to any of the data coming into the clinical trials, that is a separate decision. But as that data comes from these clinical trials, it will go into the package insert.

If we have to change something, if the clinical trials show that 15 micrograms is inadequate, then we are going to have to respond to that and make the necessary changes. Also, the policy makers will have to make decisions from that information as well.

I think from a regulatory point of view, we can be rather flexible as that data comes in. But then those decisions, that is the harder question, how those immunization decisions will be made as that data comes in, and at what point will that trigger making a recommendation.

DR. MODLIN: Is there anyone who feels like licensure of the vaccine based on a strain change supplement is not appropriate? Any other discussion about this one point? A remarkable silence.

DR. LEVANDOWSKI: This is not so much to suggest that what is being done isn't appropriate. I think it is. The comments that you made I think are the very important ones about timing and availability of data. If we are not going to have any data, in order to have some hope of using the vaccine effectively, it probably needs to be taken now.

As you pointed out, since this H1N1 strain is still -- and as CDC has pointed out, since the H1N1 strain is still circulating widely in the United States and widely around the world, we shouldn't expect that it is going to be one of those situations where we are not going to be seeing that H1N1 strain being predominant or causing significant infection and morbidity in the United States, and probably mortality as well.

I think the Public Health Service and HHS deserve a commendation for having put as much effort into this as they have at this early point in time, really. The vaccines are already being prepared. There is the possibility for doing something useful to try and protect the population.

So I guess it is more just to support everything that has gone on, but as Norman Baylor said, there is plenty of precedent for doing this very thing with new strains as they appear. It is not out of the ordinary. Therefore, I think it is something that should be supported very strongly, the approach that they are taking to begin with.

DR. MODLIN: So Norm, a strong vote of confidence.

DR. BAYLOR: Let me add, you saw the time line from some of the companies. One clinical trial started yesterday. So we will be getting information in, at least post dose one, within a month.

So even with the vaccine licensed, it is ready to

go, but I want to emphasize that recommendation part, but data will be coming in. So if the severity is not increasing, a decision may be made. We have a licensed product ready to go, but we can wait. Or if the severity increases, we have a licensed product ready to go and the decision makers can say, we can use the product now. It is a licensed product, we have confidence that this vaccine is safe.

DR. DEBOLD: Would there be a mechanism in place for letting the public know what these clinical trial data show as they come in?

DR. BAYLOR: The results of the clinical trials will go into the package insert.

DR. DEBOLD: I am assuming that you will get data in periodic reports as it unfolds. Is there a way to keep the public apprised of how these trials seem to be going, what type of immunogenicity you are seeing, or if you are starting to see any sort of safety signals that may be relevant to certain subgroups? This is such a different situation, is there a way to publicly post something on a website as things come in, so that people can be informed and make decisions accordingly?

DR. BAYLOR: Definitely as far as the NIH studies, that is funded by the U.S. government. The government owns the data. That data can be made public. The data that is

generated by the companies is owned by the companies. But we receive data and there are signs and signals that we should do something else, that will be communicated.

So I think the public will be aware of that. If something happened, a safety issue or something, the public would be aware of that. They may not be aware of the specifics or the specific company, but I think overall globally they will be aware of that. But I do have to emphasize, the clinical trials from NIH will be revealing as well.

DR. MODLIN: Norm, I think Vicky raises an important issue here. Of course, the agency has to follow the law. You have got your regulations with respect to communications with the private vaccine manufactures. But again, this case is special. This vaccine that is being made by the private manufacturers is being funded by the public, is it not, for the most part? Which is a very different situation than we have had in the past to a degree.

So I think that at least the agency needs to take that into account in terms of making information available as soon as legally possible.

DR. BAYLOR: We will work with the companies. There are also other advisory committees coming to this advisory committee or going to the ACIP or the NVAC or other advisory committees, where the government can work in

partnership to try to make sure that the public is well informed as things transpire.

DR. GELLIN: Another answer to Vicky's question is that in discussions between the Secretary and the Director General of the World Health Organization, the same request has been made about the importance of these studies to inform everyone about the result. As Norman said, the pledge was that the NIH studies supported by public funds would be available to WHO, so they would be available to others.

The mechanism and timing hasn't worked out, but I think you have raised an issue that we are going to have to ponder.

DR. DEBOLD: I think because we are asking the public to do something very special, we are asking them to consume a pharmaceutical product that has not gone through necessarily the traditional route here. I think this is part of informed consent and openness and transparency.

To the extent that I think information can be made available to people so they can take responsibility for the choices that they make, I think it is going to be better for everybody, particularly if something happens and we have some sort of a bad outcome. People will be less likely to blame others if they have had full information and been able to make decisions on their own.

DR. MC INNES: Two comments. I think it is not a

correct statement that it is going through a non-traditional route. I think it is a traditional route.

But back to data release. I think the issue of releasing data when you have been in order to inform the agency in a partnership of what is really a national -- not a crisis, but an urgent situation, is something that depends on trust from investigators to who you share data with.

We normally go through very rigorous data cleaning exercises before we are willing to expose the data to the full public. I think that this whole discussion sets up a somewhat disquieting possibility. On the one hand, generators of the data being willing to share it and on the other hand understanding that the data are in a certain state. They may not be fully clean and they probably won't be clean.

So I would rely upon, if there is a signal for safety or for totally inadequate immunogenicity, that this is not a new situation for the agency. You have seen this many times. That would bring about a response that would be communicated very quickly to the public through a change of recommendation from policy.

I just don't see -- while I understand the principle of keeping the public informed in order to build confidence, I think that has to be titrated against the quality of the data and how you can stand behind them.

DR. MODLIN: Judgments that need to be made. Thank you. Any other comments or questions about this point?

DR. GOODMAN: This is Jesse Goodman, former CBER Director, currently Acting Chief Scientist at FDA.

I would just say that we very much support, if there is information imported in public health decision making to achieve the maximum transparency about that information. I think that seconds what Pam is saying. If there is something that we think is significant and important for people to know, and certainly that pertains to the use of any product, we really will do all we can to make important information available.

I think Pam's point, which I also share, is that there are various kinds of data that rise to various kinds of meaning. That is what we count on our scientists to make judgments about. But I want to make really clear that we hear that concern.

DR. MODLIN: Thank you. Good. Any other comments? If not, let's move on to the second question, which in some respects perhaps a little bit more difficult. That is, please discuss whether recipients of the pandemic H1N1 influenza vaccine should be administered two doses of the vaccine at the beginning of the program.

Obviously there is a tradeoff here between immunogenicity or lack of immunogenicity and vaccine

availability in terms of the amount of vaccine that can be made available for a one dose versus a two dose program.

Let's open this up.

DR. DEBOLD: A technical clarification. Are you talking about two doses at the same time or two doses 21 days apart? I have seen different protocols in the materials we had.

DR. MODLIN: This would be two doses 21 days apart.

DR. JACKSON: That seems the most conservative approach. On the one hand, it takes a greater supply of vaccine. On the other hand, you are not achieving any benefit potentially with a single dose if it is not effective. Their policy is, for persons of an age who are unlikely to have had sufficient prior exposure to mount an adequate immune response to a single dose, we give two doses now. It seems that for this virus you could say that age goes up to 50 or 60.

So until we have more information, it seems like that might be the most prudent approach.

DR. LEVANDOWSKI: I think I take an opposite tack on this one. I think we have information from previous studies with H1N1 that would suggest to us that anybody who has truly been immunologically primed ought to respond pretty significantly well to a single dose of vaccine.

What population that is I think remains to be fully

defined. I would expect, based on all the data from studies with swine flu vaccine and studies with the Russian flu vaccine that showed the same thing, that those people who are old enough to have been exposed to H1N1 viruses before 1957 all responded very briskly to a single dose of the H1N1 that they were given, whereas those who were younger than that responded less well even after the two doses.

Taking that one step further just as another analogy, although I don't think it is exactly the same, there is data now from H5N1, which I think I have mentioned before in this forum, individuals who were primed by having received an H5N1 vaccine in 1997 and low doses also even, and with responses that were very difficult to detect after the first vaccine, reimmunized eight years later with another vaccine responded very briskly. Whereas those individuals who were getting H5N1 vaccine for the first time, the responses were lower in terms of the antibody titers. Even after two doses they were lower than those individuals who were being boosted, in a sense.

So I think the principle has defined itself for us. I think there is data that suggests that we would expect, we should expect that individuals who are immunologically primed ought to be able to respond very well. Who those individuals are in this case is still not entirely clear, in spite of the fact that we have had H1N1 viruses circulating for the last

30 years now. You would think that maybe everybody who is over age nine and has been exposed to all three types and subtypes of influenza A that have been circulating widely, ought to be among that population, but we don't know that.

DR. MODLIN: I presume that the question is addressed to people over nine years of age. In other words, we would continue to do just as we have done in the past, which is to give children two doses. That is not really the issue here.

DR. STAPLETON: I guess I kind of agree with both Roland and Lisa. It seems reasonable to propose two vaccinations while we collect the data in August and September in the clinical trials, because we can't predict at this point how immunologically naive nine-year-olds to 65-year-old individuals are.

But that comes back to the question of how flexible and how quickly the recommendations can be changed from two vaccinations to one. If that can be done very quickly, then we will have data by the time this vaccine is readily available.

DR. MODLIN: Doesn't this also raise the issue of what we expect demand to be like for this vaccine? I think supply is an issue. We haven't heard exactly how much vaccine you would expect to be available on August 15. At least, if we have it has passed by me. So this one dose

versus two dose I think probably is an issue here.

DR. STAPLETON: It sounds like we will be doing clinical trials. We may not be having vaccine available widely until late September, October, it sounds like.

DR. BAYLOR: That is what was presented by the manufacturers. Clinical trials have started now. We should start getting data. About a month from now we should have some data in.

DR. GELLIN: So if out of the box the assumption is we will need two doses, and information that is to come will inform us whether or not we can back off, maybe we should calcify what that information is. We know those streams of information are indeed going to come and what the presumptive time lines for it would be. I think we are going down this potential need to start early, with the assumption for two doses based on things that were already said, but in some populations that may not be necessary. So how are we going to be sure that we have outlined who is doing those studies in those populations to determine which ones we continue to recommendation two doses versus back off and a single dose would do.

DR. BAYLOR: I would just say that depending on the timing, if we are waiting before the first vaccine is used until after the first dose data comes in, there are certain triggers that we can look at as far as the results of that

first dose data that would -- not just the FDA, but the Department and others, could make decisions on what is needed.

For instance, if you are not getting any response to that first dose, or the response is very low, you may have to make decisions that either you wait for a second dose. I think there are decisions points that can be made after that first dose data is in. Prior to that first dose data coming in, you can't make that decision based on data.

DR. GELLIN: So the decision to use vaccine may be driven by other things than the availability of data. So therefore, we now know that clinical trials have begun, and we have somewhat predictable times when the data will become available to make this decision. So what I was getting at was trying to make sure we have a list of all the data streams that are going to be coming in that are going to inform this two versus one decision and when they may be available. It may be that you have had to start a program with that first dose before you know anything about the second dose.

So in my mind, we have heard a lot of information, and maybe it would be helpful to clarify, of all the different studies from the manufacturers and NIH and those other things out there, that what is going to be showing up when that we are going to be looking to to inform that

decision. It may be that that is going to happen on its own time line. I am just trying to layer that on top of what other decisions might be made about using the vaccine.

DR. STAPLETON: I think, Bruce, you are primarily thinking of immunogenicity in the age groups and different subpopulations. I would think that would be prime on the FDA's data they are looking at, besides safety.

DR. GILBERT: I want to add a statistical comment to this topic.

I have noticed from the different presentations, both from the documents we were provided and what we heard from the companies, that some of the groups would have 100 subjects, some would have 500 subjects, some would have 60 subjects. So when the FDA takes inventories of the studies that are doing one versus two dose comparisons, I haven't seen that those studies are well powered to compare those.

So due diligence. You need to check which ones have the right power for that comparison.

DR. MODLIN: Other comments, questions, comments, opinions? It doesn't sound like we have got a strong consensus, although it sounds like it is going in a direction of starting out with two doses. Norm, do you want to let us know which way you are leading?

DR. BAYLOR: Not really. I think if we follow the pattern of the seasonal, we would go with one dose. As the

data comes in, and I agree with Bruce, I think we have to map this out as to when are data coming in and the trigger points. If the data come in that suggest that one dose is not going to be optimal, then we may have to have different recommendations. But I think you start off with the seasonal, following what we have done with seasonal, children with first dose, this is the first time they are getting the dose, and they are nine and under they have received two doses and nine and above they would receive one dose.

But we wanted to get some feedback from you, the whole issue of, do we assume everyone is naive and will behave like a child less than nine years of age receiving influenza vaccine for the first time. Or based on some of the information that we have seen, it appears that those greater than 65 may be primed and they would not need two doses regardless. So looking at all of that information, and coming up with some kind of a recommendation.

DR. ROMERO: So if I understand you correctly, Norm, you are going to recommend that for the older individuals we plan on giving one dose to start with, is that correct?

DR. BAYLOR: Yes, we would follow the seasonal.

DR. ROMERO: I think the flip side of that is, the logistics of getting this accomplished, if you change in midstream, you start out with, we are going to give you one.

We educate those of us that deal with adult populations about giving one, and then all of a sudden you are going to shift gears and say, no, you have got to give two. So the logistics of getting all that set up, is that something to take into consideration.

DR. WHARTON: I think just from the communications-implementation point of view, it is far easier to say you might need two doses, but we found out you only need one, than we thought maybe you only needed one dose but it turns out you need two. I think it is way easier to go from two to one than from one to two.

I don't know whether we are going to need one or two, and I don't know that I have to guess, because there are studies that are going to be done that will answer that question. But in the meantime, it seems like from the point of view of being able to explain to people what it is we are doing, that we need to say, we think you may need two doses at the beginning.

DR. GILBERT: I was just going to add that moving from two to one would require more clinical trial data than moving from one to two, in the sense that moving from two to one would maybe need a tight enough confidence interval about the sero-conversion rate difference. Whereas the one versus two, you just have to show the superiority of two over one.

DR. SUN: This issue was brought up at the

initiation of the program, that the supply may be an issue. So if you don't really need two doses, if you say two doses you are limiting the amount of persons that you can vaccinate.

Also, we have to take into account the seasonal TIV vaccines. So the more doses, the more complex it becomes.

DR. MODLIN: Ted, you have more experience than anybody. You have probably lived through these questions before.

DR. EICKHOFF: That is a kind way of putting it. I sat here listening, wondering whether some of these projections of when data will be available are set badly on the optimistic side.

We know these clinical trials, one of them has started enrollment already, but not everybody in the CSL trial is going to receive their first dose on July 22, being yesterday. Not everybody in the NIH trials is going to receive their dose on day one. It will take some time to enroll the number of subjects that are desired, 500 we have heard, in some of the trials. So enrollment might go on for a week, ten days, or maybe even more.

Then at the other end, we come to the laboratory processing time. I assume this is going to be primarily HAI tests that are done, and they won't be done seriatim, at least they probably should not be done seriatim, but rather

done in bulk at the end of day zero immunization, so that they can all be done at once. Ditto at the end of day 21 immunizations; they should all be done at once. You could even argue that they all ought to be done at once.

But I think it could easily be into late September, October, before we have data.

DR. BAYLOR: I'll step back a bit here and also rely on Ted. Some of the decisions that we are trying to make we are basing on past experience, on historical. If I am not mistaken, in the past pandemics we have used one dose. Correct me if I'm wrong, Ted. In many of the past pandemics, time was on our side. If this had happened in January, we would be able to collect data. That happened in the previous pandemic. But we are in a position now where the virus is ahead of us.

So this is one of those uncertainties that complicate the decision making. But if we look at H1N1 in the time that they have been around, and again, I ask Ted, we started out with one dose, we used one dose, and one dose was relatively effective for most of those pandemics, if I'm not mistaken.

DR. EICKHOFF: I agree, and I am totally in sync with that kind of thinking. I agree with what Linda said earlier, that we should plan for two and back off to one if the data permit.

DR. GELLIN: I am going to concur with that. I agree, from an operational standpoint I think Melinda's approach makes a lot of sense.

Nancy told us something earlier about the population naiveté. I think maybe there are additional details that will come from that. At least the headlines suggest that people who are old, and maybe that is as old as me, are the ones who are at less risk. I think there is that general sense that there may be something different about the older part of the population than the younger. I think that has gotten into a number of things people have considered as far as their speculation of how many doses may need to be used in an individual.

So maybe Nancy wants to comment on that some more. If we have some of this population-based immunity, that may help to guide us in addition to that. That may be helpful, but it seems to me that at least in the large segment of the population under age X, which somebody will tell us, I would think the expectation would be for two doses, and if we learn something nuanced, then we might want to back off. But we still need to know what is going to happen in the elderly, and whether or not they can get away with one dose or if they need a dose at all.

So I think those are a number of the things that we need to evaluate. But I think that the expectation would be

that based on what we have seen, not what we have done before with seasonal, but what we have seen in this, that we would expect two doses and then can back off as data from a variety of things, including potentially some of these population-based sero surveys can inform us.

DR. LEVANDOWSKI: I think we are talking about two different concepts here, perhaps. What Nancy Cox was talking about earlier has to do with susceptibility to infection, not only for people who for whatever reason don't have antibodies or serious protection of some sort against the H1N1 strains that are out there, but I think that is separate from the issue of whether you have immunologic priming or not.

Seronegativity doesn't necessarily mean that you are not immunologically primed against H1N1. I think that is the point I was trying to make earlier, and maybe I didn't make it well enough, and maybe somebody wants to disagree with that. But I think that is true. That was true in the studies with the Russian flu and swine flu in the '70s, where there were individuals who were over the age they should have been exposed to H1N1. They didn't have antibody, but they still responded very briskly.

DR. GELLIN: Then your conclusion would be what Norman suggested, that therefore above nine would be primed?

DR. LEVANDOWSKI: No, I'm not saying that. I'm saying we would still want to see that proof. But I am

suggesting that there probably is an age. I don't know if you would pick one arbitrarily. Obviously the consensus is that in that direction for one dose for anybody to start with, but if you are going to give two separate doses, everybody is going to get one dose at a time. So effectively we are going to start with one dose. Maybe at some point the clinical data from the trials will catch up with what is going on.

DR. MODLIN: If you went in that direction, and it would appear to me based on the age distribution of the cases that have occurred so far that we have seen and the serologic data that Nancy and Tony presented this morning, that there is something about age 30, very roughly about age 30, that those over age 30 had much lower attack rates than those under 30.

Now, granted those are broad age ranges. There is a lot of imprecision in this, I understand that too. But if you went that direction, that to me would be a reasonable cutoff for making this first decision about whether you use one dose or two dose.

Obviously the ACIP is going to weigh in on this issue because it fits on their plate as well. I would be the last person to predict which way the ACIP is going to go.

DR. WHARTON: I don't know the answer to that question, but maybe Nancy or Tony have some feel for how the

Influenza Working Group discussions have been going on this topic.

DR. FIORE: We have largely focused on prioritization groups and not so much on the one dose-two dose thing. We are probably looking more for data that might come to this committee to help guide us on that.

But the working assumption in terms of deciding who is a priority group has been that it would be two doses. So when we are thinking about who should be at the head of the prioritization groups and how many doses you might have initially, it has been based on a two dose assumption.

DR. HOSBACK: I was also thinking about the group that gets together next week to discuss this relative to the two doses. So if you do have a limited amount and say ten, 20 million people to get immunized, are they the first in line the second time next doses are available? I think that is a real difficult issue that they are going to have to wrestle with.

Certainly we rely upon BARDA and other groups who have an idea of how many doses they might have during a certain time frame. It is going to be very, very important for ACIP. Does it reset? Do we reprioritize again? I think it is a very, very complex decision when you talk about two doses and limited availability.

DR. DEBOLD: This is a technical question. Is

there a way to tell whether or not you are primed and therefore do not need to be vaccinated at all?

DR. STAPLETON: I'm not a flu expert so I would defer to Ted. But with some other viral infections like hepatitis A, for example, you can measure proliferative T cells. But I don't think there is any correlation of that with protection in flu, is the problem.

DR. MODLIN: You will get some clue to this, Vicky, from the clinical trials because a number of the manufacturers are planning on getting post dose one sera before they give the second dose. Those sera should give you a strong clue as to whether or not you are seeing immunologic memory.

DR. DEBOLD: Just in terms of personal decision making, is there a way for an individual to go and get screened and say, I don't need this?

DR. MODLIN: No, not in a practical way.

DR. DEBOLD: I'm just asking.

DR. STAPLETON: If I had to bet, I would bet with Roland that people are primed. But I think until we have the data we don't know.

There is an interesting immunologic question about, does the reason 65-year-old people seemingly protected have more to do with cumulative exposure or to something specific about H1N1s back when 65 year olds were getting flu? I think

that is an interesting immunologic question, but we may not be able to determine that.

DR. MODLIN: Dr. Sun, you raised this before, but this is different that concerns me a little bit. I think Phil Hosbach's comment was getting at the same thing. That is one of vaccine supply. If we even initially suggest a two-dose schedule, that is going to have considerable implications for the vaccine supply. Is that something that is doable, is sustainable, based on your best projections at the moment?

In other words, we start out August 15 or August 30 recommending a two-dose schedule. It is going to be a month or so before we have any better data. Will there be adequate supply, particularly considering that there may be a brisk demand based on all the publicity around swine flu so far?

DR. BAYLOR: I would just comment on that. That is a very difficult question to answer. It is almost getting into that area of immunization recommendations. There are so many uncertainties there, that is really outside of where we want to go, because decisions will have to be made.

For instance, if the priority groups are first, defining those priority groups, and then do you take care of the priority groups with two doses. Then how do you handle those in the next year. So I think that those are discussions that are going on with the Department and other

parts of the government when you get to that level of rolling out a program.

DR. GELLIN: Robin gave us some projections about supply and hopefully the manufacturers' discussions align with that for the most part. But if you are asking the question, if we had a very scarce supply, would we want a one-dose program, the question is, does that make sense immunologically, and what would that to for population protection.

DR. JACKSON: I had a slightly different point, but I think we might need to subdivide this question into inactivated versus live vaccines. I think we have all been thinking inactivated, at least I have, and we need to consider the possibility that a different strategy may be warranted for live versus inactivated, based on data on vaccine efficacy among unprimed persons from previous evaluations.

DR. MODLIN: That is a good point. Norm, I'm not certain we have given you any clear consensus here, but at least I think we have had a pretty good discussion around the issue. Go ahead, Bruce.

DR. GELLIN: On Lisa's point, we had a presentation from MedImmune that raised the issue in a different way. If you thought that -- there are a lot of assumptions that go into this, but if you thought that was a single dose

formulation, their production capacity greatly exceeds their ability to filled and finish.

So it is a separate discussion about what they would do with that or if they would continue to make it. But maybe that is a separate conversation about, if that is the need and a single dose of that would help, we have all received their handouts to see what would be available over the next several months and thereafter that would potentially be available to use as a vaccine, should there be a way to deliver it.

DR. LEVANDOWSKI: Somebody will have to correct me if I am wrong on this one too, but it seems to me -- I think it is right, the comment that was made about live vaccine being thought of separately here from inactivated.

The reason there are two doses of the live attenuated vaccine I believe is because there are concerns that there might be some interference between the three components of the vaccine as it is replicating in the nose. The second dose is to make sure that as with polio vaccine, that there has been active replication of all three components of the vaccine.

So I'm not sure that there is a need for a second dose of a monovalent vaccine unless it is given in the presence of the trivalent live attenuated vaccine, in which case there could be other interference, and maybe all bets

are off.

But it seems to me that it should be a single dose if there is good replication. If you don't believe that you are getting good replication from the live attenuated vaccine the first time, is it going to replicate any better the second time in the case of a monovalent.

DR. MODLIN: One thing we haven't considered at all in this discussion is, of course there is going to be availability of seasonal vaccine presumably about the same time, and many people will be stepping up to get both vaccines. I think the assumption will be that both of these vaccines will be given at the same time. Even though we don't have any data yet from the clinical trials in terms of whether or not there is going to be either interference or any boosting effect or no effect whatsoever.

But the assumption is, I would guess with the licensed, it would be that it is appropriate to give both seasonal vaccine and H1N1 vaccine at the same time? It certainly makes the most sense from a delivery standpoint.

DR. MALLORY: I just wanted to put in front of the committee what our data is on the efficacy of a single dose of FluMist in immuno naive unprimed populations.

The estimates that we have in those populations range from about 60 to 87 percent. I am just elaborating a little bit on what Dr. Mendemann said. Generally we estimate

to be about 80 to 90 percent of two dose efficacy in those unprimed populations.

DR. DEBOLD: Along with your comment about delivery and giving seasonal vaccine at the same time that the H1N1 vaccine would be given, are any of the clinical trials going to look at that scenario? Then what about in children under the age of two for their regularly administered vaccines? Are we looking at what happens when this one would be given along with their six month shots or their nine-month shots or 12 or 15 months.

DR. MODLIN: There are certainly studies out there with seasonal vaccine being given concurrently with other childhood vaccines, quite a few. So I think in that case we would be relying on past experience.

I didn't hear any specific -- we may get into this discussion when we begin to talk about immunizing kids under six months or even a greater issue.

Any other questions? Norm, is there anything here we haven't covered on this question with respect to one or two doses?

DR. BAYLOR: No, I think we really just wanted to get the discussion out. Just from the discussion, it indicates how complex the situation is, and there is no right or wrong answer. I think this will be extended into next week's meeting at the ACIP.

DR. MODLIN: Good point. Let's go on to the third question. Please discuss considerations for immunizing special populations such as children below the age of six months and pregnant women.

These are two very different populations with very different considerations. Why don't we start with the easier one, which is pregnant women? I say easier, because obviously they are a high risk group. I don't think anybody is going to suggest that we should not be immunizing them, I hope, but are there special considerations that we should be taking into account? That is really the question here.

DR. DE STEFANO: I would say, if we are talking about unadjuvanted vaccines, probably not.

DR. MODLIN: We are coming to that soon.

DR. JACKSON: Just to prepare and be prepared for the certainty of temporally but non-causally related adverse outcomes that will occur.

DR. MODLIN: To be prepared for the inevitable related to, of course.

DR. JACKSON: Yes.

DR. MODLIN: We have been immunizing pregnant women with seasonal vaccine for quite awhile now, so we certainly have the experience. Granted, this is a new antigen, but we are talking about using preparations that are in essence the same formulation.

DR. JACKSON: I believe in many settings, the trend is to wait until later in pregnancy to administer even seasonal flu. That might be different here.

DR. MODLIN: I'm sorry, do you want to repeat that? I think that is important.

DR. JACKSON: My anecdotal opinion is that many times OBs and others may wait, either by just by practicality or deliberately until people are a bit later in pregnancy to give what they might view as optional interventions as seasonal flu vaccine. In this case, this might be a different timing, and that might be another wrinkle to consider.

DR. MC INNES: In fact, these two populations are so connected, because if we don't improve rates of immunization in pregnant women we are going to have problems in protecting young infants under six months of age. We normally do that through maternal antibody. If we have immunologically naive mothers we are going to have a problem addressing the young infants scenario.

DR. SANCHEZ: In terms of immunizing the pregnant woman, you can't wait too long either, because flu during pregnancy is associated with major morbidity, febrile hospitalized, fetal tachycardia. So it used to be 20 weeks cutoff, but now -- the initial recommendations were to immunize after 20 weeks gestation, but now there is no

cutoff, it is just that they should be immunized.

DR. MODLIN: From a practical standpoint when you have a flu season that is five months, six months long and you have a pregnancy that is nine months, though in practicality most women know that they are pregnant for a period of about seven months, those are going to overlap, I don't see how it is possible to make any specific recommendations about that. I think you immunize a pregnant woman when you have the opportunity to do so.

Any other questions about pregnancy?

DR. DEBOLD: To what extent are the vaccines that are going to be available to use in pregnant women going to contain thimerosal? Will there be a thimerosal free vaccine available for pregnant women and little kids?

DR. MODLIN: Yes.

DR. ROBINSON: We are making arrangements now to address issue, to have thimerosal free or thimerosal trace vaccines in prefilled syringes for both these populations.

DR. MODLIN: Why don't we go on and discuss what I think is a different issue, which is special populations, in particular infants under six months of age. Here we are talking about, I assume, use of the vaccine in a setting at which it has been determined that disease is at some point in time is unusually severe, causing unusually high rates of hospitalization, mortality, serious disease and mortality in

infants under six months of age. Obviously no flu vaccine has been licensed in this age group before. We don't have the safety and the efficacy study and the obvious complication that others have brought up, in terms of giving vaccine at the same time that we are giving a number of doses of other vaccines to these kids, so the interaction between flu vaccine and the other vaccines that they are receiving is a very complex issue, that we hope in time will be much better understood by some of these studies that the NIH are planning to do, and hopefully others down the line.

So are we assuming here a setting in which surveillance data indicates that we are seeing unusually severe disease in this age group, and the question is, what should the response be at that point in time? Is that pretty much the case here, Norm, with this question?

DR. BAYLOR: I think it is both, John. Here is a gap. If a decision is made to immunize the population, here is the gap in the population, how do we address that gap. Limited clinical data in this age group. There is some for seasonal, but very limited. Do we need to address this gap, how do we address this gap, is there a need to address this gap, or the potential to address this gap in the population.

DR. MODLIN: Well, let's open it up. I think it is an incredibly important question.

DR. MC INNES: I think if we go back and we look at

-- certainly there are other bodies of data, but if you go back and look at the Houston family studies that Paul worked on for so many years, and you look at prospectively following families and children born into those families as babies. When I look at the data, these 209 infants that they followed, 69 of them in their first flu season were infected, so about a third became infected with flu.

Twenty-six were infected in the first six months of life. The majority are infected in the second six months of life, probably attributable to maternal antibody, is one of the possibilities.

The rates for severe illness or lower tract illness associated with much higher in the children older than six months than in the children less than six months of age. When you looked at RSV and para flu contributions to lower tract disease, it was significantly more than attributable to influenza. So that is regular seasonal influenza in one section of the country, one particular look. That was very different when you looked at 1976 with the H3N2 in low income children. It was a devastating disease in very young infants.

So I think we don't immunize below six months now. We rely on circulating antibody. Only half of the birth cohort is born during the flu season, and there are all sorts of things. Here we have got an influenza that is going on,

not behaving in terms of having a season. It is with us right now, it has been with us.

So I think that whole scenario is really very different. I think we are going to rely -- we need to have maternal immunizations significantly improved and the babies are the end run. We need to be thinking about immunizing siblings in the household. All of those things need to be in place.

For me, those things become compelling as a priority. Second to me is immunizing infants younger than six months of age.

DR. MODLIN: Let's get some of the pediatricians to weigh in on this.

DR. SANCHEZ: I agree that the goal so far has been to immunize the family, and programs are in place in many places that immunize the siblings as well as the family contacts.

I think that it will be difficult. I definitely think that that is a major research area in less than six months of age. I think this vaccine, whatever vaccine gets approved, absolutely needs to be studied in the less than six month of age.

I don't know how we are going to be able to recommend giving it short of a major disease that we are seeing. I just find it difficult to say that we are going to

be immunizing at two months or four months without having any other data to suggest A, that it works and B, that it is safe. But it has to be a goal.

We have to enroll these babies in studies to tell us over the next few months whether that is something we can do and that we can push for.

DR. MODLIN: It is important to look at interference with other vaccines as a safety issue. If there is interference, then it is a major safety issue with respect to susceptibility to other vaccine preventable diseases, which I think is an important issue.

DR. ROMERO: I agree with all the comments that Pablo has made. We are paying the price today for what we didn't do in the past.

The other issues are of course that some of these babies will have been born to mothers who were immunized at some point. We need to know that data also as we go forward. So I think there are a lot of unanswered questions that need to be addressed. We don't do it now, we don't immunize them now, and I think like Pablo said, it would be very difficult at this point, short of having a disease spike that is very severe in that age group, to make a recommendation outside of what we are doing today.

DR. MODLIN: Peggy, you have done studies in this area. You are being extraordinarily quiet.

DR. RENNELS: I am still trying to figure out industry representative means. One of the major reasons we don't immunize kids under six months of age is that what limited data we have indicate that these vaccines aren't immunogenic, and particularly B.

Obviously the studies need to be done with the unadjuvanted pandemic H1N1, but I don't think we have any reason to believe that it is going to be more immunogenic than the seasonal -- reaction to the seasonal flu.

So I think if we are really serious about protecting by active immunization children under six months of age, then we have to be discussing adjuvanted vaccines.

DR. MODLIN: That is a good point.

DR. GILBERT: I just want to say I really agree with Pamela's comment. Because it may be difficult to start immunizing, or unwise to immunize kids under six months, it seems like an intelligent strategy would focus on the herd immunity effects, and looking at the epidemiology literature to try to see which groups to immunize to get the most reduction of morbidity and mortality in populations. I think that tends to be day cares and young kids in schools. They are going to have their brothers and sisters that are under six months old.

DR. MODLIN: Other comments?

DR. JACKSON: I don't disagree. At least the data

from Kathy Edwards' trial that was done in the BTUs would suggest the importance of maternal antibody or a baseline antibody in these young infants and the influence on immune response. So if the moms don't have any antibody and the babies don't have any antibody, it could be different than seasonal flu vaccine potentially.

DR. MODLIN: But Kathy's data showed that there was some protection from the moms. It was very short-lived, as I recall. It was only for a couple of months at most, was that not the case?

DR. JACKSON: Right, but the babies' immune responses were better in the ones who didn't start off with any antibody.

DR. MODLIN: So it is a complex area. Other comments or questions? One thing that I hope we are all hearing is that we really do need to be doing more studies in this age group. I think there is a pretty strong consensus at least amongst the pediatric group, because there are complexities that need to be addressed.

Secondly, I don't think it would be a bad idea to have a game plan to immunize infants under six months of age, if indeed at some point in time we are seeing very serious disease. Even if it needs to be done under EUA, even if it needs to be done with adjuvanted vaccines. At some point in time the morbidity and mortality from disease could almost

command that we begin to think about that. So having a plan to do so if some trigger is pulled, or the surveillance data, the clinical data, are strongly suggesting we need to do so, I don't think it is a bad idea to be prepared to do that if need be.

Any other comments or questions about this?

DR. SANCHEZ: At least in pediatrics, other high risk populations such as transplant and the transplant populations and oncology patients. I think immunogenicity studies should be looked at, and premature populations.

DR. MODLIN: That is a good point, although we probably don't distinguish these populations from very similar populations in adults as well. With the swine flu vaccine, with the A/New Jersey vaccine we did study special populations in children, as well as normal kids. We don't normally study special populations in children with the seasonal vaccines from year to year, is that not the case? Most of the kids that we enroll are otherwise normal healthy kids for the most part, and we just assume that kids with special health care needs would benefit from the vaccine, and we make the same assumption, that vaccines would be safe in these kids as well. But I think you raise a good point.

DR. DEBOLD: I think that is a tremendously large assumption, that enrolling only healthy kids in the clinical trials gives you information about how unhealthy children

will behave in response to vaccination. We get questions all the time from parents who have kids who have a variety of health problems, and these type kids were never enrolled in clinical trials.

So I think it is a big assumption. We need to make that really clear, when you let the public know what you do know and what you don't know about the effectiveness and safety of vaccines, that it is couched that these are the populations that were studied, and we don't know anything until we get into post-marketing surveillance for other types of populations.

DR. MODLIN: Why don't we go on to another easy question, which is, please discuss the considerations for use of adjuvanted vaccines. I guess we all heard many times there are two important reasons for considering adjuvanted vaccines, maybe more than that. One is from a public health standpoint, in terms of adjuvants being dose sparing, so that you can extend the vaccine that you have to a larger population. And of course, the other critically important issue is the immunogenicity, obviously related.

I don't know, I am struggling a little bit as to where exactly to start this discussion, but maybe I will do that by putting Norm on the spot once again. Maybe you could just give us a general overview of what concerns the agency may have with respect for adjuvanted vaccines and the safety

of adjuvants.

DR. BAYLOR: As you saw in the clinical trials that were presented, we have asked that all of the studies of those manufacturers who have adjuvanted products, that are including an adjuvanted arm. We may need -- if it comes to pass that we need an adjuvanted vaccine, that the unadjuvanted product doesn't give us an optimal response, we have asked that those studies be looked at. Also, as NIH and BARDA presented, mix and match studies using the ASO3 with the CSL product and the Sanofi product.

We presented also that the adjuvanted products would be used under an EUA. We don't have a lot of experience with these products. The regulatory pathway that we presented was unadjuvanted because we have the decades of experience with that, and we can move with that much quicker than we can with the adjuvanted product, based on the experience that we have.

We asked this in the context of, our pathway is to look at these -- to use these products under EUA. They are not licensed in the United States, although there are some of the adjuvanted products that are licensed, at least one in Europe.

But also, the issue comes up with special populations as well. We brought this to the advisory committee, the previous advisory committee we had, where we

talked about studying adjuvanted products in the pediatric population.

So we want to now get a discussion going of, are there things we should be looking at or things that we should be considering as we go forward, and the potential exists that we might have to use these products under EUA, are there any considerations that the committee would recommend that we focus on, and any advice you can give us on whether we should -- how we should potentially look at these products in some of the special populations.

DR. RENNELS: I believe Robin Robinson mentioned that there was a decision tree that had been established. Bruce, you said that this committee would be involved in discussions about EUA and use of adjuvants. It seems to me, rather than trying to reinvent the wheel, if we could see the elements in the decision tree and how they are weighted, that might be a starting point.

DR. LEVANDOWSKI: Just some general comments about adjuvants. I am thinking now about some of the study designs that we saw earlier and how those may be useful.

I think, still perseverating on the notion that there is probably immunologic priming for H1N1 viruses where there has not been for H5N1, the kinds of information that are likely to come out of the studies that are going to be somewhat different, it is pretty impressive for these

adjuvants with enough primed population for H5N1. I don't know that the differences are likely to be as huge in the study where the population has a lot of immunologic priming.

In fact, again going back to those studies in the '70s with swine flu and Russian flu, dose response curves were generated and they were pretty flat. That has been true with a lot of studies done subsequently, looking at influenza vaccines. I think there needs to be some caution in trying to make sense of whether there is any addition to immunogenicity as a marker of what we hope is going to be effectiveness. Generally we think that the higher the antibody titer, the better. But I think we need to be cautious in trying to interpret in studies where you don't have a concomitant control that is exactly the same dose.

I notice that there were some of the studies that were presented to us where it was suggested that the standard dose of vaccine, 15 micrograms, would be compared to a lower dose plus adjuvant. I think those are very difficult to interpret. It would be better for everybody if there were the direct comparisons within the same study, not in different studies.

An example that I would give that mirrors that, although in a slightly different way, are the studies with intradermal administration of vaccine. One of the original studies was a comparison of the original 15 microgram

standard dose to one-tenth of that dose administered intradermally, and it came out looking like the immunologic responses were similar. But when the study was repeated using the same dose given intradermally and intramuscularly, it turned out that they were pretty much the same across the board, even with a very low dose of vaccine, the one-tenth dose, and you really couldn't discern too much difference between them.

So I think whatever study designs are used need to have those controls that make the data more directly interpretable, to be able to determine whether there really is an advantage in terms of immunogenicity.

Then in terms of the populations, that same story, determining who is primed and who is not. Going back to the H5 story, it is very impressive that the adjuvants that have been used, not aluminum type adjuvants, but certainly the oil and water emulsions, there does seem to be a very dramatic increase in immunogenicity in individuals who are immunologically unprimed. It is very clear there, I think.

DR. MODLIN: Other comments?

DR. EICKHOFF: I'm glad Roland raised the issue of intradermal vaccine, because I was going to bring it up too as anther antigen sparing technique that always comes up in a setting such as we are in today.

None of the clinical trials that were outlined has

an arm related to the intradermal use of vaccine. So my question is, was intradermal vaccination considered and ruled out, or was it not considered at all?

DR. MODLIN: I don't know who to address that question to.

DR. EICKHOFF: Linda Lambert, if she is here.

DR. MODLIN: Linda, do you want to have a go at it?

DR. LAMBERT: It was not addressed in our presentation and our discussions. We did intradermal studies with the H5N1 vaccines. What we found was that when we gave the same dose level intradermally as intramuscularly, we saw no significant increase in antibody responses through the intradermal route. That is right now limited to our experience. With an unprimed population, it is just the H5N1 experience.

DR. MODLIN: Norm, I don't know if you can even discuss this, but have you ever had discussions regarding routes other than IM with seasonal vaccines?

DR. BAYLOR: Embarrassingly, I can't remember. We have had discussions with varying routes such as intradermal with other vaccines, but specifically putting that on the table, I can't identify studies that we have had under investigation specifically for influenza vaccines, looking at that. But that doesn't mean we haven't had them.

DR. DEBOLD: With respect to using the squalene

based adjuvants that we have been talking about, this is probably the issue that is likely to get the most amount of attention as it relates to the public that is very concerned.

The parents that we are hearing from are concerned about the safety of combining those types of adjuvants along with other vaccines in the regular childhood schedule. They are very concerned about giving vaccines with these adjuvants to populations that are predisposed to having autoimmune problems. They are concerned about the extent to which we actually have access to data on adverse events from both preclinical trials as well as the clinical trial data.

This has to be absolutely and completely transparent, or the very first time that something untoward happens to a child who gets one of these vaccines and it is a kid that has eczema, food allergies and something else, it most certainly will be a serious problem.

So I just put that out there for your consideration, because I think it is really important. As I look at some of the data that were presented today, I keep asking myself, how high is the titer we really need to have in order to have an effective vaccine. This is clearly a tradeoff here. I understand the antigen sparing and the cross reactivity and stuff, but how much of these adjuvants are necessary to get a titer that produces a vaccine that is effective? We obviously need to use as little as we have to.

DR. MODLIN: Vicky, can I turn this around and ask you a question? You did hear from a couple of the manufacturers earlier today that these adjuvants have been used in Europe now for more than ten years, that they have been given to millions of vaccine recipients, and certainly thousands if not millions of children, and with a safety database that appears to be pretty unremarkable, other than the fact that obviously adjuvants increase the rate of local reactions. We all recognize that.

But in terms of serious adverse reactions, while there is a concern here, I guess the question I would have for you is, how much of a safety database would you like to see before you would feel comfortable with adjuvanted vaccine?

DR. DEBOLD: I would like to see the data that come from trials where there was a true placebo used, a saline placebo. I would like to see that data. I would like to see the animal model data if we have that. I know there were adverse events that have been explained as being not related. I would like to see thorough detail on these data. DR. EICKHOFF: Some of this data has been published, I know because I have seen it. I can't remember the details of exactly where it has been published. The representative from GSK alluded to the experience that GSK has accumulated. I don't know if that particular data has been published, but if

it has not, then I think we would all like to see it.

DR. TSAI: I didn't have a chance to mention that the analysis of our pharmacovigilence database for Fluad, which is a seasonal vaccine that has been licensed since 1997, there also was a comparison of reporting for specific adverse events associated with that vaccine and the unadjuvanted counterpart, the TIV that is the parent of Fluad. There was no difference in the reporting rates through the pharmacovigilence systems for those serious adverse events such as Guillain-Barre syndrome and acute neurologic disorders, and a short list of others.

So there is some basis for comparison within the same pharmacovigilence system for an influenza vaccine that differs only from the unadjuvanted vaccine by the presence of MF59.

DR. MODLIN: Dr. Innes, did you want to add to that?

DR. INNES: The pre-licensure trials of the Quebec H5N1 were versus placebo. There were about 4,000 recipients of adjuvanted vaccine. The initial publication is under review. I don't know when it will be published, probably in a matter of months.

It is the policy of GSK to publish every clinical trial that we do. So the large phase III study will also be published, probably not again for another couple of months.

If it is a matter of extreme public interest, then I think the company would consider very seriously making the data that are in that integrated summary of safety, looking at the experience in 12,000 individuals, in which we looked for diseases that were potentially immune mediated and saw them, but saw them in controls as well, that we would be interested in finding a way to rapidly put that into the public domain.

I understand that what you are saying is that these kinds of decisions will be impossible without extraordinary transparency.

DR. DEBOLD: I would say if you could do that, I think that would go a long way to helping to provide information for people to make their own personal decisions with.

I would also like to add, I know in the materials that we had to review prior to the meeting, and we talked about this also at the February meeting, about the child who had autoimmune hepatitis, we need to be thinking about which people should not be getting vaccines with these adjuvants in them, order to improve safety; is there a list of people with certain health conditions that should not get those vaccines.

DR. INNES: Perhaps it would be useful to update the committee on what happened to that child and maybe some of the follow-on investigations that have taken place.

It has been subsequently determined that the child

in fact had autoimmune hepatitis prior to receiving a dose. It was asymptomatic and not recognized. That child had a fluctuating course of liver enzymes, but was never symptomatic.

In a period of months after the first dose, the child was removed from the trial, once it was recognized there were abnormal enzymes, so she never got a second dose. Enzymes went up, they went down.

We presented the case to outside consultants that were experts in autoimmune liver disease, and they felt that what happened to that child was pretty typical for what happens with autoimmune hepatitis. She was placed on therapy, had a very, very rapid response to therapy and now has normal liver enzymes and throughout the entire course remained well.

In discussing how to handle the issue of whether children or adults, because the prevalence of autoimmune liver disease is about one per 10,000 across the entire spectrum of age, their recommendation to us was that clinical trials should enroll these kinds of subjects. They are at risk, perhaps at increased risk for complications from influenza, and there is not really biological plausibility that adjuvants that are being used -- and I think all the manufacturers have presented data that shows that the effects of the adjuvants are limited in time, limited to the space

where it is injected and in the draining lymph nodes. They don't have widespread activation of the immune response, and there isn't plausibility that they would activate autoimmunity in organs separate from the muscle where they are injected.

So their recommendation to us was, please, you should screen and you should follow biochemical parameters of safety, but don't exclude these kinds of subjects in the trials. You will end up with labeling that says such people shouldn't get the product.

Now, we have had discussions with CBER about what to do, and we reached agreement that in phase I studies, it makes sense to screen out persons who have abnormalities of liver enzymes, who have abnormalities of renal function. But at some point after a phase I study when you have more certainty about what the risk-benefit profile of that is, these are the kinds of patients that then need to go into pre-licensure trials and be followed with controls.

DR. MODLIN: Good points. Did you want to follow up, Vicky?

DR. DEBOLD: I think anything you make publicly available on the topic you should, because it is not just autoimmune hepatitis that the parents are worried about. There are kids with diabetes, kids with asthma, a lot of immune activated illness out there, and there are a lot of

questions about what happens when you bump up someone's immune system to the extent that we do.

If you have information also about mechanism that these adjuvants work by, the biological mechanisms, that would be helpful, because I would like to see them myself.

DR. MODLIN: Any other comments about adjuvants?

DR. EICKHOFF: No one has yet addressed the question that Peggy addressed, namely who and how is the decision going to be made.

DR. MODLIN: Is this a decision that ultimately will be made by the Secretary as well? I would guess the answer is probably yes, with a lot of input.

DR. GELLIN: I think the input is going to come largely from here in these discussions. So I'm glad Ted re-raised it. Like any component of a vaccine, I think there needs to be a clear justification for who it is there and what benefit it would provide and at what risk. My sense is that providing this as a question was allowing this question to be explored in many ways that would then be fed in.

DR. RENNELS: I think we could all come up with a number of elements that go into the decision. It is a risk-benefit. One of the risks is how severe is the disease. One of the issues obviously is capacity and vaccine supply, cross protection.

But in each of these things, I would think you

would be able to put a weight to them, put them into a formula and say this is what would trigger an EUA for use of adjuvanted vaccines. If there is already -- can this decision tree that has been alluded to be shared with us? Unless we know what -- unless we have an opportunity to see it, we can't weigh in.

DR. GELLIN: This is not as elaborate as it has been made out to be. Basically it is more of things that should be considered along the way. You have raised some of them about the disease, you raised about the availability of vaccine, the potential for cross protections. We have had discussions about the stability of the virus. I think it is essentially the list of those things that would drive you to want to use this, and theirs would be an excess need.

I think among the things that we have raised is the timing on which vaccine could be available, because that wouldn't speed up the timing to the first dose, at least my understanding, but it would allow more doses to come out earlier, because you would have adjuvant that was already produced that could then be coupled with an adjuvant to allow more doses sooner.

So those are the elements that are there. It is more of a checklist for considerations than anything that is an elaborate decision tree with percentages at each node.

DR. RENNELS: But it seems to me that an elaborate

decision there is what we need to start growing pretty quickly. We could start throwing out, a hospitalization rate reaches this, or mortality reaches this, and then an EUA gets triggered.

DR. MODLIN: Peggy, I think you have got a great point, and I understand what you are trying to get at. But of course we can't anticipate every scenario.

DR. RENNELS: No.

DR. GELLIN: The other side of it, I think we have to also consider the recipient side of it as well. That gets into demand. There is a lot of factors that would influence whether people were interested in getting in line or anxious to get in line or anxious about being first in line. So I think is a piece of it as well. I think part of the discussions that we have had, and part of the -- we are planning to get some engagements in the public at large to get a sense and take their pulse of what they think of some of these issues as well, because ultimately they are the ones who are going to be making the decision for themselves and what they are interested in.

DR. MODLIN: Norm, I would assume at some point in time, in the middle of October or the first of November when things have changed, it looks like we are running out of vaccine for whatever reason or are in the midst of disease, there is no reason why we can't have a conference call of

this committee and have all the data that is available at that time presented, and have further discussion about this. This isn't going to be our only opportunity to weigh on in this, which I think is an important point to make.

DR. BAYLOR: Right, absolutely. In fact, as we move further into the fall, we are going to plan on providing you an update of where things are. So this is not the first.

Also, we are not asking you to develop criteria which we would use. That is not the focus of that discussion item. It is part of our pathway as we said. We have asked manufacturers to incorporate those that have adjuvants and with the mix and match, to incorporate those studies. All of this is contingency planning, so we will be getting data from those studies for the H1N1. The manufacturers have already presented data that they have on H5N1 and other influenza vaccines with these adjuvants, so you have that information.

We are also in the context of the clinical trials, what I really wanted you to do is discuss that, and are there other things that we should be considering, are there other things that we should be looking at in the clinical trials that we put forth, not necessarily to make a recommendation to use or not to use adjuvant. Right now, the contingency is, if we have to use these adjuvants, we are going to have some data to make those decisions, and are there other things that we should be looking at. That is what it was.

I understand your point, Peggy. If I was asking you to make the recommendation, I would need to give you more information as to how this would roll out. That is not what we are asking at this meeting.

DR. EICKHOFF: I don't want CBER to walk away from this meeting thinking that we are all afraid of adjuvanted vaccines. I think some of us are and some of us aren't. But speaking for myself, I am delighted that the option is there.

DR. MODLIN: I will second that.

DR. RENNELS: Third as well.

DR. MODLIN: Let's make certain that we have covered Norm's point, which is, are there gaps, are there holes in the research plan here that we are overlooking with respect to adjuvanted vaccines. You have heard all of the vaccine manufacturers' plans in some detail, and we have heard of course from the agency. Are we missing anything here, Frank?

DR. DE STEFANO: I don't know about missing. I'll make a comment. It seems like a potential concern is safety. We have heard there is a lot of experience from Europe. I just would hope that if this is brought back to us at some point, that there has been an independent sort of summary of all the safety data that are out there and available to FDA for us to review.

DR. STAPLETON: And the data do appear that adjuvants are quite effective at boosting GMTs. But as Roland said, some direct comparisons of doses would be helpful.

DR. MODLIN: Right. If Sam Katz were here, he would point out once again that we do not do AFP surveillance in this country, like many other countries do for purposes of picking up cases of polio. Would it make sense, if there are concerns about unusual diseases, I won't call them rare, but unusual diseases such as autoimmune hepatitis, would it make sense to identify gastroenterologists who take care of these patients, identify patients going forward and doing the case control studies, much as what has been done with Guillain-Barre in the past?

I just kind of throw that out there as a safety issue. Sometimes that is a more direct way at getting at some of the specific questions that Vicky was raising and others. I don't know how difficult, how expensive, these studies are to do, probably not very. So that would be one other thing to consider.

DR. GELLIN: Hector's presentation had a flow diagram that you need oil immersion to read, but if I can read it, it says that there are tier one and tier two adverse events. So maybe we can hear a little bit more of what these lists are going to be, and how they may be followed up.

DR. IZURIETA: We are still discussing the final list of tier one and tier two adverse events. But the basic criteria are adverse events which have been related to the use of influenza vaccines in the past. One example is anaphylaxis, another example GBS. Although there is no known association of GBS with seasonal influenza vaccines, the assumption is and the understanding currently is that if there were an association, it will be an attributable risk of one per million vaccinees.

So there are not many databases in the world that can resolve that question. We are currently investigating that in a Medicare database, and we are trying to get those results. We have preliminary results that are being submitted, but because of that, because of our precedent, one episode in 1976 with another swine flu vaccine, we are including this in the tier one. We are also including in tier one, other adverse events that could be considered an autoimmune nature, which has to be able to preempt questions that could come up regarding those types of events and influenza vaccines, things like Bell's palsy and others. It is a relatively short list, and because of efficiency in this type of research, the more adverse events we include, the less efficient we become to find answers, and the more time, the more work, the more interactions and problems.

So that is why in the tier two and tier three, we

are trying to include all the adverse events of concern for influenza and other vaccines. If we end up using adjuvants we will include those events of concern for adjuvanted vaccines. For those ones we will use a simpler phased design in which we will just compare observed versus expected in the large databases we are working with, and then try to incorporate and move them to the next phase, more formal analysis, if there is a signal detected either there or in the passive surveillance system.

I don't know if I answered the question at all, but that is what we are doing.

DR. MENDELMANN: I didn't see in the designs that there was a plan to look at a potential adjuvant effect of live, dead, two-dose, dead-alive, dead-dead, live-live by the NIH. There is a CREDA with the NIH, so it is freely available. But if there are 200 million doses available of live and that is effective priming, then we ought to see whether following live with dead gives you an effective boost.

I think you have got two traditionally licensed vaccines. They would be given at mixed regimen, and find out if you are seeing high HIA antibody titers. You can even look at NA antibody titers and see if you are getting a reproducible booster type response that you wouldn't get from dead-dead two-dose.

DR. MODLIN: Dr. Lambert, you may wish you hadn't stayed this long. You did show us that you were doing some mix and match studies. I don't know if you want to deal with Dr. Mendelmann's comments. This is yet another iteration on what you are doing already. I don't know if you want to say anything else about it or not. You don't have to.

DR. BENNET: No, just to say at this time we haven't considered that particular study design.

DR. MODLIN: Any other questions, or have we pretty much done adjuvants? Let's go on to question number five, which is, please discuss the proposed post-licensure evaluations for safety. Please identify any gaps that may not have been included in our proposal. It is critically important. We have been discussing safety for the last five or ten minutes, so we have already ventured into part of this question. But let me open this up and see if anybody feels that there are gaps that we are not addressing.

We haven't talked a lot about Guillain-Barre syndrome. We have talked around it. Should we be doing more here to try to look on a postlicensure basis, for what have we learned in the past about this that will help us address the issue of Guillain-Barre syndrome going forward, I guess is what I am asking.

Frank, you are the man on the spot.

DR. DE STEFANO: We focused a lot on VSD and such.

The issue really is, with this much vaccine being given, we want to detect some of these signals as early as possible. Certainly after all of these doses are given, VSD could probably confirm the signal. Obviously a signal is probably going to rise for GBS or anything else probably from VAERS, but then to verify or confirm you have a large enough database to do that.

I don't think Hector went that much into the study that we are investigating and hope to get into the emerging infections programs in ten states. They cover a population of a catchment area of 40 to 50 million people. We are involving the neurology societies to try to identify all cases of GBS there. So I think that will provide us a larger population than the VSD, to identify GBS. Perhaps this system could be adapted to other conditions if there was a signal that arises.

DR. MODLIN: Then the plan would be to do case control studies around those cases.

DR. DE STEFANO: It depends on what kind of vaccination coverage information, if there is data available from registries. If you know what coverage is in the state, you could do observed versus expected on coverage data, or yes, you could go to a case control study.

DR. IZURIETA: But it is a very difficult problem. We are talking about a potential risk of one per million or

even one per 100,000 as it was in '76. But there are a number of things we are doing together with CDC and with other partners besides the neurology study, which is going to be very large. The Canadian public health system is doing a similar study trying to put together neurologists in the whole country or in large sectors of the country as well. We are exchanging with CDC and with them and also with the Europeans other case definitions and methodologies for case abstraction forms. So eventually we can put together those results and make a larger study from it.

The same thing with the efforts that CDC is leading in the use of the Vaccine Safety Datalink. The Department of Defense has volunteered to put their data on GBS and other, let's call it tier one adverse events into the VSD system, so we get a larger system in which we can investigate signals. We will do similar efforts with whichever database we work with.

Will that solve the problem? If there is a huge problem, yes. If there is a very small problem, we will need more time, more databases. Medicare is wonderful as well for the elderly, but we need to know who is vaccinated and who is not, and so on.

DR. DEBOLD: This is something we talked about at another meeting last week. I have got some questions about how solid the tracking of the vaccine and the lot numbers and

the manufacturers, particularly if the vaccines are going to be administered perhaps in a school setting, to be efficient. If we are talking about mixing things at the time of administration, you are going to have a manufacturer and lot number for an adjuvant, manufacturer and lot number for the antigen perhaps. So there are two pieces of things that need to be kept track of, along with who the individual was who received the vaccine. There needs to be some very active monitoring afterwards.

One of the things that we talked about in the meeting we had last week is something that the Department of Defense is doing through their MILVACS program of an active post vaccination surveillance form that could be maintained by the parents somehow, so that you could get some data to begin to keep track of what happens, rather than waiting for someone to call in and say, is this related or is not related.

DR. MODLIN: Other comments or questions about safety?

DR. IZURIETA: We are working with the Department of Defense. The better design we are planning to use is, get absolutely every case that is registered in the system. You have 100 percent or near 100 percent coverage of the cases, and then you know who is vaccinated.

The voluntary reporting systems have advantages and

disadvantages, and the reporting is a problem. But with regard to vaccine distribution, which seems to be the second part of your question, maybe CDC can comment, unless something has been said earlier.

DR. MODLIN: Thank you. Any other discussion?

DR. GELLIN: The question is about international. It is going to vary a lot because different countries are going to use different products. But I would like to hear a little bit more about how we might be able to share, or are there plans for sharing information at some level between health agencies or regulators or somehow, so that the overall number is increased.

DR. MODLIN: We certainly heard earlier that there is communication amongst the various regulatory agencies. Do you want to go over that again?

DR. IZURIETA: The first thing is, this outbreak has been an important opportunity for us to improve the efficiency of our work and the degree and intensity of our cooperation. So I want to make this clear. That also means this is also -- many of the things we are doing are first, and we will have to advisory committee that.

We are in FDA through the international office and with HHS, NVPO, CDC and other institutions -- we have two types of international regular contacts with WHO and also with other regulatory agencies at the more potential level at

which decisions are made. We also started two months ago with a more technical discussion with researchers from institutions with whom we have agreements for confidentiality, and even in some cases with institutions for which we have no confidentiality agreements, to exchange information, methodologies and even study designs.

We think this is a good step. We think we will get something from this in regard to amount of data and exchanges of information in regard to, signals detected in one system will be confirmed by an independent study in another system, which is a significant contribution.

I don't want to be overly optimistic. The safety surveillance of adverse events is very difficult. The more complicated the event case definitions are, the more complicated the whole process. So I don't want to give the impression that we have everything resolved and this is La-La Land. It is not. It is very difficult, it is complicated, and we are doing all we can.

DR. MODLIN: Thank you.

DR. GREENBERG: Good afternoon. Michael Greenberg from CSL. I think some of the recent comments have touched on this a little bit, but I think just to bring it more explicitly, it is very impressive, what the safety surveillance systems are that we will be relying on to look at post-licensure safety.

But again, with the situation of having vaccine from up to five manufacturers and at least as many formulations, if not possibly more, what mechanisms are in place to be able to differentiate between the vaccines? Will it be possible to discern vaccine by manufacturer in the existing surveillance systems, should there be any differences in the safety profiles.

DR. DE STEFANO: I can answer. The VSB does capture manufacturer and lot number. This is a concern about capturing that information in systems where like health plans that receive claims data, or have an issue where there is a CPT code that will indicate that the H1N1 pandemic vaccine was administered, but it does not go beyond that to identify manufacturer.

There is some interest in seeing if an additional digit could be added for that purpose. A vaccine may be given through the public program, even if it gets into registries and stuff may not identify the manufacturer.

So I guess there is some discussion of providing this information or making sure it is recorded, either with a provider or the patient, that they are given a shot card or something that they could refer back to with this information.

DR. MODLIN: Why don't we go on to the last question, which has a couple of parts to it. First is,

please comment on approaches to assessing vaccine effectiveness. Second, consider the potential need for diagnostic methods to distinguish pandemic H1N1 strains from circulating seasonal strains and other influenza-like illness. These are pretty much two different questions.

In terms of assessing vaccine effectiveness, we had heard a nice presentation from Dr. Fiore this morning about the plans for surveillance and a menu of studies that were planned to assess vaccine effectiveness that I thought were pretty impressive. I don't know if anyone wants to add to what we heard about, or has additional suggestions for assessing effectiveness.

I don't know if Dr. Cox or Dr Fiore or anyone else want to address that any further. I think you gave us a nice presentation this morning on that topic. Are we missing something here?

DR. DEBOLD: I have a question. How do you know whether someone who got the vaccine and then didn't get the flu when exposed to the flu was because they got the vaccine or perhaps they had previously had the flu this past year. How do you know that? In the trials, do we know who didn't get the flu this past year?

DR. MODLIN: You do it on the basis of case control studies and others. Dr. Fiore, do you want to address that question? It is the scientific method.

DR. FIORE: Your concern is that someone who gets vaccinated in the fall might have had H1 in the spring and they don't get infected in the fall, and is it that they have immunity from their previous infection or the vaccine.

DR. DEBOLD: Right.

DR. FIORE: We can't tell that. If there are people who have had a lab confirmed infection, we potentially could screen them out. But we won't exclude people because they say they had a respiratory illness sometime in the spring. The number of people who will know that they had a lab confirmed flu who are in the study will be small, probably none actually.

So yes, it could happen. This kind of thing is always an issue in studies. You always have some people who get mis-assigned.

DR. MODLIN: But they should fall out equally between the case group and the control group.

DR. FIORE: Yes.

DR. MODLIN: That is how you adjust for that factor. That is the point.

DR. FIORE: That is a key point.

DR. SUN: This may be a little bit outside my lane, but part of the issue that may be very, very important to know, especially with something like an influenza vaccine, will be some of the indirect effects of a vaccination on the

population. Vaccine effects may be direct in terms of preventing infection in the individual or it could be preventing symptomatic disease but not preventing infection, or it may decrease infectiousness or shedding of the virus, lowering transmission to the population. All of these combined has an effect over and beyond the individuals.

In any measure of effectiveness of a vaccine, ideally you want to measure all those effects. I think it is especially important for something like this, where we are talking about vaccinating communities.

DR. MODLIN: You are asking, how do you get at the question of how much herd immunity the vaccine may produce.

DR. SUN: Correct.

DR. DE STEFANO: I don't have the answer to that. I was just going to make a comment on this issue of distinguishing between natural infection and vaccination effects. It is relevant to adverse events as well.

In GBS for instance, there is some evidence that natural influenza infection can increase GBS, so trying to distinguish if a GBS case of a vaccinated had had actual disease, and which cause may be tricky.

DR. MODLIN: Lisa, do you have any insight?

DR. JACKSON: Not to that question, so I can wait.

DR. MODLIN: Please go ahead.

DR. JACKSON: I think the proposed plans for VE are

very reasonable. In the ideal world, in the absence of an experimental design, perhaps the gold standard would be something that involved active surveillance.

These all appear to involve people coming in to see medical care, and that may be the limits of feasibility. You could argue that that is looking at more severe cases. However, people vary greatly in their predilection to come to seek medical care for illnesses of the same severity. In addition, there is a time element with how quickly they come in and our ability to find out that they have this particular infection, which is critical.

So if resources and time were unlimited, ideally I think you would have a large cohort. You would do some sort of active follow-up, as you would in a clinical trial of influenza vaccine efficacy, and you would have people within the cohort who had been vaccinated and who had not. Even if they had not been randomly assigned to that, that would still be perhaps one step up.

DR. DE STEFANO: If I could just comment, we are looking into the possibility of doing that, at least in a web-based or telephone follow-up.

DR. FIORE: I think that the Dod studies might be a little closer to that. They have a very large group of vaccinated persons. They will follow up, and have been very active with reporting measures also to the committee in the

past.

DR. JACKSON: They might have a limit of not having very many unvaccinated people.

DR. FIORE: Yes, that is an issue potentially.

DR. MODLIN: Presumably there will be some, for whatever reason, but your point is very well taken. It is not a large number. Schools, school based surveillance is certainly another possibility. At least it is a narrower age group but an important one. I think one can easily do active prospective surveillance in schools during influenza season. There have been many, many of these types of studies done.

Other approaches to assessing effectiveness that we haven't considered? Let's go on to the next question then very important. Consider the potential need for diagnostic methods to distinguish pandemic strains from other circulating influenza strains and other non-influenza respiratory illnesses.

It is a big problem. It was discussed at some length at the NBSB meeting a few weeks ago. Dr. Robinson, do you want to give a brief two-minute summary of that meeting with respect to diagnostics? It was discussed in some detail at that time at the NBSB meeting. Sorry to put you on the spot, but it might help us.

DR. ROBINSON: No, because I have my colleagues from CDC here, who can also comment. I think it was fairly

clear that diagnostics are going to be limited as far as the diagnostics, but they may be important as surveillance tools.

Some of the point of care diagnostics that have been shown as experimental products so far may have a big role in surveillance at sentinel places across the country. So the idea is, we are in year three of a five-year plan, and this is where we are. In two more years we will be in much better shape, but this is what we have right now.

DR. MODLIN: It seems to me that the current state of the art is such that for routine cases of influenza or influenza-like illness in patients that you would not anticipate treating with an antiviral agent, that there probably is very little reason for applying diagnostic tests. This is much more important when we are talking about surveillance.

DR. ROBINSON: I think the state of the art where diagnostics are right now, and what is bubbling right now with the antivirals as far as drug resistance, I think it is a very complex issue. It would be very difficult to give finite things on that, except that I think we all know that the diagnostics we have have limitations, let's put it that way.

DR. SANCHEZ: I don't know if that is accurate in pediatrics. Certainly we may test some of these kids for influenza in order not to provide antibiotics, even if we

don't provide antiviral therapy.

But short of the diagnostic methods that are utilized, which is another issue, I also think that there is a lot of variability in the testing. I think in pediatrics we test a lot more than in adults. That is my impression, at least from our hospital.

DR. MODLIN: I think you are probably right. I think the critical issue is the reliability of the tests we currently have available, and if they are so unreliable as to whether or not to be useful in a clinic setting, particularly when you are dealing with a child or even an adult for that matter who otherwise are unlikely to be a candidate for antiviral therapy, whether or not there is a need to test everybody who comes in. I think most of us would agree that the answer to that is no. It is the hospitalized patients and others where you need to be able to distinguish amongst flu strains in order to make appropriate therapeutic decisions.

Ted, help me out here.

DR. EICKHOFF: You are doing okay all by yourself. It depends also in terms of measuring vaccine efficacy, which strains happen to be co-circulating. If the pandemic strain and the seasonal strains, or at least two of the seasonal strains are co-circulating, that is one problem. If on the other hand we have only the pandemic strain

circulating, as happened in 1957 and 1968 both with H2N2 and H3N2. Then it is much easier to determine vaccine efficacy.

DR. MODLIN: But that is a surveillance issue. If you are assessing vaccine efficacy, you have to do surveillance to do so. We are talking about the routine application of diagnostic tests. Well, maybe we are not talking about that as the only thing.

Norm, was there something specific that you were hoping to get out of this discussion, other than the fact that there clearly is a need -- I think we would all agree that there is a need to have improved point of care diagnostic testing.

DR. BAYLOR: Yes. Just to make it known that this fall, if we have the 2009 H1N1 circulating, the seasonal viruses circulating, plus all of the respiratory viruses we have circulating, the effect on the program. If we are looking at benefit-risk of these vaccines post deployment, and having a reliable way to distinguish between those who are truly infected with the 2009 H1N1 virus, and how effective that vaccine was idividuals who may be infected by another vaccine, a seasonal vaccine or other respiratory disease, you could lose confidence in the program if an individual says, I was immunized with the 2009 influenza vaccine, I still caught flu.

That is the usual thing we get every fall, but this

will be escalated this year because we will have the potential for lots of things circulating, and we are immunizing against two of those things, and trying to distinguish that, and making sure that if those diagnostic tools are not in place, do we need to try to get those in place, what do we need to do to do that.

DR. COX: I would just like to make it clear that for the four sites plus the EIP sites, they are using the real time PCR tests. So we will be able to have type and subtype specific vaccine effectiveness as we move through the season.

DR. MODLIN: Thank you.

DR. ROMERO: I had a question regarding the diagnostics. There is clearly a process for licensing diagnostic tests for public use. So the question is, are you getting these types of tests, newer tests, being submitted by companies trying to fill this niche of specific diagnostics? Is there a mechanism similar to this where you can license them based on previous data if you are just adding another antigen? I would suspect that those companies are very interested in getting these out into the market.

DR. GOODMAN: I would comment two things. FDA is working through the Center for Devices as part of our management of these emergency, both with our colleagues at BARDA and HHS, and with numerous diagnostic companies, to try

to facilitate availability of better testing.

I think the rapid point of care tests are a longer term project. There are a lot of challenges with their performance, as you know, even with seasonal flu, but we recognize that even for this current event there is a need for more testing. Again, we are trying to work on accelerated pathways. For example, emergency use authorization is potentially available if there is an unmet need, and we can assess it and show that the tests meet a reasonable standard of benefit versus risk.

DR. LO: If you want to do a serology, diagnostic test, there is a stretch in the hemagglutinin of the seasonal and also the pandemic that are very different. That is, the CSVAGH, that is for the seasonal one, and for the pandemic it is CNIAGW.

These two stretches in the hemagglutinin, they are very antigenic. If you do the MHC-2 binding affinity, they are very high. So that means that the host should be producing very high titer of antibody to those two stretches in the pandemic as well as in the seasonal one.

So if you want to try to distinguish these two, you might want to try to prepare the antibody for either one of these, and then test and see if you can get a differential.

DR. MODLIN: Thank you. That is a nice observation, but of course the trick is translating that into

a usable product that we can all use. Thank you.

Any further discussion on diagnostics? Did we get enough information out on the table, Norm, to address this question? Is there anything we haven't discussed?

DR. BAYLOR: I think we have covered all that we had. Like I said, we will keep you up to date and update the committee even if we do a conference call as this unfolds, and as we move forward.

DR. MODLIN: I would like to thank everybody for a terrific discussion. We covered a lot of information in a very short period of time, so thank you, everyone. It is only five past four. We will see you in September.

(Whereupon, the meeting was adjourned at 4:05 p.m.)