

Overview of H1N1 Vaccine Safety: Licensing, Clinical Trials, and Vaccine Safety Monitoring

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Coordinator: Good afternoon and thank you for standing by. I would like to remind all participants your line will be in a listen-only mode throughout the presentation. To ask a question, please press star 1. To withdraw your question press star 2. This call is being recorded. If you do have any objections you may disconnect at this time. And I would now like to introduce your host for today's call, Alycia Downs. Ms. Downs, you may begin.

Alycia Downs: Thank you. Good afternoon and welcome to today's COCA conference call -- overview of H1N1 vaccine safety, licensing, clinical trials and vaccine safety monitoring. We are very excited to have four subject matter experts present on this call. Each is going to hand off to the next presenter throughout the presentation.

We are going to begin with Dr. Bruce Gellin, Deputy Assistant Secretary for Health Director, National Vaccine Program Office, U.S. Department of Health and Human Services.

Dr. Theresa Finn, the Associate Director for Regulatory Policy Office of Vaccine Research and Review Center for Biologics Evaluation and Research, Food and Drug Administration

We will then have Dr. Richard Gorman, Associate Director for Clinical Research Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Disease, National Institutes of Health

We will then hear from Dr. Claudia Vellozzi, Acting Deputy Director Immunization Safety Office Centers for Disease Control and Prevention.

We are using a Power Point presentation for this call that you should be able to access from our Web site. If you have not already downloaded the presentation, please go to emergency.cdc.gov/coca. Again, that's emergency.cdc.gov/coca. Click on conference call information summaries and slide sets. The Power Point can be found under the call-in number and pass code.

After this activity the participants will be able to recognize the vaccine safety systems put into place by the Department of Health and Human Services and its agencies, define FDA's Licensure process for 2009 H1N1 influenza vaccine, discuss results from 2009 H1N1 influenza vaccination clinical trials conducted by NIH, describe several post-licensure vaccine safety monitoring systems managed by CDC and FDA and know how to handle reporting of any potential adverse events post-vaccination.

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CDC, our planners and our presenters wish to disclose they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services or commercial supporters. This presentation does not involve the unlabeled use of a product or products under investigational use. There is no commercial support.

I will now turn the call over to Dr. Gellin.

Bruce Gellin: Thanks a lot and thank everybody for joining and we appreciate all your interest in this.

As you know, from the introduction and from the titles of the first slide that our focus today is on the H1N1 vaccine safety. So, it's always important to remember that we're talking about safety in the context of the performance of the vaccine at large. And, like any decisions in medicine, it's the balance of the risks and benefits, but we wanted to make sure that the people who dialed into this call had a clear understanding of what we know about this vaccine, particularly in the context of influenza vaccines and the kinds of influenza vaccines we've had in the United States for many, many decades.

But, also to know that this one we have in place to both identify potential adverse events and then to clarify whether or not they seem to be caused by a vaccine or may just occur in proximal timing to that vaccine.

So, with that I have a series of slides. And, my job here is really to give you an overall orientation to the vaccine safety system. So, the first slide you'll see there has got a bubble diagram that really just says that there is a lot of pieces

to this system. Now, what's focused here is largely the Department of Health and Human Services and its many components you are going to hear later from FDA, CDC and NIH about where they fit into this. There are other parts of HHS and in fact, there's more to the federal government's vaccine safety system than the HHS components.

Not on the call today are the Department of Defense and the Veteran's Administration and I'll make some reference to some of these other parts of the system, but we wanted you to know that there is a system out there and many of the things you're going to hear about today are the system that we've had in place for some time and some of the enhancements that we've put in place as part of the monitoring of the H1N1 vaccine response.

The next slide is a snap shot of a subset of these many components that I mentioned. I'm not going to talk anymore about the National Vaccine Program Office, which is here at the Department of Health and Human Services in the Secretary's Office and you're going to hear later from CDC, FDA and NIH.

But, just to give you other pieces of this broader picture, the Health Resources and Services Administration are first to operate the vaccines with a compensation program. CMS and Medicare also has vaccine safety as part of the data that comes in through their population. And, the Agency for Healthcare Quality and Research looks more broadly at some of the other issues and they have been helpful in providing some of the background rates of medical conditions. It's important to think about the context of these medical events, which in the setting of an immunization program, might be seen as vaccine adverse events.

The next slide is more lists. Again, I've mentioned that the Department of Defense and Veteran's Affairs, but know that the system is more broad than just the federal players. And it's very important that those who are involved in the immunization enterprise are aware of this and particularly to make sure that they are aware of some of the reporting mechanisms so that we're able to collate that information and get the best snap-shot of what's happening.

So, we really depend on the clinical community to help us by knowing what it is that you're seeing. And, you're going to hear more about some of those aspects later in the presentation. But, there's state and local health departments, academic researchers, the vaccine manufacturers, parent groups, professional organizations, the Institute of Medicine, philosophical organizations -- and it's not just a U.S. thing.

We have a number of partners internationally and we're also working with the World Health Organization, as we do all the time on vaccine safety, but a special effort now because many of the vaccines that we're using are going to be used by other countries as well.

The next slide is now focusing on the H1N1 vaccine piece. As you'll hear from FDA and many of you may be aware of the process by which FDA goes through to license our seasonal vaccine each year. And again, it's a process that they've used for the H1N1 vaccine because essentially it's an identical process. Because of the way that the virus has been used, the H1N1 virus has been used to develop this vaccine.

But, in the setting of a large immunization program, which is - which we are on the cusp of beginning, we know that a lot of vaccine will be given to many people over a very short period of time. And, we also know that medical events will also occur in that period of time. So, I think the key job for all of

us is to discriminate some of these medical events and determine whether they are in fact caused by the vaccine or some of them may be caused by the vaccine versus those things which are really medical events that just happen to occur in the setting of an immunization program.

And, overall many of these - again, many of these systems have been in place for some time. We had some enhancers that you'll hear about, but I think that this is a large part of the larger immunization program and the things that we do in the vaccine development, in its licensure process and its monitoring once it's used are also to help everyone understand what we're doing and to make sure that people understand the system and have as much confidence in it as we do.

On the next slide -- it's labeled HHS Vaccine Safety Monitoring Activities. I want to divide this into two sections. These broad initiatives on this slide are some of the things that we have in place all the time.

We have put together what we refer to as a Federal Immunization Safety Task Force, which is not just the Department of Health and Human Services and its agencies, but again, broadly all the parts of the federal government that have a stake in vaccines, particularly vaccine safety sit together on a task force that's chaired by the Assistant Secretary for Health here at HHS.

We have, and some of you may be aware, that we have in development a draft national vaccine plan that was developed and circulated at the end of last year. I'd urge you to take a look at that, but of the five broad goals for the nation's vaccine program, one of them is dedicated to safety. And, many of the things that we're doing across the government are linked into that plan.

We have a National Vaccine Advisory Committee, which is a federal advisory committee that reports to the Assistant Secretary for Health and they have a vaccine safety working group that's been in place for some time looking at some of the broad issues in vaccine safety. You won't be surprised to learn that we've engaged them in this effort as well.

Among the things that we've done is also going out to the public to try to get a sense of what their understanding of vaccines is as far as how they place their value on vaccines and their understanding of vaccine safety and the systems that are in place to monitor safety. And then upcoming is advertisement for, what I believe will be in the end of the year issue of Supplement To Pediatrics, which is really an in-depth look at what you'll hear about today, which is many components of the system. And I'll tell you about another document that will be coming up soon as well.

On the next slide is the Federal Immunization Task Force. I've already mentioned that. So, I don't think we need to spend any more time on this, other than to look at that last bullet.

We have prepared a document that's called the Federal Plans to Monitor Immunization Safety for the 2009 H1N1 vaccination campaign. This is in its final stages of clearance, a very government thing. But, we hope that this is going to be available to everyone next week. And again, that will give you in a very short order an in-depth look at the various components of the system that we're going to be talking about today.

We're also in the process of developing some more consumer friendly materials that I think are going to be more practical for clinicians. But, we know that there are a range of audience and someone may want the 101 version and some may want much more depth and we're going to provide as

much of that array as possible for both the clinical community and the broad public.

The next slide is entitled H1N1 Vaccine Safety Monitoring Activities. I'm not going to read this to you because you'll be able to see it. This is essentially the table of contents for the document I just mentioned, the Federal Plans to Monitor Immunization Safety for the H1N1 Immunization Program.

So, many of these things you'll hear about on this call today, some you won't. So, that'll give you a chance to then drill into these and get a better understanding. I'm going to just feature one of these, which is the fourth row down, the Post Licensure Rapid Immunization Safety Monitoring Program with an acronym. Of course, we have to have an acronym called PRISM.

But, again I want to just orient you to the many components. Essentially, there are ten different sources of data that we're going to use across the government to monitor the safety of the vaccine that's going to be used shortly.

The next slide is about PRISM. This Post-licensure Immunization Safety System. And, I'm really going to be very brief here and just say that this is a program that is essentially an enhancement of something that you'll hear about in the presentation from CDC, which we call the Vaccine Safety Data Link. And what that really is in this sense is that we've been able to put together two different data systems, immunization registry records and then health plans to make sure that in some states we have records of what vaccines people received that can be readily linked to the health outcomes of these people. It gives us another enhancement to look and to take an active look at any adverse events that may occur following an immunization in a more specific way.

So, as we start to see signals that might come from a variety of different monitoring programs, this will give us a chance to try to look more specifically and link the receipt of an immunization to potential health outcomes that may occur following immunization.

The next slide gives you sort of the summary and why we're so excited about having developed this system and thank those many partners who contributed to both the health plans and some of the academic researchers who have been working on it. But, essentially this is going to be able to monitor 15% of the U.S. population and add maybe 10 to 20 million people that come into this through the state registries. And again, as you'll hear from CDC at the end, this now gives us a much broader population to look at. So, if we're looking for rare adverse events this greatly increases the number of people that we can look at.

And, then my final slide, entitled The Coordinator View of Monitoring Data, this gets back to a comment I made before about our national vaccine advisory committee.

As I mentioned, the advisory committee has taken a hard look at the safety component of our immunization program for the H1N1 vaccine and they made a recommendation that you'll read here. But, I'd like to read it to everyone. They asked that we consider developing an independent committee, which is a transparent and independent review of the vaccine safety data as it accumulates. And, you can go back and read more about that meeting.

We took this recommendation very seriously. We are going to have such an independent evaluation. We are in the process of pulling the people together and we hope to be able to announce that in the near future. So, on top of all

the other assessments that we'll make and all the analysis that goes on within the federal government, we're going to have an outside group take a look at it with us to make sure that we're not missing anything.

So, again, my goal here was to give you a broad overview of the many components of the system and you're going to hear now some more specifics from each of the agencies.

And with that, I want to turn to Theresa Finn from the FDA in their Office of Vaccines. So, Theresa, over to you.

Theresa Finn: Okay. Thanks very much, Dr. Gellin and good afternoon to everyone.

I'm on the first slide, which is just to give the header, influenza A H1N1 2009 monovalent vaccines. And, I'd like to point out that I'm working at the Office of Vaccines, which is the section of FDA that's responsible for licensure of influenza vaccines, including the recently licensed vaccines against the pandemic H1N1 2009 virus. And, I've been asked to give a brief overview of the licensure of these vaccines, which I'm going to generically refer to as H1N1 vaccines as I proceed through the presentation.

So, if you turn to the next slide, this is just a brief overview of my talk. Because the licensure of H1N1 vaccines is based on the way that the yearly seasonal influenza vaccines are licensed. As Dr. Gellin referred to I'm going to present a couple of slides illustrating how FDA licenses these yearly changes in the influenza formulation. And, then I'll describe the H1N1 vaccine licensure and finish with an overview of the currently licensed H1N1 monovalent vaccines.

So, let's move to the next slide, which is - shows the manufacturers of the U.S. licensed seasonal influenza vaccine. The proprietary names and the age groups for which each vaccine is approved for use. And, you can see there are five manufacturers of inactivated vaccines. And, these are the vaccines that are administered by intramuscular injection. There is one live attenuated vaccine. This is the intranasal vaccine, which is manufactured by MedImmune. And you can see that these are licensed for use in different age groups.

And moving to the next slide. It should say U.S. licensed seasonal influenza vaccines.

For each seasonal vaccine is trivalent and contains two influenza A strain and one influenza B strain. And, I'd like to point out that although the currently licensed seasonal vaccine contains an H1N1 subtype, this is different from the pandemic H1N1 vaccine virus that is circulating. And the seasonal vaccine will not provide protection against a pandemic H1N1 virus. And, as you know influenza virus changes and these gradual antigenic changes require annual assessment of the vaccine strains as well as annual administration of the seasonal vaccine.

The WHO Surveillance Network including CDC monitor and characterize these circulating strains and each year the formal selection for optimal strains for inclusion in the next seasonal formulation is made at an FDA Advisory Committee meeting. Following strain selection each manufacturer submits a strain - something called a strain change supplement to their license.

So, if you move to the next slide, which gives us a little bit more about these strain change supplements.

So, with the exception of the strain specific information in each strain change for that particular year - with the exception of the strain specific information for that particular year. Each strain change supplement relies on information, which is already included in the license. And, this is because each new seasonal vaccine is made using the same egg based manufacturing process. In addition, the same in-process controls are used and the same lot release requirements are in place.

Each new inactivated seasonal vaccine is licensed without additional clinical data. The new live attenuated vaccine is licensed with limited clinical data to confirm safety. The safety and effectiveness of each new seasonal is extrapolated from data already included in the license application as well as the post marketing experience with the preceding seasonal vaccines.

The next slide, please.

Now we move on to the H1N1 vaccine and licensure. The licensed vaccines are manufactured by U.S. licensed manufacturers of seasonal influenza vaccines. And, the licensure of the monovalent vaccine was done via strain change supplement to each of these manufacturers license application.

The next slide.

From now on a slide that says H1N1 vaccines strain change supplements. These H1N1 vaccines that have been license as strain change supplements are manufactured using the same egg based manufacturing process as the seasonal vaccine.

The in-process controls and the lot release requirements are the same as those used for the seasonal vaccines. Similarly, the clinical data requirements are

the same as those for seasonal influenza vaccines. In other words, no clinical data were required for the inactivated H1N1 vaccines and limited clinical data were required for the live attenuated H1N1 vaccine.

So, next slide. Now I'm one that says H1N1 Vaccines. And, this slide notes that on September 15, 2009 FDA approved supplements to each manufacturer's license application. And, this was for license four monovalent H1N1 vaccines. Three of these are inactive vaccines for intramuscular injection. These are manufactured by Sanofi Pasteur, by Novartis Vaccines and Diagnostics and by CSL Limited. The fourth monovalent H1N1 vaccine is a live attenuated vaccine for intranasal administration and this one is manufactured by MedImmune.

And, moving to the next slide.

Each of these H1N1 vaccines is licensed for use in the same population as the seasonal vaccine made by that manufacturer. So, this Sanofi product, for example, is approved for use in persons 6 months of age and over. The Novartis product is approved for use in persons 4 years of age and over. CSL for those 18 and over and the MedImmune, which is intranasal, is approved for use in both 2 to 49 years of age. I'd like to note that like the licensed seasonal vaccines these monovalent H1N1 vaccines do not contain an adjuvant.

So, moving to the next slide.

The next speaker is going to go into more details about the clinical studies, but I'd just like to point out that while clinical data were not required for licensure that the manufacturers and NIH are conducting studies to determine the optimal dose, the number of doses and the optimal schedule.

And, moving to the next slide, which is the dosing regimen.

The current dosing measurements, the H1N1 vaccine, is that children 6 months through 9 years of age should receive two doses and everyone 10 years of age and older one dose. And, this dosing regimen was supported by the available (unintelligible) data, which indicated that children 9 years of age and younger were essentially immunologically naive to the H1N1 pandemic virus.

Thus far, the preliminary immunogenicity data from NIH and manufacturers sponsored studies show that children 10 years of age and older respond well to a single dose of vaccine while children 6 months through 9 years of age have a less robust response to one dose and are likely to require two doses. And, the preliminary safety data show these vaccines to be well tolerated.

Next slide, please.

So, in summary therefore, FDA has licensed four monovalent H1N1 vaccines. For each manufacturer these are approved for use in the same populations as the specific manufacturer's seasonal vaccine. And, each of these is manufactured using the same process as the seasonal vaccine from that specific manufacturer.

And, that concludes my presentation and thank you all for your time. And I'd like to turn the call over to Dr. Gorman at NIH.

Richard Gorman: Thank you, Dr. Finn. I will be representing the Division of Microbiology and Infectious Disease, the group in NIAID that was responsible for performing the clinical trials. And, I was asked to focus on the safety aspects of these trials.

The second slide, which is the outline of my presentation, will deal with our trials on the monovalent H1N1 vaccines. There were three basic areas that I'm going to cover in this brief presentation. One is the policy focus of these particular trails. I'm going to give you an outline of the seven ongoing protocols that we are performing at this time. And, then a brief overview of the safety oversight of those trials.

Next slide. The trial focus for the trials policy focus.

The department asked us to help inform policy or gap areas that might be left after the companies did their trials. We were to accelerate the availability of one versus two dose data in different populations. We were to perform trials that administered the monovalent vaccine with the seasonal influenza vaccine. We were asked to do a study with different agivalent products. And, to do that we needed to mix different vaccines. Vaccines from one manufacture with agivents from another manufacturer.

These data were not intended to support licensure of these vaccines, as Dr. Finn from the FDA has already spoken to. They were supposed to be complimentary. Our trials were supposed to be complimentary to the companies' planned trials and we were asked to generate safety and immunogenicity data in general and special populations. The special populations included young infants, pregnant women and the immunocompromised.

Next slide, please.

The first three protocols that we initiated were done in adults between the - above the ages of 18. The first two trials included a trial of once dose versus

two doses unadjuvanted CSL vaccine in healthy adults. The enrollment of that particular study is complete and there were 400 people enrolled equally divided between individuals less than 65 and greater than 65.

The second protocol was a mirror protocol for that, which looked at the unadjuvanted Sanofi Pasteur vaccine in healthy adults and an identical study designed with half the people being below 65 and half the individuals of the subjects. These studies being above 65.

We also did a co versus sequential administration of TIV and H1N1 vaccine. That was done in four groups. Each group had 200 subjects in it. Again, half below 65 and half above 65 and above 18. And, it gave the four different possible combinations of the administration of TIV and H1N1. At the time when this trial was designed we had assumed that there would be a necessity to do two doses for the H1N1 and that's why there's four groups in this particular study.

After we had accumulated sufficient safety data from these first three protocols we moved into the pediatric population, which was the next two protocols that were performed or enrolled. We did one versus two doses of unadjuvanted Sanofi Pasteur vaccine in healthy children. That had 600 children enrolled and they were divided into three groups following FDA guidance -- 6 months to 36 months, 3 years to 9 years and 10 years and above -- 10 to 18 years.

And then we also performed a study or in the process of performing a study of co versus sequential administration of TIV and H1N1 vaccine in children. The enrollment of that is complete as well. It was divided as well between the three age groups and has totally enrolled 600 subjects.

Next slide, please.

The NID H1N1 vaccine trials have two protocols that are presently enrolling. And one was what we call the mix and match, where we mix and match agivents and antigens from different companies. The trial that is presently ongoing uses the Sanofi Pasteur H1N1 vaccine with a GSK AsO3 agivent. These agivents are mixed up on site with the antigen prior to administration and the protocol has five dosing groups -- 3.75 micrograms of the antigen plus the (unintelligible). And, then 7.5 and 15 micrograms of antigen with and without the agivent.

The study design is two doses for these as well separated by 21 days. That study started on 24 September and is presently enrolling. There will be a follow-on study using the CSL antigen with the agivent the IND for the particular study has not been filed.

The other protocol that's presently enrolling is using the monovalent H1N1 in pregnant women. It's using the Sanofi Pasteur unagivented product. One does and two doses 21 days apart. We are enrolling second and third trimester women. That study was initiated on 9 September. The target enrollment is 120 and it is presently enrolling.

Next slide, please.

There are many layers of safety oversight for any study going from the initial part of the good scientific design to the ethical investigative review to the IRB's review. But, I want to focus for the rest of this talk on the group that is concerned only with the safety. It is their only focus of this particular group is on the safety of these trials and that's the Safety Monitoring Committee.

There is a Safety Monitoring Committee that we instituted. It's independent of NIH and DMID and NIAID. It is composed of five members. They all have infectious disease expertise. And the additional expertise is on this group. There's an individual with expertise in HIV. We have an obstetrician gynecologist on the group, an internal medicine physician, a pediatrician and a gentleman with a PhD. in biostatistics.

To augment this group we've also hired two special safety consultants. One with an expertise in large clinical trial pharmacal vigilance and another with an expertise in adjuvants as they're presently used in vaccines.

At each clinical site there is an independent safety monitor. So, the independent safety monitor is someone not associated with the trial and someone who does not report to the principle investigator at that trial who is available to look at events as they occur to do a medical evaluation that is independent of the study. And, then those reports are forwarded to DMID and to the Safety Monitoring Committee.

Next slide, please.

The Safety Monitoring Committee reviews all the protocols prior to their implementation for safety concerns. So, the Safety Monitoring Committee has looked at our halting rules and our withdrawal rules. They review all our serious adverse events, subject withdrawals and subject terminations.

Subject withdrawals are when the subject chooses to withdraw themselves from the study. Subject termination is when in the opinion of the principle investigator at that particular site they feel that it is no longer in the subject's best interest to be in a study for either safety or efficacy concerns. They look

at protocol deviations as well. After analysis of the safety, the (unintelligible) determines a study should proceed, be modified or stopped.

Next slide, please.

At this time, the Safety Monitoring Committee has not recommended a modification or a halting of any of our seven ongoing trials. And the observed pattern of reactogenicity and adverse events is compatible with a seasonal influenza vaccination.

Next slide, please.

As Dr. Gellin mentioned before, it takes a lot of people to do things. And, this is the group of people who are involved with the H1N1 trials that we have performed. So, while DMID is actually executing these trials, all of these other individuals are essential and necessary for the execution of these trials in the safe and rapid way in which they were done.

Thank you very much for your attention. I'd now like to turn this presentation over to Dr. Vellozzi.

Claudia Vellozzi: Good afternoon. I'm Claudia Vellozzi and I work in the Immunization Safety Office at the CDC. And, in the interest of time I'm just going to jump right ahead three slides to the one that begins with background.

And, just to reemphasize what the previous speakers have been saying, that when seasonal influenza vaccines are used according to the indications they are considered to be safe. And, it is anticipated that safety profile for the influenza A H1N1 monovalent vaccine will be similar to seasonal influenza vaccines.

Skip to - go to the next slide. Continue with background.

To emphasize this point a review of adverse events following TIB among adults reported VAERS, the vaccine adverse events reporting system for 15 years of data there was approximately 750 million doses distributed and in overall adverse event reporting rate of 24 per million vaccinations, which further - there were 3.4 serious events per million vaccinations reported during this time.

And, these reporting rates have been fairly constant over time and no new safety concerns emerged following this comprehensive review. So, that just gives you the background.

If you go to the next slide beginning with the goals for our 2009 H1N1 vaccine safety monitoring.

These are to identify clinically significant adverse events following the receipt of this vaccine in a timely manner, to rapidly evaluate serious adverse events following receipt of the vaccine and to determine the public health importance. We will also evaluate if there is a risk of Guillain-Barre Syndrome associated with the 2009 H1N1 vaccine and communicate vaccine safety information in a clear and transparent manner.

If you go to the next slide I'll - I'm just going to - the next slide is entitled vaccine adverse event reporting system. And this is a system that's a voluntary reporting system that's been in place and jointly managed by the CDC and FDA since 1990. It is national in scope. It is primarily our signal detection system. It's flexible. And, we encourage reports from health care providers, such as yourselves and we accept reports from vaccines and

caregivers and anyone. Many enhancements have been put into place to increase the staffing during H1N1.

Next slide is entitled VAERS limitations.

The VAERS does have some limitations as any voluntary reporting system would. We cannot usually assess causality. There is variable quality of data. There's no one vaccinated comparison group and the (unintelligible) data are lacking. Under reporting because it is passive and voluntary. And, sometimes there is variation of reporting. Sometimes there's simulated reporting that could occur during times of heightened awareness, such as possibly current with this current vaccination program.

If you go to the next slide entitled the vaccine safety data link or VSD and Dr. Gellin mentioned this earlier. But, this is our collaboration with eight managed care organizations, which represents approximately 9 million US individuals. And, they are able to rapidly assess pre-specified adverse events using sequential analytic methods. And, they have - simultaneously they can do the analysis with the appropriate comparison group. And, this requires accurate vaccination (unintelligible) information within the managed care data base.

The next slide, just comments on the VSD limitations.

There can be up to a two week delay for available outcome data. And, adverse events with longer risk windows can add to the delay of analysis. And, that just means that the risk following exposure could be more than two days. It could be up to 42 days or whatever risk is. Sometimes it may not be sufficient power for very rare outcomes or with limited vaccine use. And, the vaccination information must be within the managed care organization.

If you skip to the next slide. I just want to comment on another mechanism in our office called the Clinical Immunization Safety Assessment Network.

And, this is collaboration of - between six academic centers with vaccine safety experts. And these experts can provide vaccine safety clinical expertise in the evaluation of serious events. And, they will support us during the H1N1 vaccination campaign.

You go to the next slide. I just want to briefly run through other surveillance systems that are available to us for monitoring adverse events. And one is the collaboration with the DOD, CDC and FDA, which utilizes the defense medical surveillance system.

The next one is a system in collaboration with the Johns Hopkins School of Public Health and CDC. And, it's an automated Web based active surveillance system called Real Time Immunization Monitoring System.

Then, there's the PRISM system that Dr. Gellin already spoke about. And, also we are doing active case surveillance finding for cases of GBS.

If you skip to the next slide entitled Guillain-Barre Syndrome. I just wanted to briefly remind you about this syndrome, that it's an immune mediated (unintelligible) And, it has an estimated annual incidence - background incidents of 1 case per 100, 000 population. And, as someone - many of us are aware and it weighs on our minds about in 1976 that there was a type of influenza vaccine that was causally associated with Guillain-Barre Syndrome. But, subsequent studies of influenza vaccines have found small or no increased risk of GBS and if there is a risk it would be about one additional

case per million people vaccinated. And, there have been many studies since that time and I think only one or two have noted this potential additional case.

But, because it is weighing on our minds if you go to the next slide.

As I mentioned, we are going to do GBS active case finding in our emerging infections program sites, which are existing hostile based surveillance system. And, we are also collaborating with the American Academy of Neurology to increase - primarily to increase awareness for reporting to VAERS And, to also enhance GBS reporting in these sites.

If you go on to the next slide.

I just wanted to mention how CDC is supporting the public health officials that are participating in vaccine monitoring. And, the Immunization Safety Office at CDC has collaboration with CDC Safety Coordinators in 62 state and territorial and local health departments. The plan is to assist states with technical and epidemiologic investigation as necessary and also to engage in regular communications.

If you go on to the next slide and then the next. So, go to the slide that says what to report to VAERS.

I think this is very important as practicing clinicians. And, it emphasizes reporting to VAERS. And basically we're asking that you would report any clinically significant adverse event following immunization. And, the Web link is there. And, you should submit reports of concern even if you're not sure that vaccine was responsible for the event. And, we would like you to include as much information s possible, which would include vaccination date, lot, type, dose.

And, on the right side of the slide is a sample form, but you know, when you go on the Web it's pretty clear how to complete this form. And, it would be best to report as soon as possible, but we accept reports at any time.

If you go to the next slide it's just tells you how to submit to a VAERS report. And, I won't belabor this, but there's an URL or you can fax or actually mail and there's a phone number as well if you need help.

If you go on to the next slide. This is entitled clinician's role in vaccine safety monitoring during the 2009 H1N1 vaccination campaign.

And, these bullets are very important. Properly stored administered vaccine, screened for contraindications and precautions, educate the vaccine about risks and benefits of vaccine by providing the vaccine information statements, use the influenza vaccination card, which will be provided with vaccine this year. And, it's a card that has places where you can put in all the pertinent information about the vaccine. Evaluate and treat a patient if an adverse event occurs and then report clinically significant events promptly to VAERS.

In going to the next slide, I just wanted to provide some resources for 2009 H1N1 vaccine safety questions and answers. And, they're basically three URL's here that might help you with some of your questions or your patient's questions.

And, finally if you go to the last slide I just wanted to summarize that for the 2009 H1N1 vaccine safety monitoring we are basically using our established vaccine safety infrastructure and putting in enhancements as necessary. We are developing new collaborations. CDC is providing support to states and territories, vaccine risk communication is very important component of

vaccine safety monitoring. And, clinicians play a very important role in vaccine safety monitoring.

And, finally acknowledgements, as everybody else had said, this is like very many people helping in this effort. And, thank you.

I'm finished.

Alycia Downs: All right, Kerry, if we can go ahead and open up the lines for the question and answer session. And, as a reminder to those on the phone if you want to address your question to a specific speaker that might help expedite the process.

Coordinator: Okay, if you would like to ask a specific question, at this time please unmute your phones, press star 1 and record your name. We will have to have the names recorded in order to proceed with questioning.

Once again, to ask a question please press star 1. To withdraw your question, press star 2. One moment for the first question.

Okay, our first question. And, I'm sorry I didn't understand your last name. Please repeat your name. Your line is open.

Question: Okay. I was just trying to find - I found it anyway. It was the outline, but I did find the URL for that. So, thank you very much.

Coordinator: Our next question. You may ask your question.

Question: Hi. I have a general question about influenza vaccinations and latex allergies. I believe that an (unintelligible) reaction to latex is a contraindication, but I was just wondering if the speakers could comment more on that?

Abbigail Tumpey: Yes. FDA, could you comment on that?

Theresa Finn: Yes. The FDA is just pulling up packaging inserts. Certainly within the package inserts it says, for example, on some of the products it will say whether or - on all the products it will say whether or not they contain latex.

So, for example in the Sanofi Pasteur product the (unintelligible) stop that's in the syringe plungers do not contain latex. So, in that type of a situation there would be no information in the package inserts. If the package insert or if the product should I say, is contained in a packaging where latex is contained that should be on the - in the package insert and also in the cartons. And information on whether it should also be a warning if it contains latex.

Did that help you?

Question cont'd: Yes. And if somebody gets hives after exposure to latex and, let's say, shortness of breath, but it improves with Albuterol and Benadryl, I presume that it would be safe to administer the vaccine, but to, you know, have - make sure that they have their inhaler and Benadryl with them?

Theresa Finn: You know, I'm going to defer that question to the CDC representative, who might be able to help on the recommendation. Certainly, the package inserts say that if you have allergy or if you - that in case of allergic response you should have the appropriate precautions in place. But, I'm going to defer to CDC on those specifics.

(Caron Burder): This is (Caron Burder) from the Immunization Safety Office.

If a person has an allergic type reaction to the latex then that would fall under the contraindications for using the product. In some cases, a person could have a very mild type contact reaction to the latex and that wouldn't necessarily be considered a severe reaction. But, if there's a question in the mind of the clinician about whether this is a true allergic reaction or not, then one option would be to consult with an allergist immunologist before vaccinating that person. Or, to just use a product without the latex in it.

Question cont'd: Thank you.

Coordinator: Okay, our next question. You may ask your question.

Question: Hi. I have a question about the clinical trials of the monovalent H1N1 vaccine in pregnant women. Were first trimester women included in the trials?

Richard Gorman: First trimester women were not included in the trials and although there is a recommendation from ACIP for women from - in the first trimester to have - to be vaccinated as well.

There were several rationales for this decision, but probably the most telling or the most pressing was that we're trying to determine the best dose for this particular vaccine. So, we were going to give, as we said, one versus two doses and there were two different dosages. And, to sort of make our population a little bit more homogeneous, to look for antibody responses we chose to limit the enrollment to second and third trimesters.

Coordinator: Okay, our next question comes from Sacred Heart Hospital. You may ask your question.

Question: Is there going to be a separately issued VIS for the H1N1 vaccination i.e. the live and attenuated?

Claudia: Yes, there will be a separate VIS for H1N1.

Question cont'd: Do you know how soon?

Claudia: (Unintelligible).

Kris Sheedy: This is Kris Sheedy from CDC and we will have those out before Tuesday.

Question cont'd: Thank you.

(Crosstalk)

Coordinator: Okay, our next question. You may ask your question.

Question: Yeah, thank you. Regarding the vaccine adverse event reporting system, it says to report any clinically significant adverse event following immunization. How long following immunization would you suggest before you say no, there's no need to report this?

Claudia Velozzi: Yeah, there's really no duration. I mean, if you are concerned and it was following vaccination, there's no time frame in terms of reporting. Obviously, the sooner your concern is apparent then that would be the item to report.

Question cont'd: So, you're saying that any significant event a year out you want to know about it?

(Undetermined): The decision to report and determine whether something is clinically significant would be in the eye of the clinician. So, if a clinician had concern a year out about the vaccination and the adverse event, even if they are not certain whether it causally related, then a report would be encouraged.

(Unintelligible)

Coordinator: Okay, our next question. You may ask your question.

Question: Yes, thank you for the program. Since the trivalent of vaccine already has an H1N1 component if this current H1N1 strain continues to affect the population is there a chance in future seasons the two vaccines will be combined? That's number one. And, if that for now as we have to give them separately and they both have some of them have the - the injectible have based on eggs, is there from previous trials any increased risk of egg allergy versus using one vaccine - from using the two vaccines?

Abbigail Tumpey: Dr. Finn, would you like to tackle that question?

Theresa Finn: Yeah, I'll certainly tackle the first one.

So, your first question was since it's an H1N1 and if we get and we already have a trivalent with an H1N1, could they be combined.

Question cont'd: In the future.

Theresa Finn: Yeah, in the future. And, you know I think I eluded to the fact that every year we have an assessment of the circulating strains and I, you know, of course nobody knows what's going to happen in - over the next few months and whether in fact the pandemic H1N1 strain will remain the prevalent H1N1

strain or whether it will be superseded by another one. But, if there was a scenario that it remained in circulation and it was in circulation and went through the winter and was the dominant strain, I think it's possible that it would be considered for inclusion in the trivalent vaccine and would become the H1N1 vaccine strain in the seasonal vaccine, but not being able to predict the future I can't be sure about that. But, I would say its not impossible.

And, then your second question was about the vaccines being made in eggs, whether there would be an increase risk of egg allergy if you were to give one vaccine and then the other. And, I would - first of all I would like to point out that not only are they inactivated, but the attenuated live vaccine is also made in eggs.

Question cont'd: Oh, yes.

Theresa Finn: And, they're all made in eggs actually - the licensed ones.

Question cont'd: Right.

Theresa Finn: And, so I would - if a person doesn't have an egg allergy I don't see any reason why you would have an increased risk of egg allergy, but I defer to CDC for a comment on that as well.

Question cont'd: Well, we do give it right now to kids who have mild reactions to eggs, so the question was there any data showing that if the reaction to eggs, let's say, was of a rash around the mouth whether the - was giving twice the dose would that increase risk? That was partially concerned.

Abigail Tumpey: CDC, do you want to take that?

Claudia Velozzi: Well, I'll just comment that basically if there's an indication - if there's an egg allergy that you're aware of then that's a contraindication to being vaccinated primarily. And, then secondarily I have to agree with Dr. Finn. There's no reason to believe that being vaccinated with two different vaccines without a history of egg allergies should increase your risk of developing an egg allergy and just logically, particularly people that get repeated seasonal vaccines and every year those same vaccines are made in eggs and it would be repeated exposure and there's no - we haven't received any information or data that would (unintelligible).

Question cont'd: Thank you. Is there a risk for people who already have the H1N1 and getting the vaccine? Who had the disease?

Bruce Gellin: This is Bruce Gellin. Let me comment about that one because that's a question we get often about people who had the disease in the last spring and summer. I think that the - while our understanding of the immunology is that those who've had that disease and confirm probably have had a pretty good immune response. But, the problem is the majority of people who had influenza like illness didn't have definite confirmed H1N1. So, I think that would - that's definitely a clinical issue to have to deal with and to a degree to which there's some certainty of what people actually had when they had their influenza like illness. And, that's going to become more of an issue during the fall and winter.

We had conversations with some of our colleagues in Australia who, again, during their winter noted that about 25% of influenza like illness was attributed to H1N1. So, there are a lot of other things that can cause influenza like illness (unintelligible) respiratory symptoms other than H1N1. So, I think it really gets down to the degree of certainty these people actually had this disease.

Abbigail Tumpey: Operator, we'll take one last question.

Coordinator: Okay, our next question. You may ask your question.

Question: Yes, I was interested what the (unintelligible) .

Alycia Downs: Could you repeat the question?

Question cont'd: What is the (unintelligible) that is being used in (unintelligible) clinical trial right now?

Richard Gorman: This is Rich Gorman. The (unintelligible) that's being used in the (unintelligible) clinical trials is ASO3. It is manufactured by GSK.

Question cont'd: Do we know what that is?

Richard Gorman: I'm sorry? It's a squalling derived (unintelligible).

Question cont'd: So, we don't know what (unintelligible) is? If it's aluminum based or ?

Richard Gorman: It's not aluminum based.

Question cont'd: Okay, thank you.

Bruce Gellin: It's worth clarifying. This is Bruce Gellin again. And (unintelligible) right into this, but just to clarify that the vaccines that are licensed by the FDA are the same types of vaccines that we use in seasonal vaccine. And, the extent of work that the NIH and others have done to do clinical trials on (unintelligible) is so that we would know as much as we could about them. So, I think just to

reiterate that the clinical trials were designed to have the best understanding of how they perform, but (unintelligible) vaccines that was described by the FDA are very similar to the approach that the same manufacturers make each year with the seasonal vaccines. That's without an (unintelligible).

Abbigail Tumpsey: And, Dr. Gellin do you have any last comment before we close out the call.

Bruce Gellin: No, I just thank you for the attention to this. We're - we know that this is a very important area for all of you. It's obviously something we've been paying a lot of attention to. We know that this (unintelligible) disease in the United States. We expect that to continue. We know that we know have a vaccine that's going to soon be available that is essentially built on a long standing history of influenza vaccines and their use in the United States and we're glad that this clinical community is learning as much as they can about these vaccines in the setting of this disease.

I think that there - it may be (unintelligible) we'll wrap up. But, we know that there's more interest and more questions and these are very good questions that you asked and I think that there are probably additional questions maybe the moderator can give some information on where people who have additional questions can submit them to make sure that you get all the answers you need.

Alycia Downs: Absolutely. I would like to thank our presenters for providing our listeners with this very important information I would also like to thank our participants for joining us today. In the case that you were not able to ask your question please send an email to coca@cdc.gov. That email address is coca@cdc.gov and we will do our best to get your response.

As a reminder, the recording of this call and a transcript will be posted to the COCA Web site at emergency.cdc.gov/coca within the next week. You have one year to obtain continuing education for this call. All continuing education credits and contact hours for COCA conference calls are issued online through the CDC Training and Continuing Education online system, www2a.cdc.gov/tceonline.

I'd really like to thank our presenters again for a wonderful call and I hope everyone has a wonderful day.

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