H1N1 Epidemiology and Clinical Features and H1N1 Vaccine Development, Manufacturing and Program Implementation

CAPT Joseph Bresee, MD
CAPT Pascale Wortley, MD MPH
LCDR Tom T. Shimabukuro, MD, MPH, MBA
July 15, 2009

NOTE: This transcript has not been reviewed by the presenter and is made available solely for your convenience. A final version of the transcript will be posted as soon as the presenter's review is complete. If you have any questions concerning this transcript please send an email to coca@cdc.gov.

Operator: Welcome and thank you for standing by. At this time all participants are in a listen only mode until the question and answer session at which time you may press Star 1 to ask a question. You will also be prompted to record your name. Please unmute your phone and record your name clearly so that I may introduce your question.

Today's conference is being recorded. If you have any objections, you may disconnect at this time. And I would now like to turn the call over to Alycia Downs. Thank you ma'am you may begin.

Alycia Downs: Thank you. Good afternoon and welcome to today's COCA conference call. This is going to be an H1N1 update on the Epidemiology and clinical features as well as on the H1N1 vaccine development, manufacturing and program implementation.

We are very excited to have Dr. Joe Bresee, Dr. Tom Shimabukuro and Dr. Pascale Wortleyresent on this call. Dr. Bresee is the Chief of the

Epidemiology and Prevention Branch in the Influenza Division. Dr. Shimabukuro is the Pandemic Influenza Vaccine Coordinator.

And Dr. Wortley is the Chief of Health Services Research and Evaluation Branch and Lead Epidemiologist both in the Immunization Services Division. All are located here at the Center for Disease Control and Prevention in Atlanta, Georgia.

We are using a Power Point presentation for this call. And you should be able to access that from our Web site. If you have not already downloaded the presentation, please go to 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 understand the epidemiology of novel H1N1 influenza, understand the antiviral recommendations for novel H1N1 influenza, understand novel H1N1 vaccine development and production timelines and supply and understand current plans for delivery of novel H1N1 vaccine.

In compliance with continuing education requirements all presenters must disclose any financial or other relationships with the manufacturers of commercial products to suppliers of commercial services or commercial supporters as well as any use of unlabeled products or products under investigational use.

CDC, our planners and our presenters wish to disclose that they have no financial interest or other relationships with the manufactures 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 Bresee, you may begin.

Joe Bresee: Thank you. Good morning, this is Joe Bresee. Most of the talk today is going to be about vaccine development and give you all an update on the vaccine status and some of the issues related to that.

We thought that we would start with about a ten minute overview and status of the Epidemiology and clinical features of the disease as both an update and to set the stage for the vaccine discussion to follow.

Next slide please. This slide that you're looking at should be labeled Increase Swine Influenza Detection in Humans 2005 to 9. I wanted to start here because I think it's important to know that for pandemic planning purposes in 2007 novel influenza A was made a nationally notifiable disease by CSTE the State and Territorial Epidemiologist Group.

This is important because it allowed all the states to start developing the skills to detect novel influenza A which they did over those three years. And then started the states thinking about both referring interesting viruses to CDC and investigating clusters that may have interesting viruses. Next slide.

This resulted in, as you know, the detection of the first two cases of what at the time was called Swine Influenza Virus in the United States now called Novel H1N1 or Pandemic H1N1.

In March 2009, the two cases, two children showed up with (febrile) illness in late March in two adjoining counties in Southern California. They were

interesting because neither had common exposures to anything. And neither had pig contact. Both had a mild illness with (benefit) for recovery but the viruses from those children turned out to be flu positive. It turned out to be Influenza A positive at local or reference labs and were referred to CDC because they couldn't be typed as one of the common influenza viruses circulating at the time.

As you know, Swine Influenza Viruses, the Novel Virus was first detected in mid-April at CDC. It was interesting again because both of the viruses from these children who didn’t have anything to do with each other otherwise had genetically identical Swine Influenza Viruses that had a consolation of genes that was unique and hadn’t been seen before either in North America or globally.

As you know since that time, the identification of additional cases of infection and the illness is associated with the Swine Virus have occurred and if you look at the next slide, which is a line graph, you'll see that over the next few months leading up to now there's been a dramatic increase in the number of confirmed and suspected cases with this virus.

If you look at the next slide, the current status as of July 10, which is our last reporting period, indicated that 37,000 people had been confirmed to have infection with the virus in the United States of which 4,132 had been hospitalized and 211 have died.

Importantly, from the initial characterization and discovery of the virus in Southern California just in March as of today all 50 states and territories of the United States have had their first case of H1N1 Swine Influenza or Novel Influenza.

You see some of the epi-characteristics there. I'll go into those in just a minute. If you look at the next slide, you'll see the current status, it looks like a world map with colors. You see that 94,000, a little over 94,000 positives confirmed cases have been identified throughout the world involving 134 countries. So in a very short time, the few months we've gone from two cases in Southern California among two kids to 134 countries and more then a 100,000 identified cases and probably 7 million cases overall world wide.

So what do we know about the Epidemiology in the United States? If you look at the next slide which looks like a bar graph of symptoms, it’s a black and white slide; you'll see some features that I think are important to know about.

These are among hospitalized patients but the symptoms are consistent with those non-hospitalized as well. And if you look at the left side of the slide, what you'll see is what you'd expect that with influenza infections and illnesses, fever, cough, shortness of breathe, fatigue and weakness and chills, (myalgans) are the most important and common symptoms.

If you look at the far right side of the graph though, I wanted to highlight diarrhea. Early on this was a sign that we saw in about 20% to 30% of the early cases and can clearly this continues, diarrhea continues to be an interesting and common symptom and sign in people who had this illness and occasionally people have been presented just with fever and diarrhea alone and developed respiratory signs later. So something to keep in mind foe clinicians.

The next two slides look at the age distribution. And the single point I want to make about both these, the first slide is looking all cases the age distribution of all cases and what we saw early on continues to hold and that is the highest

rates of infection are in the youngest children and the young adults with declining rates of infection or risk of infection as you get older. And again, a very small proportion of the confirmed cases have been in elderly people over 65.

If you look at the next slide after that, you see the sorts of age distribution this time for severely hospitalized patients and you see it looks very similar. The highest rates in the youngest folks. You see an increased rate now in the over 65 year age group, but still not similar to what we see in seasonal flu where the lion share of hospitalizations and severe diseases are among the oldest age group.

If you look at the next slide, this is the same sort of distribution just for seasonal flu and you see what the normal j shape curve of age distribution for influenza with again the lion share of severely ill people in the oldest age group, clearly not what we're seeing so far at least with Novel H1N1 where the infection rates are predominately among the young kids and young adults.

The next slide is another histogram that should have light blue and dark blue and this is just to illustrate another important feature and that is that among hospitalized patients and among patients who have died, most of the patients over 75% of the hospitalized patients have some underlying disease associated with the higher risk of severe complications of influenza. And these are the traditional high risk conditions for influenza like asthma, COPD, diabetes, etcetera.

And so what we're seeing that predisposes people to high risk of complications if they get this disease or basically the same things we commonly think of for flu and the same things for which we recommend vaccination.

The one thing that I did want to point out is obesity. Obesity has gotten some press. The fact that a lot of the or some of the early severely ill cases were found to be obese or morbidly obese which led to the notion that obesity might itself be risk factor for severe complications or severe disease with this bug that's still under investigation but as this slide shows that the proportion of severely ill cases in hospital at least that have been identified with this virus that are obese is below the national rate of obesity in that age group.

And so, so far it looks like obesity is not likely to be an independent risk factor, more likely to be a sign for other risk factors for the disease. The next slide shows us a third important Epidemiologic feature, your looking at a national map now, a multi colored map. The darker the color is the higher the rates of disease in those areas.

And what you see here is a key feature of this disease like seasonal influenza is there are spotty or focal transmission of disease and so like we see in the seasonal influenza year some areas are affected at different time worse then others and I think that’s exactly what we've seen so far with Novel H1N1 with places like Texas and New York, Illinois with the relatively high rates of disease and sparing in other parts of the country.

Let me just finish up with two things. First the current status of what we're seeing in terms of circulation. The next slide is a graph that shows the proportion of clinic visits for influenza like illness that show up at the CDC surveillance system clinic. These are 2,400 clinics around the country and so offer a good sign or a good indicator of the level of influenza activity and the trends in influenza activity over time.

And if you look at the far right side of the graph, the red curve shows the proportion of clinic visits in the system that are due to influenza like illness which is fever and respiratory symptoms.

And what you see is an initial spike on the right in the spring time which represents that little spike on the right side followed by a fairly level line now showing some declines. I think in a lot of the systems that we're looking at we're starting to see declines in disease which makes us hopeful at least, that we'll see declining activity of this bug through the rest of the summer.

The next slide shows the virologic data which shows basically the same thing. These are histograms of the proportion positive of all the tests done in influenza labs that are positive for influenza. The colors represent the sub-types and what I want you to look at is the orange bars which represent Novel H1N1 detections which shows again the large increase in detections in the spring time and early summer and hopefully in the last couple of weeks the trend towards declining detections of this virus which may indicate declining trends in disease.

The other thing we do for viruses which you'll see on the next slide is monitor them for sensitivity to the anti-viral agents. If you look at the far right side of this box, you'll see the sensitivity patterns for the Pandemic H1N1 virus which hasn’t changed at all and which still shows its susceptible to Oseltamivir and Zanamivir but uniformly resistant to Adamantanes like (Amansidene) and (Rhimansidene).

We have seen three on the next slide globally there have been three Oseltamivir resistant strains detected. I put this on just for your use only to say there are three single specimens, two among people treated which is not unexpected, one among a person who is reportidly did not receive Oseltamivir

but it appears at least so far that virus was not transmitted in the community any further.

So to finish with a few slides. First the anti-viral recommendations as a reminder because of the resistance patterns haven't changed and because of the predominance of H1, the anti viral treatment recommendations have not changed recently and are not likely to change over the next couple of months.

And indicate that we should think about priority treatment for hospitalized patients with confirmed or suspected H1 disease or any out patients with influenza like illness that have an underlying risk factor that predisposes them to complications.

The next slide is the data on anti-viral prophylaxis which again has not changed and indicates that prophylaxis should be considered in three groups -- close contacts of cases who are themselves at high risk of complications, healthcare personnel in some cases, two groups I'm sorry, healthcare and the (chemo) prophylaxis is like it is for seasonal flu, seven to ten days of once a day dosing after the last known exposure and the specific recommendations are available on our CDC Web site.

So finally a summary of key points. Next slide. Once the virus emerged it spread to all 50 states and most countries in the world very quickly as expected. Some areas are affected more then others and probably will be during the fall like we'd see with seasonal flu. We do expect continued summer time circulation with (focal) outbreaks, we're seeing that now in camp outbreaks and when school starts up in August in Georgia and later in other parts of the country, we would expect increasing clusters of disease then.

Elderly so far seemingly relatively spared and that pattern seems to be holding up through the summer time season. But we know that the virus is capable of causing severe disease but most severely ill disease is occurring in people with known high risk conditions, highlighting the fact that vaccination is key for those people.

So what's next on the next slide? Summer time clusters will continue we think. We do expect a fall epidemic similar to what we'd see in seasonal flu. We're planning for an epidemic that might occur earlier but the nature of the epidemic, the timing and the magnitude like any flu year is a bit uncertain.

And I'll stop there and turn you over to the vaccine experts to give you an update on the vaccine issues.

Tom Shimabukuro: Thanks Joe. This is Tom Shimabukuro and I appreciate the opportunity to speak to you today. This afternoon I'm going to provide an overview of Pandemic H1N1 vaccine development and (unintelligible).

Before we get started I want to review some of the national strategies. And the national strategy for Pandemic Influenza and this is (unintelligible) plan, provide vaccine to everyone in the US within (unintelligible). The H1N vaccine strategy follows the pandemic playbook for vaccine development production and administration.

Clinical studies will inform vaccination formulation and safety profiles. So the key decision issues are what type of vaccines or vaccine product type use of (Thymerasol) preservative in the vaccine, use of oil on water (adjetents), close vaccination safety monitoring.

Next slide. There are really four phases of a vaccination program, vaccine development, commercial scale manufacturing, distribution and administration, and finally post launch effectiveness, safety and utilization monitoring.

My presentation will focus o the first two, vaccine development and commercial scale manufacturing. So here I've listed the key steps in vaccine development. The first step the vaccine reference strain development is an activity that occurs once the virus is isolated. CDC, the CDC labs and other labs as well identify the vaccine, characterize it and then send off what's called reference strains to the manufacturers.

The manufacturers then take these reference strains and them what are called master seed strains. Once these master seed strains are produced, they can move into production of vaccine and one of the first steps in vaccine development is production of clinical investigational lots. These lots are used to conduct clinical studies to assess immunologic response and safety. And these are the studies that form the formulation decisions.

What strength of vaccine you need to receive an adequate immunologic response and is the vaccine safe and effective. And before I move onto the next slide I just want to mention that all licensed vaccine production for influenza vaccines (unintelligible) is egg based.

So another step in the process is commercial scale production. And one of the most important steps in this process is the (potency ascent) agent preparation and calibration. It's necessary to have these potency reagents to confirm potency of bulk antigen. These are the reagents where that are used to actually confirm that your dose is safe. For example, 15 microgram or 7.5 micrograms or some other potency.

And there's also commercial scale bulk antigen manufacturing without adjuvant. Bulk antigen is the basic ingredient for a vaccine. And there is also commercial scale bulk antigen manufacturing with adjuvant. This is, and I want to mention that decisions around using adjuvant vaccine have not been made yet, they will be included in clinical trials, but no decisions as far as will we or wont we use, (unintelligible) will we or won't we use an adjuvant vaccine are to be determined.

However, if you are going to use a reformulated vaccine with adjuvant one of the steps you would take in commercial scale production is make that bulk antigen with the adjuvant.

There's also bulk adjuvant manufacturing which is making separate adjuvant pennant from antigen. Adjuvant manufacturing is a simplified process then antigen manufacturing cause your not growing a virus. That’s really oil and water a (unintelligible) product.

Its also commercial scale syringe and needle manufacturing. A certain amount of lead time that needle and syringe manufacturers need in order to gear up for a potential vaccination program of (unintelligible) that we may need to be (unintelligible) in the fall.

Then there's vaccine formulation and finish. And that’s putting the final product into either multi dose vials or into (hooded) syringes. Next slide is a timeline and this slide is a little bit dated but I think the steps and the processes are still relevant.

The green up top you see the vaccine developments steps that I described. Below that, you see some red lines, these are the vaccine manufacturing steps.

And you have a couple other steps below which have to do with seasonal vaccine production and immunization, implementation of an immunization program. But the take home message from this slide should be that vaccine development and vaccine manufacturing can occur simultaneously. Vaccine development, those are steps we would take when any Novel Influenza A virus is detected and its isolating the virus, creating reference strains, master seed strains and pilot lots and performing clinical studies.

The same time this is going on, and initiate steps for commercial scale manufacturing which is occurring right now, presently there are pilot lots being prepared for clinical studies and there is also commercial scale manufacturing of bulk antigen ultimately will be formulated product.

Moving onto the next slide, this is a listing of the vaccine manufacturers which are expected to provide vaccine for the US market in the fall. These are all licensed producers of US flu vaccines. And so (Novardis) we expect to produce roughly 46% of vaccine for the fall. (Novardis) also manufactures MF59 adjuvant which is an oil water (unintelligible) adjuvant which could be potentially reformulated with vaccine. And I want to emphasize again that decisions around the use of an adjuvanted vaccine are to be determined but will be included in the clinical trials.

The next manufacture is (unintelligible) 26.4%, (BSL) which is an Australlian company producing 18.7% and finally (Medamune) which produces live attenuated vaccine at 5.8% and (GSK) has facilities in Germany and Canada producing a relatively small amount 3.4%. (GSK) also manufactures a adjuvant called (ASO3) which would be in a separate vial. They do not preformulate.

Moving onto vaccine products in general. The top three bullets list the unadjuvented products that we expect. So there would be unadjuvented multi dose vials, those would be 5 mil vials, 10 doses per vial. I just want to note that all multi dose vials will contain (thimerasol) preservative or it will also be unadjuvented (P) free preloaded syringes produced and nasal sprayers.

The preloaded syringes and nasal sprayers which could be up to 20% of vaccine produced will be (P) free and pediatric formulations. Potentially there could be multi dose vials, preformulated with adjuvant. Those would be coming from (Novardis) that is an adjuvanted vaccine which is in a 5 mil, 10 dose vial, it does not require mixing. And there would also be multi dose vials formulated for an adjuvant and separate adjuvant vials which would have to be mixed at the site of administration.

Next slide. So here is a listing of vaccine ancillary supplies that the US Government has made a commitment to provide. They include needle and syringe units for multi dose vials, sharps containers, alcohol pads and mixing syringes if adjuvanted vaccine is used.

Next slide. Moving to specific products, again (Novardis) which produces roughly 46% can produce standard unadjuvanted multi dose vials. And they can also produce if need be multi dose vials, preformulated with their (MS59) adjuvant. Both of these products would contain (Thimarisal). (unintelligible) again with 26.4%. they can produce a standard unadjuvanted multi dose vial and they also have the potential to produce a multi dose vial formulated for an adjuvant.

(Santifee Pasture) would an unadjuvanted vaccine that’s formulated for an adjuvant would be mixed with (GSK)"s (ASO3) adjuvant. So that would be a separate antigen and adjuvant vial to be mixed at the site of administration

(Santifee) can also produce (P) free, preloaded syringes as well. The next slide moving onto some other manufactures.

(DSL) similar to (Santifee Pasture) can produce a standard unadjuvanted multi dose vial and also a multi dose vial formulated for an adjuvanted vaccine and this would involve mixing (GSK)'s (ASO3) adjuvant at the site of administration and they can also produce a (P) free pre loaded syringe and (Medimune) produces live attenuated vaccine.

These are all in nasal sprayers and they're (P) free. (GSK) can produce standard unadjuvanted multi dose vials and they also produce a multi dose vial formulated to receive their proprietary adjuvant (GSK)'s (ASO3) even though this is (GSK) antigen and adjuvant and they feel separately so there would be have to be mixing at the site of administration.

Moving onto to storage and handling. These vaccines, these influenza vaccines have the same storage and handling requirements as regular flu vaccine, (Trivalant) and activated vaccine and (LAIV). The inactivated pandemic H1N1 vaccine would have to be stored at 2 to 8 degrees (centigrade), same for the live attenuated vaccine. The oil and water adjuvant also needs to be stored 2 to 8 degrees (centigrade) it has a fairly long shelf life, 2 to 5 years.

When a vaccine is mixed with adjuvant at the site of administration this is stable for up to 8 hours after the mixing. There hasn’t been any data collection on how long that is stable if stored at 2 to 8 (centigrade) so the recommendation is once you mix the vial with the adjuvant that should be used during the day at that clinic.

The last thing I'm going to mention is emergency use authorization. An emergency authorization is use of an approved medical product or an unapproved use of an approved medical product during a declared emergency. The FDA Commissioner has the authority to authorize this. So unadjuvanted pandemic H1N1 vaccine may be licensed in a matter similar to seasonal flu vaccine. This would be a similar to a strain change and therefore would not need an EUA. However, we anticipated that any adjuvanted vaccine if used for this upcoming season would be administered under a EUA.

That is the end of my presentation. And I will turn it over to Dr. Pascale Wortleyto talk about some of the programmatic issues around vaccination.

Pascale Wortley: Good afternoon, this is Pascale Wortley and we are going to switch gears a little bit now and talk about some program implementation issues.

So we'll go to my first slide which is titled Vaccine Purchase, Distribution, Allocation and Distribution. And as you may already know this program in some respects is going to unfold quite differently from how the seasonal vaccination occurs. And one of the biggest ways in which its different of course is the vaccine is being procured and purchased by the US Government.

And then once the vaccine starts to become available it's going to be allocated across states proportional to population. It's going to be shipped to sites that are designated by states. And that will be a mixture of local health departments and a number of other private sector settings. So this is different from having vaccines shipped directly from manufacturers to providers.

And there are a number of unknowns at this point. And as you might imagine there's a lot going on at the federal level as well at the state and local level with respect to planning because this is a huge endeavor that we're gearing up

for but because of the unknowns we've had to establish some planning assumptions to help planners get to work.

At this point we are assuming the vaccine will start becoming available in mid October. One big unknown is exactly how much vaccine is going to becoming available and we a quite wide range of possibilities here ranging from 40 to 160 million doses over a one month period. And that's what we call this initial (bullis) that represents several weeks of production and then after that there will be weekly production amounts that total up to somewhere between 10 and 30 million doses.

And this is coming from all five manufactures that (Tom) mentioned. So they would be not all coming out exactly at the same time, but fro those five manufacturers. So under the highest case scenario there could be enough vaccine for the entire population over the space just a few months. And then under the lowest case scenario it would take quite a few months longer.

But either way this is actually quite a bit more vaccine then we had hoped to get previously when we were planning under an H5N1 scenario. Another planning assumption is that two doses of vaccine will be required for most of the population and finally, as (Tom) mentioned there will be preservative free single dose syringes for young children and pregnant women.

One thing I might also mention is that of course there's interplay with seasonal vaccination which we haven't really discussed. But we are anticipating that the seasonal vaccine will be becoming available a little earlier then usual this year starting by the end of August. And with a fair bit of it out as predicted by the end of September. But something to keep in mind. And of course that will be going out through the normal channels, there's nothing changing there.

We also have made some vaccine planning assumptions around populations to think about planning for. And I want to make clear that these are not ASIP recommendations. The ACIP is meeting at the end of this month and is going to be making recommendations for priority groups for vaccination but because planners have such a huge task ahead of them, a document was issued last week providing some guidance about based on the best information we have to date, what are populations that may well be priority groups and that planners ought to be thinking about vaccinating.

This was especially important because this information is quite different from past pandemic planning documents. As you heard earlier from Joe Bresee there has been a high incidence of illness in children and children up through age 18 in past pandemic planning were not among the initial populations to vaccinate. The youngest children were but not up through age 18.

And as I'll get to later, there are some challenges around vaccinating that group. Other groups that have been identified as potential groups that planners need to be planning for include pregnant women, the youngest children, 6 months to 4 years, new parents and household context of the youngest the children under 6 months who themselves cant be vaccinated, non elderly adults that have medical conditions increasing the risk of influenza and then finally healthcare workers and the emergency services personnel.

Next slide please. So generally speaking what the planners out there throughout the country in preparedness and immunization programs are planning on given this potentially large amount of vaccine available is they're thinking of what we're referring to as a blended model of delivery of the vaccine which will include both what people traditionally think of in the context of pandemic vaccination which is large scale clinics that are organized by public health.

But also getting the vaccine out through the private sector and we're defining the private sector broadly including provider offices, including obviously pediatricians but also internist and potentially obstetricians, so all the providers who would see the target populations once priority groups are set.

And also other settings for example, retail settings which are the prevalence of which varies depending on where you live, potentially through work places etcetera. So really trying to take advantage of all kinds of venues.

So then the question arises well how will a vaccine be delivered to all these potential partners? And what's going to have to happen especially for the providers who don't normally get vaccine through public health and I'm referring to the pediatricians participating I the VFC program for these other providers there's going to have to be relationships created with public health so that they can be designated as vaccine recipients.

And they would receive this vaccine at no charge to administer to their population, to their patient population. Next slide please. So some of the key things that are going on right now at the state and the local level is planners are in the process of reaching out to these private providers so state and medical chapters, professional organizations also reaching out to private sectors such as retail based clinics who may be interested and able to vaccinate and community immunizers and potentially also talking to work places, large business etcetera.

Pharmacists also may be able to play a role in this. Certainly we know a lot of states are in the process of approaching pharmacists at the same time so together with this private sector approach, they are planning large scale clinics, this is often a local county health department responsibility. This is

going to be probably very important for vaccinating school age children assuming that that school age children are designated as priority group because these are kids who really are not in the doctor's office very much. And to vaccinate that group would really be a huge demand for a pediatric offices. So a lot places are trying to figure out how to staff up for clinics targeting school age kids. As well as other populations, there's going to be enough to do for everybody here.

Next slide. I just wanted to bring up a few issues that are going to come up for provider offices. So, pediatric practices or internal medicine practices etcetera. One of them is especially for pediatricians and also for obstetricians will be storage capacity because of vaccine for young children and pregnant women coming in single dose syringes and obviously that takes up more space at a time where refrigerators are already occupied with seasonal influenza vaccine.

Another issue will be trying to administer the vaccine according to the recommended priority groups. At the same time we really want to avoid the situation like in 2004 where people may have been turned away only to be told later there was enough vaccine. So this is going to be a tricky thing to figure out hoe to do right and when we get to the point where we know what the priority groups are and we know how much vaccine there is, it will be important to try to get the right message out so that people aren’t turned away.

We also will be requiring some reporting of doses administered on a weekly basis so that we can know how many people have been vaccinated and that is in part important from a safety monitoring point of view so that when adverse events are reported we have a denominator, we know of how many doses administered.

And then finally in terms of insurance reimbursement for administration at CDC we have been working closely with AHIPP America's Health Insurance Plans and according to AHIPP planners can assume that similar to seasonal influenza vaccination health plans will reimburse claims for the administration of Novel H1N1 vaccine and of course that is important for providers to know.

A few words about monitoring vaccine coverage briefly. So as I just mentioned initially states are going to be required to report doses administered on a weekly basis so that we can keep track of what's going on and then by the time enough doses have been administered that then can be picked up on population surveys we'll be using some of our usual tools to monitor who's getting vaccine and potentially identify populations that are under vaccinated and try to make some intervention there.

So those will be important tools. Next slide please. So here I'm on a slide called Monitoring Vaccine Safety, just a few words about that. The (VAERS) system which many providers are already familiar with Vaccine Adverse Event Reporting System will be the backbone of this system.

It allows for signal detention in of itself it cannot determine whether there's a relationship between the vaccine and signals detected but that’s where another system called the Vaccine Safety Data Link which is a network of managed care organizations representing about 3% of the US population comes into play and that allows for doing analytical work and looking at the relationship between vaccination and these signals that have been detected.

In addition there's a lot of work going on to develop active surveillance mechanisms for things that we expect to happen such as (Giamveray) syndrome. So there's work they're going on through the emerging infections program.

And lastly I just wanted to say a few words about monitoring vaccine effectiveness because of course that would be important once we're implementing this large scale vaccination program. There will be one system set up at four community base sites looking at the vaccine effectiveness for prevention of PCR confirmed medically attended influenza.

There will also be a vaccine effectiveness program looking at the prevention of influenza hospitalization diagnosed by provider order clinically available tests and that also will be happening at through the emerging infections program and that’s at ten sites nation wide.

And in addition our colleagues at the Department of Defense have systems in place to be able to test vaccine effectiveness in their active duty service members.

Now with that, I'll conclude my comments and open it up for questions.

Operator: As a reminder, if you do have a question, please press Star 1 at this time. Please remember to unmute your phone and record your name clearly so that I may introduce your question. Again, that would Star 1 for any questions. And one moment for the first question please.

Our first question, your line is open.

Question: Hi, yes. My question pertains to the vaccine, I was just curious, I had heard previously a time delay between administering dose and dose two of the H1N1 vaccine. And I wondered what is that going to - is that time delay? If its still applicable? And if it would vary with the adjuvant vaccine use?

Tom Shimabukuro: Typically, this is Tom, typically the recommendation is a 28 day interval which translates really to a month. The clinical trials are going to be looking at a zero day, seven day, 14 day and 21 day as well as, 0 day actually means getting one shot in one arm and one shot in the other on the same day. So I think the clinical trials will give us better information on what type of time interval is actually, what type of time interval we need between doses.

As far as the adjuvants, I mean typically adjuvants can give you a more vigorous immunologic response and also a broader immunologic response but I haven't heard any information about reducing the time interval between the first and the second dose. I mean there is some evidence that you can get a better response at least these are from H5N1 clinical trials studies, you can get a better response on a first dose with an adjuvented vaccine, but I cant comment on whether that's going to reduce the interval.

Question cont'd: Thank you.

Operator: Our next question. Your line is open.

Question: Yes, actually two quick questions. I just want to validate in terms of the administration of the seasonal flu and also the Novel H1N1, we're talking about three doses all together? Is that correct? And I'm not a microbiologist obviously but PB1F2 in the event that that mutant gene rears its head, you know what would be our stance please?

Pascale Wortley Well just, I'll quickly take the first question and that is true for many people that would represent three shots and actually for some children who are getting seasonal influenza vaccination for the first time that could be four shots.

And then for the second question, and it sounds like its one for you (Joe). Are you on mute (Joe)?

Alycia Downs: Dr. Bresee are you on the line?

Joe Bresee: I am, I'm sorry I got cut off for a minute. I didn't hear the question. I apologize.

Alycia Downs: Could you please repeat your question?

Question cont'd: Sure. The PB1F2, I believe mutant gene, if it does rear its head in terms of this flu, what would be our stance or how would that change this scenario that your envisioning here?

Joe Bresee: Well I think I'd say two things, first the planning we're doing for the fall assumes a severe year. And so I think that if the virus behaves as it has or behaves differently then it has depending on mutations that it will acquire, I think our planning is for a severe year and so and we can scale that down in some respects if it turns out to be milder then we think.

I think part of the surveillance plan that's ongoing now and is being enhanced is to monitor closely the development of mutations associated with increased transmission or increased severity. So I think we'll pick that up relatively quickly. So probably not immediately, but I think we'll see those, the (fena) type of that as the clinical characteristics of that relatively quickly and can respond.

And so I don't think our panning a response is going to be dictated so much by mutations that occur except in the case of (unintelligible) resistance mutations and that will certainly change clinical care and clinical guidance.

But I think the development of plans have really assumed a sever year and we'll assume that the virus will behave somewhat differently then it did in the spring.

Question cont'd: Thank you very much.

Operator: Our next question. Your line is open.

Question: Yes the question that I have has been answered, thank you.

Operator: Our next question. Your line is open.

Question: Hi, thank you. Very informative presentation today, I appreciate it. My question is regarding the delivery of vaccines and the supplies that we will need. Did you indicate that the government is planning to also provide syringes and alcohol wipes etcetera along with the vaccine or is this something that we have to be concerned about given back ordering of recently the (SID) testing apparatuses?

Tom Shimabukuro: The Federal Government will provide needles and syringes and sharps containers and alcohol swabs to support vaccination. And they'll provide vaccine as well. So those are the products that the Federal Government will provide to health departments, providers, other sites that are vaccinating.

Let me just say those again. That's vaccine, needles and syringes, sharps containers and alcohol swabs.

Question cont'd: Thank you.

Operator: Our next question. Your line is open.

Question: Yes I had a question about public sector providers. Are the, is public health reaching out to the hospitals to get these agreements in place so that we can immunize our healthcare workers?

Pascale Wortley Yes, absolutely. So that's generally the way that public health is planning on getting healthcare workers vaccinated, hospital healthcare workers. For healthcare workers that in the out patient sector it's a little more complicated and I think that one of the ways that places are planning to do it is potentially have the vaccine, have the local health department be a repository for the vaccine and then get the word out that if you are in some geographically defined area, you would come get the vaccine for your, you know the healthcare workers within your practice at such and such location

Question cont'd: Thank you.

Operator: Our next question. Your line is open.

Question: Oh, yes I have two quick unrelated or two quick related questions. First there's been a lot in the media about the manufacturers of the H1N1 vaccine having trouble growing the antigen and egg. Do we think that will materially delay that mid October date for the amount of vaccine that might be available?

And related to that, do you think (ASIP) will be making some recommendations about perhaps starting the seasonal flu vaccine season earlier so that most of that vaccine is in people's arms before the H1N1 vaccine is out?

Tom Shimabukuro: Hi this is (Tom). As far as the yield that the manufacturers have been getting, I mean they have been, they probably have been on the lower side, however when we do our projections and when we factor in, I mean we do a variety of scenarios and when we come to our projections. So that's why we've given the state and local health departments the, you know the 40, the 80, the 160 million doses becoming available as a (bullis fog) by the 10, the 20 and the 30 million weekly shipments.

That really is to represent what kind of supply we might anticipate. Supply would also be affected by how we have to formulate the vaccine. If you can imagine if we the standard right now is 15 micrograms. If the clinical trials show we need 30 micrograms, you've essentially doubled the amount of antigen you need for a dose. So, but we have tried to factor in these variables into our supply estimates that we've given state and local health departments to plan for. And I'm going to let (Pasqual) address the ACIP issue.

Pascale Wortley I actually don't have a good answer for you. This issue did come up at the last meeting which was just a few weeks ago. And I don't know if the ACIP plans to make a formal recommendation about that. I mean there's obviously advantages to doing that. It also poses some challenges in that it then requires more visits.

So there's pros and cons. But I think a lot of people think it would be great to at least try to get one out of the way as quickly as possible.

Question cont'd: Thank you.

Operator: Our next question. Your line is open.

Question: Thank you. First I'd like to say that this is one of the best of the COCA that I've been involved with, excellent information, things that we've been wanting to hear for a while. Unfortunately Shimabukuro's mic was kind of cutting on and off at the beginning of the sentences and I would like some clarification on the method of production of the vaccine.

I was under the understanding that some of it, if not all was going to be cellular production, but I think you said egg production. If you could clarify that?

Tom Shimabukuro: Yes, so the department health and human services and within the department there's an office that's call (BRADA). They manage the contracts for the vaccine manufacturers. The have what's called Tier One manufacturers, Tier Two and then there may be some Tier Three. But Tier One manufacturers, the ones that we expect will be providing product for the US market are all licensed manufacturers of flu vaccines for the US. All egg based.

There are some Tier Two manufacturers that are, that use other processes, cell based and other processes. That is more of a, that's more of a, they're more in the R&D stages as far as FDA is concerned, so right now when all of our projections and with the initial (bullis) and the weekly projections are based on the five Tier One manufacturers which are all licensed for the US and which all use egg base processes.

Question cont'd: Thank you.

Operator: Our next question. Your line is open.

Question: I was wondering id the seasonal and H1N1 immunizations can be given simultaneously? And are we going to have to deal with different supply chains for the two different vaccines as well as the ancillary materials come with the H1N1 but not with the seasonal?

Pascale Wortley At this - you know, we feel quite confident that both, that co-administration will be possible but we won't know for, you know for sure until the clinical trials are done. But we think that that is very likely.

In terms of the supply chains, you're correct. There will be two supply chains in that you will be getting your seasonal vaccine how ever you normally order it. And you'll be getting the H1N1 vaccine through a distributor and we're not, we're still working out the details of that but it will arrive at practices but it will be a separate shipment from where ever your getting your regular seasonal vaccine.

Another thing that we're working on right now is coordinating the shipment of the ancillary supplies with the vaccine because obviously if they don't arrive at the same time they wouldn't be much good. So those are all things that are currently in the works.

Question cont'd: Okay, thank you.

Operator: Our next question. Your line is open.

Question: Hi, thank you. I do have a few questions. If one of the kids say came in for their vaccine but they were actually confirmed case of H1N1 do they still get vaccinated?

Pascale Wartley: Well I guess if they had, well maybe this is a better question for (Joe) really. Are you on the line (Joe)?

Joe Bresee: I am, I am. I think the answer would be yes. For a couple of reasons. We for seasonal flu we don't often ask that question clearly. It might come up more commonly in this situation because people are paying attention. But for a couple of reasons because the history may be on reliable and so you want to vaccinate. But more to the point that the even after national infection 100% who develop immunity and as things drift the virus your exposed to later in the season may be some what different then the virus your exposed to early in the season.

So I think (unintelligible) practically I think it would be difficult to use that as a screening criteria and try to implement. So my quick off the cup answer would be that previously history of Novel or suspected Novel H1 wouldn't preclude vaccination.

Question cont'd: Okay, thank you,

Joe Bresee: Pascale would you say the same thing?

Pascale Wortley: I agree with you Joe.

Question cont'd: And my, I have two other questions, sorry. Do you know where we had our meeting here at the health department and we were talking about retractable syringes to protect people from getting injured by the needles. Do you know if the Government is going to just send us, you know the plain needles, plain syringes or will they be safety syringes and needles?

Tom Shimabukuro: We're making every effort to procure the safety syringes, the (OCEA) compliant ones. That said, I mean I don't work directly on procuring the needles and syringes but from my discussions with the folks at HHS, every effort will be made to do that. However, the goal is to provide needles and syringes for all doses of vaccine and if its not possible to get all safety needles, I mean they may have to make that up with the non safety type needles. But we are, we would like to procure all safety needles.

Question cont'd: Okay. And my last question is do you foresee like when probably kind of hard to determine now, but what the timeframe will be? You know we have to vaccinate so many people in such a such time?

Pascale Wortley You know that's a really good question and I think it is going to depend on a number of factors that would have to do with has there been a change I severity of disease etcetera. I mean its actually something I've been thinking about a lot and its challenging because putting out those types of timelines is hard across the country because of , you know variations in infrastructure and also not really knowing what demand will be which of course is going to be a big driver of what happens.

I mean a lot of people right now are concerned there's just not going to be a lot of demand for this vaccine. That's a really good question and we don't have a good answer for you right now.

Question cont'd: Well that's okay. I just thought I'd ask. Thank you very much.

Operator: Our next question. Your line is open.

Question: Hi, several of my questions have been answered but the last one that I have remaining is that you all have mentioned that the vaccine would probably be

available mid October. Yesterday in the newspaper they were saying its been pushed to December. Is there any validity to that?

Tom Shimabukuro: I saw that report and the conversations I've had with HHS, I don't believe that's true for the US market. You know the October timeframe that we're looking at I think is a fairly aggressive and optimistic timeframe and assumes a lot of things are going to happen according to schedule.

Again as (Pasqual) mentioned there's five manufacturers of vaccine. We don't expect them to all have vaccine available on the same day in October. So it may be spread out over a period of weeks to a month. But I haven't heard anything official that we would expect a delay in vaccine availability into the December timeframe.

Question cont'd: Okay, thank you.

Operator: Our next question. Your line is open.

Question: Hi, thank you. Yes is there any (serology)? Meaning antibody tests to determine previous exposure? And although you mentioned it, would it preclude vaccination would that be a group that would not necessarily need vaccination?

Joe Bresee: That's a great question, this is (Joe). The answer is there is a serologic (asa) for the antibodies against this under development. The problem as you can imagine is that since this is an H1 virus its different but not that different from circulating H1 that have been circulated since 1976, 77. And so the background level of antibodies that look very much like antibodies to this virus exist in all of us because we've all been exposed multiple times to similar viruses.

So it will be difficult to (tee) that out. So there will be a serologic test that will be a good test to document acute infection if you get (unintelligible) one before or one early infection and one later to look at a rise in antibodies.

I think it will be very difficult to run single blood tests to assess immunity to this virus because of the cross reactivity between the other antibodies we have.

Question cont'd: (unintelligible) propensity for the virus to effect young children who would not have been exposed to those previous H1 outbreaks?

Joe Bresee: Yes in young children it will be a little cleaner. Still your right, but even so it would have to be a pretty young kid to not have been exposed to H1 because they circulate each year. So, but your right there will be the test probably will work a little better in young kids because they are relatively naive. But I think it will still be a tricky test to interpret and probably not (unintelligible).

Question cont'd: Great, thank you.

Operator: Our next question. Your line is open.

Question cont'd: My question has been answered.

Operator: Our next question. Your line is open.

Question: Hi, thank you. This is Joan Potter. And the US Government is shipping the vaccine to designated sites. Who will determine what are designated sites beyond the health departments and when will that be determined?

Pascale Wortley Well that's a major planning activity at the state program level over the summer. And that is figuring out beyond local health departments who are the private sector partners that are interested in administering H1N1 vaccine? So different states are going about reaching out to their private providers in different ways.

And of course the providers which with whom they already have links and those are the providers who get the vaccine for children vaccines. So a good bit of the pediatric providers, they already have relationships with. And that's easy. What's more challenging is reaching out t internists and obstetricians for example because they don't really have those preexisting relationships. And so they're working through the state Medical Societies etcetera to get the word out.

Some states are planning on putting out on the web what they call pre registration sites so that providers who are interested can pre register and be receiving information and that's not a commitment, its really just sort of, you know that way you know what's going on. And the once everything is known and, you know then comes the time to actually say yes we want to do this. So different states are going about it differently.

Question cont'd: Thank you.

Operator: Our next question. Your line is open.

Question: Hi and thank you for a very informative call. I'm a Director of Out Patient Pharmacy Service in Appalachia and we have several pharmacies in rural clinics. And I would like to find out how we, I mean my pharmacists are certified to give immunizations, I'd like to find out how we let somebody know that we're interested in being a private sector provider?

Pascale Wortley Okay, so you need to contact your state health department and I would focus on contacting the immunization program because typically although this is a joint immunization and preparedness program activity, really the out reach to private sector is in my understanding largely happening through immunization programs. And they'll be thrill to hear from you.

Question cont'd: Okay, so just contact the Ohio State Department of Health and go from there?

Pascale Wortley Yes.

Question cont'd: All right, thank you so much.

Operator: Our next question. Your line is open.

Question: Hello, hello. I'm actually calling regarding on the first slide set regarding treatment. I have a question that seems keep coming up from the medical community regarding effectiveness of (TAMA) flu. Should there be any retesting done after a patient has been treated to ensure that they have been quote, unquote cured or the infectivity has decreased? Just our general perception is no, but I didn't know if that has been looked at in general?

Joe Bresee: That's a great question. And it comes up a lot in institutional settings when your chording patients or when your trying to put patients back with their roommate, things like that. The base answer is no. We think its relatively impractical and its difficult in a sense that if you do in studies that have looked at serial samples during an illness and after an illness, you can often get a positive and the next day get a negative, next day get a negative, next day get a positive.

And so the question then becomes how many days negative does a person have to be to be non infectious? Instead I think the studies are compelling that the highest viral (unintelligible) that a person sheds is correlated pretty well with fever. And so when a person (unintelligible) are clearly we think and studies would bear out at the highest risk of transmission to others. And when their fever is finished the viral pattern goes down by a couple of logs in the next day and a couple of logs the following day probably.

And so the guidance, the traditional guidance with seasonal influenza is probably going to look much like the guidance for this influenza and that is stay away from other people, keep people away form people during the (unintelligible) for 24 hours after they get well and then they can probably go back.

So I think the base answer is no except in very special situations maybe like bone marrow transplant units.

Question cont'd: Thank you.

Alycia Downs: Melanie, we can take one more question.

Operator: Our next question. Your line is open.

Question: Thank you. If a person receives only one vaccine what would the coverage rate be?

Tom Shimabukuro: You mean what could you expect their immunological status to be?

Question cont'd: Right. Compared to the two.

Tom Shimabukuro: Yes I don't have a good answer to that. The clinical trials will give us some information on what type of immunologic response from one dose. But assuming that, I mean there is some evidence that elderly people who have either had multiple H1N1 infections or vaccinations have a certain amount of cross reactivity but I think for the bulk of the population it's a fairly naïve population.

And one of out assumptions is that you would need two doses to have an adequate immunologic response. But I think, I'm going to let (Joe) weigh on that one too if he has any thing to add. (Joe) are you there? Well, yes I guess I mean especially for younger, for children and younger adults I think its safe to assume that we have a pretty naïve population and we would most individuals would probably need two doses. But again, we'll get better information on that from the clinical trials.

Question cont'd: Okay, thank you.

Alycia Downs: Well I would like to thank our presenters for providing our listeners with this information and I'd also like to thank our participants for joining us today. I apologize if anyone had any trouble hearing any of our speakers, we had some technical difficulties. So we apologize for that.

In case you didn't get the chance to ask your question, please send an email to coca@cdc.gov, that is C-O-C-A @CDC.gov. COCA would also like to hear from the call participants concerning any proceved barriers regarding recommending the H1N1 vaccine to their patients when it becomes available.

So please send an email to again coca@cdc.gov with any comments or thoughts you may have. The recording of this call and the transcript will be posted to the COCA Web site, emergency.cdc.gov/coca within the next week.

You have a year to obtain continuing education credits for this call. All continuing education credits and contact hours for COCA conference calls are issued on line through the CDC Training and Continuing Education online system, www.2a.cdc.gov/tceonline. Thank you again for participating and I hope everyone has a wonderful day.

Operator: That does conclude today's conference. You may all disconnect at this time.

END