Recent Developments in Seasonal Influenza Epidemiology and Prevention
Anthony Fiore, MD MPH
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Coordinator: Welcome and thank you for standing by. At this time all participants are in a listen-only mode. After the presentation we will conduct a question and answer session. At that time to ask a question you press star then 1 on your touch-tone phone. Today's conference is being recorded. If you have any objections you may disconnect at this time.

I would now like to introduce your host for today's conference call, we have Miss Alycia Downs. And ma'am, you may begin.

Alycia Downs: Good afternoon and thank you for joining us for today's COCA conference call entitled "Recent Developments in Seasonal Influenza Epidemiology and Prevention."

We are very pleased to have Dr. Anthony Fiore present on this call.

We will be using a PowerPoint presentation that you should be able to access on our Web site. If you have not already downloaded the presentation, please go to www.emergency.cdc.gov/coca. Click on Conference Call Information Summaries and Slide Sets. The PowerPoint can be found there.

Dr. Fiore is a Medical Officer in the Influenza Division within the National Center for Immunization and Respiratory Diseases here at the Centers for Disease Control and Prevention in Atlanta, Georgia.

Some of his duties include developing and promulgating seasonal influenza vaccination policy, conducting and supervising epidemiologic investigations

of influenza outbreaks and assessing influenza prevention strategies.

The objectives for today's call. After this activity the participants will be able to: describe at least two recent developments in influenza epidemiology and prevention, describe recent vaccine effectiveness study findings, and three, describe changes in vaccine recommendations for the 2008-2009 influenza season.

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CDC, our planners and the presenters for this seminar do not have financial 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.

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

Dr. Anthony Fiore: Thank you, and thank you all for tuning in today. I wanted to provide you with some information about the past influenza season and also describe some of the more recent information we have about what happened during this season, the vaccine effectiveness, and the vaccine coverage data that currently exist. Let's go to the next slide which should be titled Overview.

Now so as I said, we'll start out with a fairly elementary brief review of the clinical presentation epidemiology of influenza, with the idea that there are folks with a number of different backgrounds on this call. We'll review the

season, talk about vaccine effectiveness overall in a general sense and also the preliminary data we have from this current season, give you some of the updated recommendations that have accompanied advisory committee on immunization practices, which is CDC advisory committee that makes vaccine recommendations, and then finally give you the coverage data.

Next slide please.

Human influenza is a highly transmissible respiratory illness caused by influenza viruses. And it results in yearly winter epidemics which are referred to as seasonal or inter-pandemic influenza.

Every once in a while though there is a pandemic, sporadic and unpredictable. As you probably know, we've had three of these pandemics in the last 100 years or so. And the what happens with a pandemic is that a new strain of virus shows up that virtually no one is immune to.

Attack rates can be very high and morbidity and mortality are elevated compared to the annual epidemics.

Now these annual epidemics though are not to be underestimated. In an average epidemic year, anywhere from 2.5% to 20% of the population can fall ill with influenza. The highest rates are typically in children. In some towns you'll see children attack rates of over 30%.

On average, 36,000 deaths a year are attributed to influenza. But this ranges widely according to the severity of the season.

Over 90% of the deaths in most seasons are in persons greater than 64 years old.

On average over 200,000 hospitalizations occur each year. Again, this is a wide range for the reasons I just gave for mortality.

About 50% of those who are hospitalized are more than 64 years old. But what's also interesting is that the risk of hospitalization for children younger than two years old is actually similar to the risk in the elderly. So the extremes of life are where you see most of the most severe illness.

Influenza epidemics annually result in a substantial economic impact. The burden was recently estimated at $87.1 billion annually, and that is accounted for both with hospitalization and other medical costs and lost work and then of course the cost of people having long term effects of influenza.

Now influenza viruses come in a variety of different types: Influenza Virus Type A is the one that typically is of most interest and causes the most morbidity and mortality.

Influenza Viruses Type A are subtypes based on the surface glycoproteins. And these proteins exist on the structure of the virus. There are 16 hemoglutinin proteins and nine different neuraminidase proteins that influenza virus can have. Influenza virus just has one of each. But the various combinations result in a large number of different potential influenza Type A viruses.

The currently circulating human subtypes are called H1N1 and H3N2. Influenza Type A viruses are a large proportion of seasonal influenza. They're also the only influenza virus type that can actually cause a pandemic.

These viruses can infect multiple other species, and they can jump between

these species amid birds, pigs, horses, dogs and other mammals -- and - other mammals for the most part can be infected with this influenza virus and potentially can serve as a source for other animals.

Birds are the main reservoir though for the new subtypes - that is the new hemoglutinin subtypes.

Now just a word about two different concepts about how influenza viruses change. One of them - and this is antigenic drift and antigenic shift.

Antigenic drift is what's going on all the time. These are small mutations in the viral genes, a continual process that's occurring during the influenza season.

And the result is that over time people have diminished immune responses to strains they've previously been infected with or been immunized against.

So in other words, an H3N2 strain that you were infected with three or four years ago, when it shows up this year it's changed enough that your immune system no longer gives you full protection against it.

The result is that you get yearly epidemics because there's a new wave of susceptible people every year. And this also requires that the vaccine gets updated yearly.

Antigenic shift is a more radical form of genetic change. And that means that you change out the entire hem agglutinin and neuraminidase subtype. And by the way, we should be on the slide entitled Antigenic Drift and Shift. I'm sorry, I don't think I said shift slide.

And this is a sporadic or unpredictable event that result is that there's no immunity within the population. And this is what can result in a pandemic.

However, it's important also to remember that there are many reports of transmission of animal influenza viruses of different hemoglutinin types to humans. And these don't always result in a pandemic.

Obviously you probably have heard about the H5N1 or the so-called bird flu cases. And I'll mention that more in a minute.

But there are also other ones - N7N2, H7N9 - of the various swine influenza viruses that occasionally infect humans, but have not resulted in pandemics.

Next slide.

The influenza A H5N1 is the one of most interest most recently. And this has been a very deadly virus for birds. There have been large scale bird outbreaks in Asia, Africa, Europe, and the Middle East.

The virus is highly lethal to domestic poultry. And we, at any given time, have multiple outbreaks going on around the world, and has resulted in 382 known human cases so far including 241 of those cases that have died since 2003.

Now almost all of these people had very close contact with infected domestic birds. There's been no efficient human to human transmission of N5N1 however, and now obviously H5N1 is the influenza virus of greatest concern at this moment, partly because several hundred humans have been infected, but also because of the high lethality. But there are other influenza viruses that we are also tracking.

Next slide please.

Influenza Virus Types B and C are two other forms of influenza viruses. Type B is only found in humans. It certainly does circulate in the US and worldwide every year, causes lots of illnesses in general, causes less mortality in most years compared to Type A; although that doesn't always hold true.

And its associated with the annual winter epidemics but not pandemics. And every year the influenza vaccine contains one influenza Type B strain.

Influenza C is not well understood. It appears to cause mild sporadic disease. It's not included in the vaccine and not usually discussed much beyond what we just discussed.

Next slide please.

The influenza clinical diagnosis, it's important to remember that these clinical symptoms are non-specific, and they overlap with many other pathogens. There are lots of respiratory illnesses that circulate, especially in the winter. And only a proportion of them are due to influenza viruses.

So what you need in order to establish the diagnosis: laboratory data. There are rapid tests now available that can be done in clinics or in hospitals, and you can get results in 30 minutes or less. But these are most often used, but they sometimes have poor sensitivity in adults, meaning that they don't pick up every influenza case.

Culture and preliminary chain reaction (or PCR) are available. But these are not typically going to be timely enough by clinicians with much information that they can actually use to treat patients.

So again, to make the point that not all respiratory illnesses is influenza even at the peak of influenza season, only about 25% to 35% of specimens who have an acute respiratory infection end up being positive for influenza.

Next slide please.

Now I'll just describe to you some of the information from this most recent influenza season which we just have more or less wrapped up at this point. So this is the 2007-2008 information.

Next slide please.

This diagram depicts how information about influenza surveillance flows into CDC and what we do with it. We get influenza information from a variety of different sources: from laboratories, from providers who agreed to send us specimens and provide us with clinical information about cases, from population-based surveillance systems that look at hospitalizations, from the states territorial epidemiologists, from the vital statistics, and then also through national reporting systems.

There are two types of influenza that are on nationally reportable. One of them is deaths in children due to lab confirmed influenza and the other is a novel influenza virus that's not one of the typical ones circulating.

And we send this information back out to the public and public health officials and clinicians and so on.

Next slide please.

Just describe to you in a little bit more detail about influenza surveillance. We'll start off with geographic spread. Next slide.

This is a publication that we've just started this past year that summarizes by week information about the influenza surveillance in the US.

And what you see here is a map of the US. And I'll show you over the next, I guess five or six slides, a series of maps that sort of give you almost a moving picture of what the influenza season did in this last year as far as widespread across states and the severity within these.

In the first slide what you see is for the week ending November 10, we really didn't have a whole lot going on with influenza, just a couple of states reporting local activity.

Things stayed pretty quiet with the next slide, with just a few more states reporting local activity going all the way to the end of December and starting to actually get into the typical Influenza season.

We still had relatively little activity out there with most states reporting only sporadic activity and just a few reporting local or regional activity.

January 5 things started to pick up a little bit. We had our first state report widespread activity.

Again, going to January 19th on the next slide you'll see the few more states added. And then things really hit in February. And February is the peak month for most influenza.

We have multiple states by February 2 reporting widespread activity. By

February 23 the whole country was sucked in. And this was a relatively more severe influenza season compared to the last couple where we had widespread activity nationwide for the first time in a couple of years all in the same week.

And then finally on March 15, you can see activity starting to lighten up a bit. And then the last slide I have here is April 26 with most states down to no activity, or just sporadic activity.

I'm sorry, there was one more slide ending May 10, again, showing just about everything gone.

We also monitor influenza by looking at the viruses that are sent in to us for characterization. This is another way to kind of follow the season. What this is showing here is the number of isolates and the percent that are positive for influenza. And remember I told you back even at the peak of the season only 25% to 35% are going to be positive influenza.

And here what you see is by February of this past year we were up over 40% that were positive for influenza.

Now what the pie chart is telling you is that this was a predominately H3N2 year with over half the isolates that were sent to us being characterized as being the H3N2 subtypes, with B coming in second and relatively mild years as far as H1N1 strain goes.

CDC, the laboratories here also do a fairly laborious characterization of the viruses to determine how closely matched the circulating strains are to the vaccine strains.

What you see here is a couple of bullets on the next slide titled Strain

Characterization that showed that influenza A H1N1 isolates that have been characterized; 381 have been characterized thus far, and we're continuing to do this.

Sixty-nine percent of them were a pretty good match with the vaccine strain that was in last year's vaccine. That is the 2007-2008 vaccine.

Now for the H3 viruses, the match between the circulating viruses and the vaccine viruses was less good. And then only about 21% matched.

For Influenza B the characterization is a little bit different. There are two main lineages is what they're called, two main subtypes of Influenza B. And we did not match the subtype very well this year with the circulating strain. You can see only 3% of them were in the same subtype.

Next slide please. We'll talk a bit about mortality in the next slide. What you're looking at now is a modeling estimate of pneumonia and influenza mortality that's based upon vital records reporting from 122 US cities. In other words, cities send us the cause of death of people that die in their cities over the course of the influenza season, the two wavy sort of sine wave type lines there are a predicted seasonal baseline on the bottom line and on the top a threshold of which we say there's epidemic influenza causing mortality.

And the red line is the actual data plotted. And so what you see here is five seasons worth of data. If you look to the far right you see that data from this recent influenza season. You see we were well up over the epidemic threshold for, you know, about 10 weeks there.

And this is by comparison to the last two seasons, where you can see we just barely got up above the epidemic threshold. They were much milder seasons

and what we just saw.

Going back all the way to the 2003-2004 season you can see on the far left there, a real sharp peak with the red line. And that was the most severe season that we had until this season over the last five years.

In other words we have three relatively mild seasons book ended by the 2003-2004 season and the last one.

I mention that influenza associated pediatric deaths are reportable disease. As of May 14 we've had 71 influenza associated deaths reported. The median age of children that died was 4.5 years. Only five of them were fully vaccinated.

Bacterial co-infections are a source of continuing concern to CDC and some of you may have actually seen some of these.

Among those children that died, 43% had a Staphylococcus aureus co-infection, including 12 that had a methicillin-resistant Staphylococcus aureus infection: something we're keeping an eye on.

Just by way of comparison, compared to the last couple of years we've had anywhere between about 40 and 70 deaths per year. So but the data isn't all complete for this year. It looks like, as far as number of children that died, it looks like a little worse than it had been in the past couple of years.

We also follow outpatient illnesses. We do this through our Sentinel provider system. And in this system providers who - clinicians that is - who see persons with respiratory illness keep track of how many persons with respiratory illness come into their offices.

Some of these same providers also send us viral specimens. And they can get a sense of the influenza season and in general the respiratory virus season by following the trends here.

What you see here is three years worth of data. You see this previous two seasons with the red and blue lines. There's two different systems that are a little complicated to explain here.

But in both of those two different systems we just had a little bit above the expected baseline.

And then in this past season we had a pretty substantial spike up above the baseline. That's the spike on the far right there. Again, just another reflection of this season being somewhat worse than the last couple.

We also follow hospitalizations. We do this in several population-based surveillance systems. I'll just show you one of them here. In this system what you see is this is a three city area of a couple million people.

And we're following hospitalizations in children that are between zero and 4 years old. And you see five years worth of data here.

The most recent year, the one that we just went through is in the red line, and this by comparison can be looked at compared to the 2003-2004 season which is the line that's well above the others, that's -at least on my computer- is light blue and then the past three seasons which are more less the 2007-2008.

And then finally something that probably will be of interest to you which is that the trend of antiviral resistance among influenza isolates.

As of May 10 we tested 1591 isolates to see whether they were resistant to neuraminidase inhibitors. Neuraminidase inhibitors are the class of drugs that are recommended for treatment of influenza right now. Oseltamivir is the oral drug that's used. Zanamivir is the inhaled drug that's used.

And what we found is that 11% of the 969 influenza A H1N1 viruses that have been tested were actually resistant to oseltamivir. All of these had a single particular mutation. And this compares to the 2007 season when only 0.7% of influenza A H1N1 viruses tested for resistant oseltamivir.

But there is some good news here, which is that of the 332 H3N2 viruses and the 290 influenza B viruses, zero of those were resistant to oseltamivir. So and all the tested viruses did remain sensitive to zanamivir.

So overall, given the fact that only one of the three strains, and it wasn't the dominant strain this year, has any resistance to oseltamivir. The overall rate of resistance there's only about 2% this year.

Now, Adamantanes are another class of antiviral drugs. These are rimantadine and amantadine. These drugs are no longer recommended it in the US for treatment of prevention of influenza because of the very high rates of resistance that have been observed.

And you can see here 99% of the H3N2 viruses tested were resistant. And about 14% of the H1N1s were resistant. Next slide please.

Now how does this compare worldwide, because there is worldwide surveillance for antiviral resistance?

Well looking at this slide you can see a list of countries down the Y axis there

with - we've put in Canada in the US and a couple others that weren't part of this main reporting system down at the bottom there just by comparison.

What you can see is that Norway at the top leads the pack with 66% of their H1N1. France has over 40%. The USA came in - at least when the graph was made at 10.5%. And - but a number of European countries were around the same range. So clearly this is a worldwide phenomenon.

And interestingly enough, it doesn't appear to have a whole lot to do with actual use of oseltamivir. Because Japan loses uses a lot of oseltamivir and only has 2% resistant. A lot more oseltamivir per capita certainly than Norway or France or Netherlands or any of those other countries you see with very high rates of resistance.

Next slide please.

I wanted to talk a little bit about vaccine effectiveness also because I think that was a source of some confusion in this past year.

There are a number of things that go into just speaking generally now, that go into how people respond to the vaccine.

Of course the obvious one that you probably have seen in your own practice is age: persons that are elderly, and that are infants and the chronically ill, they generally have lower antibody responses to vaccine.

So prior exposure to the virus strains that are similar to those in the vaccine also determines your response to the vaccine.

Of course immune competence, people that are immunocompromised respond

less well.

The amount of antigen that's in the vaccine that's - makes it so not such a source of clinical concern, but it does - it is generally true that higher amounts of antigen give you a better response.

And then the viruses themselves differ somewhat as to how robust the immune response is.

Next slide please. And actually my slides were slightly out of order. You can go onto the next slide which is how to measuring seasonal influenza vaccine effectiveness.

Now I mentioned how effectiveness, but before we talked about immunogenicity. And effectiveness is actually how well does the vaccine present disease. And this varies also according to age group and according to risk group. It also varies according to the timing of the season and the intensity of the season.

And finally, it varies according to how well the circulating strains match against the vaccine strains.

Now when you look in the literature or you hear about the studies that talk about vaccine effectiveness, it's important to keep in mind that comparisons across studies are surprisingly difficult to do.

First of all as I say, vaccine effectiveness varies a great deal season to season based on the factors that we just mentioned above. But also studies have different sorts of outcomes that they measure.

For example, some studies might just measure influenza like illness like fever and cough, sore throat as a case definition.

This is a nonspecific outcome. It’s relatively easy to ascertain. But you can see that there would be a lot of people who wouldn’t actually have Influenza included in this measurement.

So your vaccine effectiveness is going to be somewhat low in these sorts of studies and speaking generally.

Now laboratory confirmed influenza is the best sort of outcome to use. Then you know that everyone who gets sick, you know whether or not they actually had influenza and you know whether the vaccine should have prevented it.

But these are tough studies to do because it requires a lot of laboratory work, a lot of set up ahead of time. And so these are the Cadillac type studies but also the ones that are most difficult to do and represent a minority of what’s actually in the literature.

So generally speaking what we found over the years is that vaccine effectiveness conducted in years when what we call drift years when the predominant circulating viruses significantly drifted from the vaccine strain -- and let me pause here and just mention we should be on the next slide which is entitled Vaccine Effectiveness, when vaccine strains are not - circulating strains are not well matched.

In general in these drift years what you see is that the vaccine effectiveness is somewhat lower in preventing this most specific outcome of laboratory confirmed influenza.

In fact when you look at the confidence limits around that estimate of vaccine effectiveness, in some of these years you might actually see that the confidence limit includes zero which means that we can't actually be certain statistically speaking that the vaccine had effectiveness.

However, in some studies in some of these years what we still see is that even if it doesn't - vaccine doesn't prevent actual influenza infection, it might provide some protection for some of the more severe outcomes which of course are the ones we care most about. And that is hospitalization and propensity to seek medical care.

This is presumably due to the fact that the vaccine even when it doesn't match well to strains they're circulating gives some partial protection. [At] the bottom of the slide I listed a couple recent publications that illustrated this phenomenon of partial protection.

Next slide please.

So this slide is a summary slide of the range of effectiveness that we've seen over the years according to age and risk group.

So for example in children that are six months to 16 years, healthy children with a specific lab confirmed outcome of influenza virus infection, effectiveness ranges anywhere from 50% to 90%. And that's also true with healthy adults less than 65.

And for persons that are elderly, the vaccine effectiveness ranges have been generally lower and also can sometimes even be a wider range. So you see effectiveness assessments going down to 30% or even lower. And that's even in years when we think there's a pretty good match.

For elderly in the nursing home lower still in general -- 30% to 40%. But it's actually against hospitalization for those elderly nursing home patients can be more in the range of 30% to 60%.

Next slide please.

So with that in mind, we've had a lot of interest in recent years with getting data more rapidly about vaccine effectiveness so we could tell people even within the season how good the vaccine is working. And this was the first year that we've been able to get this data out within the season.

This next slide gives the title of a publication in our CDC publication Morbidity and Mortality Weekly Report published back in April that was entitled the Interim Within Season Estimates, the Effectiveness of Inactivated Vaccine in Marshfield, Wisconsin which is where our population-based surveillance system exists to actually do this.

So the objectives of this study were to estimate effectiveness for preventing medically attended acute respiratory illness, lab confirmed as influenza.

What that means in shorter words is that we were trying to measure lab confirmed influenza in persons who actually came to see the doctor. So we weren't measuring effectiveness against actually any infection. It was infection that was enough that made people come to see the doctor.

And so the intent here is to provide an interim vaccine effectiveness estimate which is what you'll see in a minute. And then also at some time after the end of the season - probably the end of the summer - to give you sort of the final version of it.

So that final version isn't out yet, but the interim estimate is where you'll see there.

So this study included patients that were enrolled throughout the influenza season in this Marshfield area. They were in 14 different ZIP codes. The moment began when their influenza season picked up on the 21st of January and this interim data goes through February 8th.

So cases in this instance were persons with medically attended acute respiratory illness that were confirmed influenza and controls for persons that came into the doctor with some sort of respiratory illness that turned out to be negative for influenza.

What we found is that despite the fact, that as I mentioned earlier in the surveillance portion, that the match between circulating strains and vaccine strains was not as good this year as we had hoped. In fact two of the three strains did not match well.

The vaccine effectiveness estimate was 44%. And for persons who had H3N2 infection it was actually 58%. However, the vaccine effectiveness could not be distinguished from zero. In other words, we don't know how effective it was but it wasn't very against Influenza B.

So what this is telling us is a couple things. One is that we have to be cautious when we interpret that antigenic characterization data I gave you before, that is the data that in the laboratory tries to match the circulating strains against the strains that are in the vaccine.

We have to interpret that with caution because in fact the clinical effectiveness

might be pretty good. And in this instance it was 44% and 58% against the influenza A H3N2 strain.

It also showed us that it is feasible, and it's something that we presumably would be able to do each year: to base within season estimates the vaccine effectiveness. And we will have that final estimate for this year later on this summer sometime.

So in summary for the 2007-2008 flu season: what we saw was a moderately severe season. It had a typical February/March kind of peak. We saw a number of different viral types. But it was Influenza A, H3N2 predominating.

Now for the first time significant levels of oseltamivir resistance which means that we need to increase our global surveillance to monitor the trends and then study to figure out what exactly the clinical impact is of being infected with influenza virus that's resistant to one of the main drugs we used to treat it.

And finally, the vaccine effectiveness most likely moderate, not as good as we'd like but likely did provide some protection despite the fact that the strains circulating were somewhat different than the strains that were in the vaccine.

Next slide please. We're now on the new and updated recommendations from the Advisory Committee on Immunization Practices. And I'll just briefly go through these. There was one major change and a couple of minor ones I'll tell you about in a minute.

First of all just by way of background, there's been increasing interest, as you all know, in universal vaccination against flu. And that's due to a couple of reasons. I think one of them is because there's been a better understanding of

the health and the economic impact of influenza, not only among the elderly and the younger children, but also among older children and adults.

There is also recognition that the vaccine doesn't work as well as we'd like particularly in the groups that are at the highest risk for complications such as the elderly or persons with chronic illness.

There's also the idea, although not well proven yet, that if we could reduce community transmission by vaccinating schoolchildren and healthy adults and if we got high enough coverage we could reduce transmission within the community and sort of indirectly protect some of those persons who don't respond so well to the vaccine.

We're also not as concerned as we once were about the vaccine supply. We've gone from two to five manufacturers and we'll probably have a least one or two more in the next couple of years now that we have multiple sources of vaccine now, and they're producing more vaccine than we actually use.

There's the belief that if we could expand the age groups that are recommended for vaccination we might get better coverage overall because the vaccination recommendation would be pretty simple.

And finally there's been increased concern as we alluded to earlier about an influenza pandemic. And we need to learn how to vaccinate a whole population against influenza if we can in the case of a pandemic, and what better way to start then with seasonal influenza, which as we discussed has a substantial impact all on its own.

Now the rationale for expanding vaccination beginning with all school age children and adolescents is summarized on this next slide. And I have listed

here the rationale.

And this is not the ACIP words, but sort of a general idea of why we would do this. And it's three main lines that are driving this.

One is that influenza has a substantial adverse impact among school age children in ways that we hadn't typically measured before, so not really talking about hospitalization here and severe outcomes but in things that are more common and take their toll, such as increasing school absenteeism, use of antibiotics inappropriately, medical care visits, and causing their parents to miss work.

There is also evidence - lots of evidence - that the vaccine is effective and safe in school age children.

And finally there's this idea that if we made the vaccination recommendations somewhat simpler that we'd improve the load vaccine coverage we have among the approximately 50% of children who already have an indication for vaccination.

In other words what I didn't tell you before I'll tell you now is that about 50% of school age children already have a reason to be vaccinated. Either they have a chronic illness like asthma or something like that or they have contact with persons in their households. With these contact persons being at higher risk for influenza complications.

In other words, they might have a baby sister. They might have an older brother with asthma. They might be living with the grandmother.

For that reason those children already are recommended to be vaccinated.

The committee has also noted that there is this idea that we could have an indirect effect that I mentioned before if we could reduce influenza among persons who have close contact - sorry, if we could reduce infections among young children, school age children, we could reduce infections overall. That's going to require substantially higher vaccination coverage that we currently have.

Next slide please.

So with all this rationale and discussions in mind, the ACIP this past February approved a recommendation to begin vaccinating all school age children. And the way the recommendation is worded is that they say they would like to see this begin in this coming influenza season, that is in 2008-2009, but recognizes that in some instances this may not be feasible. Practices or immunization programs may not be set up to begin vaccinating all children.

And so therefore this recommendation to advance to all children beyond the current recommendations is supposed to begin no later than the 2009-2010 season. It really should begin in 2008-2009 if possible.

Next slide please.

So here the recommendation changes over time for use of influenza vaccine. Just to give you a sense of how quickly these have advanced. Because I know some folks have been somewhat impatient with the pace but I think it's been really pretty fast.

And before 2000 the recommendations were focused on persons 65 and older and persons who had chronic medical conditions that put them at risk,

pregnant women, contacts of those persons, and healthcare workers.

And in 2000 the recommendations were advanced to adults 50 and older. In 2004 the recommendation for the first time was all children aged six to 23 months as well as their contacts. And the recommendation for pregnant women was broadened somewhat to include all women who would be pregnant during the flu season.

In 2006 the child recommendation was expanded up to 59 months as well as the contacts of those children. And then in 2008 this new recommendation I just mentioned to you. Now it's for all children aged six months to18 years. Next slide please.

Let me give you a little bit, and wind this up and open it up for questions, with the discussion of some of the influenza vaccine coverage data that's available. Because it gives us a sense of how well we actually dealing with all these new recommendations.

First looking at the coverage in young children. Now remember I mentioned back in 2004 was the first time that children six to 23 months old were recommended for annual vaccination.

And here's some coverage data over three years at six different sites. So what you see is six sets of bar graphs, six sets of three bar each rather, bar graphs. And I think I'd like you to focus on the bottom graph which is entitled Fully Vaccinated. These are children that got, if appropriate, got two doses in their first year.

And what you see is a fairly low coverage, and unfortunately not a whole lot of progress in each of these six sites over the course of these three years. In

other words if you picked just looking at the middle of the graph if you picked say Michigan you'd see that they had gone over the course of three years from about 10% to about 20% coverage - you know, some progress there.

On the other hand there was some sites that bounced around or actually even went down a little bit for example Minnesota.

And what this is telling us is that we're really kind of stuck at the 20%, 25% coverage over the last three years for children who are 6 to 23 months old.

And that's not great. I mean I think it reflects the challenges of actually doing this. But it doesn't compare very well to some of the other recently introduced vaccines as I alluded to on the slide here. For example, Varicella, Hepatitis B or pneumococcal vaccine. They actually boosted their coverage up a lot faster than flu vaccine has, recognizing that flu vaccine poses a number of unique challenges which we haven't talked about today.

Next slide please.

This slide shows information from the National Health Interview Survey. And this is mostly adult groups here, actually all adult groups. And what you see is that over time we've had some increases in vaccine coverage, particularly among 65 year olds such that we are now running about 70% or so coverage for 65 year olds versus 65 and older.

Other groups though have had very modest increases or have stalled out in terms of increases. For example, pregnant women, still run about no more than 12% to 15% coverage each year.

For persons, health-care workers for example, shown in the green triangles we

see coverage is no more than 40% each year. For high risk 18 to 49-year-olds, those are persons who are recommended for vaccine because of their chronic illness that they have - asthma or sickle cell anemia or cancer or what have you - their coverage is only around - this is looking at the yellow bar - their coverage is not much over 20%.

So really pretty - two things I get out of this - these graphs here. One is that coverage is not very high in most of the groups. The only group that we really are getting anywhere near our goals is in the elderly.

But the others that we've sort of stalled out in our ability to get vaccine to folks. And there are lots and lots of challenges to actually doing this. But certainly the issues of supply that we had a couple of years ago are no longer there. And we have to just figure out how this could best be utilized.

The next slide please.

A couple of the key updates from the 2008 recommendations, and I think that will wrap it up and we'll be able to open it up for questions.

First of all, this is the first annual recommendation that includes the new age group for use of the live attenuated vaccine that's reviewed as your LAIV.

So in other words now you can use either the shot, the TIV or the intranasal Vaccine, LAIV when you're vaccinating healthy persons aged 2 to 49 years old.

There are a couple other wrinkles with this new expanded recommendation. One is that the children being vaccinated for the first time who are eligible for two doses in that first year should have the doses separated by four weeks for

both of those two vaccines. And that is children being vaccinated for the first time age 6 months to eight years, have two doses separated by four weeks.

And it used to be a little bit different for the two vaccines, but now it's the same, that is the gap in time between the two doses.

So for children who are 2 to 4, 2 to 4 years that is, 2 to their 5th birthday who are going to get LAIV, they should be screened for reactive airways disease because of a low but significant association among those young children getting LAIV with some wheezing, the wheezing with - handled generally with just inhalers. But the suggestion is that person's who have a predisposition for wheezing, in other words, who have had wheezing in the past should probably discuss with their doctor whether a TIV might be a better vaccine for those very young children.

And in the MMWR I listed here there are some very detailed screening recommendations for determining who would be eligible for LAIV among young children.

Finally the last point I have here is that a healthy as defined here means no chronic underlying medical illness. It doesn't mean a bad knee or psychiatric illness. It's something that puts you at risk for influenza complications.

And so in other words, anyone 2 to 49 who is relatively healthy and then has no chronic medical condition that puts them at risk for flu complications can get either TIV or LAIV.

The second big change for this influenza season is that all three of the strains have been changed out. So the new strains have their names listed here. I won't go into the viral nomenclature. But it is the first time we've changed out

all three of the strains for the annual vaccine. Usually one or two strains are changed out.

And finally, keep an eye on this problem with neuraminidase inhibitor resistance that was identified where there may be a fairly - if the resistance were to increase substantially that we may need to keep an eye this coming influenza season on antiviral treatment recommendations because they could change according to what the early surveillance shows us.

But it's important to keep in mind that the Adamantine class of drugs, that is Amantadine or Rimantidine which has not been recommended for several years now continue to not be recommended really high levels of resistance against those drugs.

Next slide please.

That wraps up the talk. So thank you very much for your attention and I'll turn it over now to Ms Downs. And any questions that may come up I'll be happy to answer them.

Alycia Downs: Yes, thank you very much. That was a very informative presentation. So we can go ahead and open up the lines for the question and answer session.

Coordinator: Thank you. If you would like to ask a question, please press star then 1 on your touch-tone phone. Please record your name when prompted. I do need your name in order to introduce the question.

If you do have to withdraw a question you can press star 2. And let's hold a moment for the first question.

The first question your line is open ma'am.

Question: Hi. Thank you Dr. Fiore for your presentation. I have two questions. One is does increasing - how can we increase the numbers of pregnant women who are getting vaccinated?

Anecdotally we've seen a lot of healthcare providers who are hesitant to give flu vaccines even during the second and third trimester much less for women who are thinking of getting pregnant.

Does the CDC have information regarding their effectiveness and risk of any type of adverse reactions with pregnant women that we don't have any information on that. So that will be my first question.

And then the second question is regarding the therapy or LAIV being used for vaccinating healthy persons.

The two doses, does that go up to eight years or is it children younger than 9? Because I'm looking at the CIS and that sort of indicates there so just a clarification on what should be said to the public when we give them that advice for the two dose for the first time? Thank you.

Dr. Anthony Fiore: Okay. Two good questions. Let me tackle the second one first…

Question Cont'd: Okay.

Dr. Anthony Fiore: …because I think that's potentially - it's confusing the way we write it. And that's something we - I wish we could do a little better.

The long dash that's between the two ages is meant to include that upper age.

So in other words, the two doses in their first season. That upper range limit for kids is out to their 9th birthday, so through age 8.

So sometimes you'll see that listed 2 long dash 8. Sometimes you'll see that listed less than 9. It's all meant to be the same.

Question cont'd: Okay.

Dr. Anthony Fiore: So for the first question you had, how do we get pregnant women vaccinated better? That is of course a continuing source of concern, not just in CDC but also, for example, the American College of Obstetricians and Gynecologists which has endorsed vaccination of pregnant women for many years.

I think there's a natural reluctance for providers to give anything to pregnant women because of concerns that it could adversely affect either mom or the baby. And then that's of course dates back many years and includes all sorts of medications - not just flu vaccine.

But we have accumulated data over the years that show a couple of things. One is that pregnant women are at higher risk for influenza complications. So you see sort of your calculation of risk and benefit, have to take that into account also.

There's also evidence that protecting the mother against influenza may have some benefits for the baby. It may have direct benefits through passage of antibodies to the baby around the time of birth.

But also remember that the children less than six months old can't be

vaccinated because the vaccine doesn't work well in them. And so their only protection is to protect those around them and to avoid having them getting exposed to flu in the first place.

So having mom protected before she gives birth will mean she's protected right after birth so the baby's really at a very vulnerable stage and we don't have anything else to protect them.

There is evidence for safety and for effectiveness out there. They're not CDC publications necessarily but there have been trials showing both safety and effectiveness in women - in pregnant women that is.

And we do carefully track adverse events through a variety of different reporting systems here. And we don't see increases in adverse events associated with giving flu vaccine and pregnancy.

And that being said, I do think we need more studies and we might also benefit from having the labeling be a little bit more clear because the way you these things – vaccines and other medications are labeled for safety in pregnant women really the labeling is fairly stringent. There has to be very specific sorts of trials having been done.

And of course you're between a rock and a hard place a little bit when you're talking about doing trials in pregnant women. Nobody wants to do them. And so you end up not ever being able to prove definitively safety.

So I think we are moving towards better ways to study safety and to assure safety and we continue to monitor it. It's endorsed - vaccination for pregnant women is endorsed by a number of different groups. The American College of Obstetricians and Gynecologists I mentioned, of course CDC and then

American Academy of Family Practitioners, American Academy of Pediatricians all endorse it.

There are a number of different people who've looked at safety and effectiveness and come to the conclusion that on balance it's - taking the vaccine is a good thing to do.

And I think just continuing to provide education to clinicians and to pregnant women themselves is really the only thing we can do with the hopes that some of that will eventually become more accepted.

Question Cont'd: Thank you.

Coordinator: The next question.

Question: Yes hi. Can you please provide additional information regarding oseltamivir resistant influenza. Regarding that clinical significance, has treatment failure been documented with oseltamivir resistant influenza as well as what about potential treatment options for resistant isolates?

Dr. Anthony Fiore: Okay, that's a good question also. The places that we've seen oseltamivir resistance has in a sense been by accident. I mean we collect lots and lots of viruses to characterize them around the country. And we are in the process of following-up on everyone who is found to have a resistant virus. But what we're finding is that they just had typical flu.

So they weren't people who came in with a severe infection, got oseltamivir, failed treatment and, you know, did poorly because of that. They're people who are getting a virus that really acts - appears to act the same but for whatever reason is resistant to oseltamivir.

It’s not - doesn’t appear to have anything to do with use of oseltamivir. It’s something the virus is - there must be some other advantage to the virus or at least that’s the current theory to being resistant to oseltamivir. It may have nothing to do with oseltamivir itself. I am getting a little too detailed with the virology here. But there may be other advantages to carrying the genes that have resistance without necessarily being exposed to oseltamivir.

So we’re not seeing treatment failures, at least not that I’ve heard about. There were previous to this season, instances of people, you know, predominately immuno-compromised who shed virus, who were treated with oseltamivir for many weeks and eventually began shedding resistant viruses.

But that’s not what we’re seeing here. What we’re saying is it’s just part of the mix of H1N1s to be resistant.

So that being said, there are options for treatment. I mentioned that none of the viruses thus far have been resistant to Zanamivir which is another similar drug that’s given by inhalation. So you could, if you were concerned about it you could use Zanamivir. And that’s probably your best option.

I mean some people - we have not advocated or studied any of this. And some people have given dual therapy. It really depends on how ill the person is and how much Oseltamivir resistance you believe to be in your area.

But as far as clinical significance goes, remember last year was a year was predominately H3N2. It was somewhat less B. And then H1N1 came in third place out of three. And it’s the only place we’ve seen resistance is in that H1N1 group.

So overall it's less than 2% of the viruses in the US that were resistant. But we are going to very carefully monitor that.

Did that answer the question?

Question cont'd: That's great. Thank you.

Alycia Downs: Well I want to thank Dr. Fiore again for providing our listeners with this information. And I want to thank the participants for joining us today.

If you think of other questions please send an email to coca@cdc.gov. That's C-O-C-A@cdc.gov.

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Again, thank you Dr. Fiore and I hope everyone has a wonderful day.

Dr. Anthony Fiore: Thanks.

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