Antiviral resistance among influenza A viruses and interim guidance for use of antivirals
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Coordinator: Welcome and thank you for standing by. All participants are currently in a listen-only mode. To ask a question during the question and answer session, please press star 1. As a reminder, today's conference is being recorded. If you have any objections, you may disconnect at this time.

I would now like to turn the conference over to your host, Miss Alycia Downs. Ma'am, you may begin.

Alycia Downs: Thank you. Good afternoon. And welcome to today's COCA conference call entitled antiviral resistance among influenza A H1N1 viruses and interim guidance for antivirals. We are very excited to have Doctor Anthony Fiore present on this call.

Doctor Fiore is a senior medical epidemiologist 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.

Doctor Fiore is going to cover a lot of information in this presentation. And we may go over time by just a few minutes. So if you don't get a chance to ask your question at the end of the call, please remember that you can e-mail COCA at coca@cdc.gov . And we will work to get you a response.

We're using a PowerPoint 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 www.emergency.cdc.gov/coca, click on Conference Call Information Summaries and Slide Sets. The PowerPoint can be found there under the call-in number and pass code.

The objectives for today's call -- after this activity, the participants will be able to describe resistance patterns among influenza strains, recognize alternative antiviral treatment options when resistance is suspected, and identify ways to assess likelihood of resistance.

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I will now turn the call over to Doctor Fiore. You may begin.

Anthony Fiore: Well thank you very much for inviting me to be on this call. This is a rapidly moving topic especially in this season. And I think it's great to have an opportunity to update listeners to changes that have just been made in the antiviral recommendations guidance.

And so without further ado, I'll launch right into it. I'm looking at my title slide now which is antiviral resistance among influenza A viruses and interim guidance for use of antivirals.

And moving to the next slide, I've just provided you with a brief overview here. We need to do a little bit of background on influenza testing and treatment in order to make sense of the guidance.

I was going to describe the current status of antiviral resistance in the United States, talk about the interim guidelines which came out in late December, and then provide you with some indication of what you might see later in the season as far as additional guidance and provide a summary. Next slide, please.

This slide's title is Human Influenza. And just a very brief background -- it's a highly transmissible respiratory illness caused by influenza viruses. We of course have yearly winter epidemics. And often this is called seasonal influenza or interpandemic influenza.

There are sporadic, unpredictable pandemics which we won't discuss today. There are three strains of influenza viruses in circulation among humans at this point. There are two influenza A subtypes called H1N1 and H3N2. And this is fairly critical information for understanding the rest of the talk. And influenza B is the third type of influenza virus circulating in humans, so three different types, two subtypes of A and influenza B.

Influenza A viruses mutate. Or influenza B viruses do also. But A viruses do it more quickly in two different ways. One's called antigenic drift and one is called antigenic shift. Antigenic drift is a continual process. It involves point

mutations or small recombinations within the viral genes. It results in a diminished immune response among those that have been previously infected or immunized because the virus is a little bit different.

The next time it shows up -- and that's referred to -- those strains are referred to as drifted strains. The result is that we have yearly epidemics and that we have to update the vaccine yearly. But one other consequence of antigenic drift is that these changes can occur in the sites that the antivirals attach to and the active sites that is. And they can cause changes in susceptibility to the antiviral just by the process of antigenic drift.

Antigenic shift is a sporadic and unpredictable event. That's when an entire gene segment is replaced. The hemagglutinin gene or the neuraminidase genes -- and these are sometimes derived from animal influenza As. There's no immunity within the population. This is what results in a pandemic. That's not what we're talking about here thought.

Next slide, please -- now which is entitled Annual Interpandemic Influenza Impact. Every year 2-1/2 to 20% of the population become ill. The highest rates are in children -- an average of 36,000 deaths with over 90% of them among those greater than 64 years old.

An average of over 200,000 hospitalizations each year, but there's a wide range from year to year. About 50 to 60% of those are in people over the age of 64. The risk of hospitalization, however, for children who are under two years old is similar to the elderly. It's something we didn't really appreciate until the last 10 or 15 years.

There's a substantial economic burden associated with influenza. And you can see the number $87 billion in one recent study was estimated. Clinical

diagnosis is important to think about because that's often how influenza is diagnosed. However, the clinical symptoms are not specific. And they overlap with other pathogens.

And this is a -- the terminology often used for this is the person has influenza-like illness. So it could be caused by influenza. But it could also be caused by other respiratory pathogens, particularly other respiratory viruses. You need laboratory data to verify the diagnosis of influenza.

And even in peak influenza season when a community is really getting whomped with influenza, you still see about 25 to 35% of specimens actually being positive for influenza. And so there's lot of other stuff out there. And it's important to keep in mind. Next slide, please.

Laboratory testing for influenza virus is somewhat complicated and not available to some extent to the clinician at the bedside. Viral culture is the gold standard. But it takes seven days easily. It's not going to be helpful in managing your patient most likely.

But the viral culture from our perspective is really important because it's the source of our viral strain surveillance, and the reason that we know about antigenic drift and which strains should be in the vaccine and then also the antiviral resistance.

Serology is sometimes still used. You have to use paired serum samples which means that you're going to take two weeks or more to get your diagnosis. Immunofluorescence is a good test. But it's somewhat user dependent. And you need skill and experience in your laboratory to use it successfully.

Reverse Transcriptase-Polymerase Chain Reaction or RT-PCR is actually the most sensitive test available. It's becoming more widely available in fact and can even be used to distinguish influenza A subtype. But typically this can only be done at the state health laboratories or in some reference laboratories.

Rapid antigen tests are really the mainstay of the influenza diagnosis. And I'll spend the next couple of slides talking about them, because it's important to understand their uses and their potential pitfalls when you're interpreting the results from rapid antigen tests.

So for in most of the studies including the licensure studies, these tests were 70% plus or more sensitive and 90% or more specific in children particularly. But it's actually probably a lot lower in terms of sensitivity in adults, maybe more in the order of 50 to 60% in some recent studies.

You can get results, however, from rapid antigen tests that, you know, understanding these shortfalls. These results are very useful from a clinical point of view because you can do a test in the clinic. You can get a result back in 30 minutes or less sometimes. Next slide, please.

So again expanding on the topic of rapid influenza diagnostic tests, the advantages to them are the speed at which they can be done and the ease of getting the specimen itself. They're useful for detecting outbreaks and for management. It's a simple procedure.

Some of them can distinguish influenza A from B. And that's actually going to be important later on in the discussion. But not all those tests can. Some of the tests can only tell you influenza -- yes/no. The disadvantages are that they're less accurate than viral culture. Again, there's a problem with sensitivity.

So the positive predictive value is going to be highest during peak influenza activity. And I'll expand on that in just a minute. You get limited information. You're not getting this virus itself. And so it doesn't do much in terms of surveillance for what strains are in the community.

And none of these rapid tests that are currently available can distinguish which of the two influenza subtypes is present. And that's important because we only are seeing the oseltamivir resistance that I'll talk about later in one of the subtypes. Next slide, please.

The predictive values of the screening tests for influenza viruses are shown on this slide. And you have to -- when you look at predictive values, you have to take into account the prevalence of the disease. And so in times of high influenza prevalence when there's a lot of influenza in the community at peak activity, the positive predictive value is high.

If you have a positive, that's great. It's a pretty good chance that you have influenza on your hands. A negative predictive value, however, is lowest at this point. And that's where that sensitivity problem comes in. You can have people who look as though they have influenza who get a negative test and in fact their negative rapid test.

And in fact when you do a more sensitive test -- a PCR or a culture or something like that -- you might find out that they do actually have influenza. And so as a result there are instances when clinicians might do a rapid test and end up treating someone as if they have influenza, even with a negative test perhaps because that person's at high risk for complications, or perhaps because they're very sick or they're just convinced it's influenza.

During times of low influenza, the prevalence -- the opposite is true. The positive predictive value is the lowest. You have to worry about false positives. Next slide, please. So during periods of high activity within the community, I mentioned that sometimes clinicians will rely on clinical diagnosis. And I told you the clinical diagnosis is not particularly sensitive specific.

However, if you are in a situation where you are convinced someone has influenza, they're a severely ill patient or they're patients at higher risk for complications you're going to treat anyway, you might go ahead and not even do a testing for influenza. Some clinicians do that. And it's perfectly defensible to go that way. And the rationale of course is that the predictive value of a negative test is low during the peak season. Next slide, please.

The next two slides are going to summarize, the most recent annual influenza recommendations by the Advisory Committee on Immunization Practices. And this has been -- these recommendations for antiviral treatment are a lot more specific than they have been in the past. And this is this year's recommendations.

And of course with the resistance problem that we've seen, we've had to go and alter these recommendations. But going into the season this is what we had in terms of influenza treatment and who should be considered for treatment. If possible, you want to treat within 48 hours because the effectiveness of initiating treatment more than 48 hours after the illness has started has not been established.

Persons who are -- should be considered for influenza treatment include the ones that you'd expect -- persons hospitalized with lab confirmed influenza, those with influenza pneumonia, those who have influenza and a bacterial

coinfection, those at higher risk of complications, and then of course anyone who has a want or a need to try to reduce the duration or severity of their symptoms can be treated. So outpatients are perfectly legitimate to provide treatment for outpatients. Next slide, please.

So persons that for whom antiviral chemoprophylaxis should be considered are listed on this slide. And chemoprophylaxis is when you give an antiviral to someone who you think might be exposed to influenza, or during a period in the community when there's lots of influenza going around and you can't or are not sure the vaccine worked or something like that.

So this is given to a person before they're actually ill. Persons for whom you might consider giving a chemoprophylaxis include those at higher risk for complications during the two weeks after vaccination. If there's a lot of influenza in the community, persons for whom the vaccine is contraindicated -- it's a small group. But if it's a person at higher risk for complications, you might think about it.

Family members or healthcare providers who are unvaccinated and likely to have ongoing exposure to persons at high risk, persons at a higher risk and their family members when strains in the community are not well matched to the vaccine strains -- that might be a consideration for chemoprophylaxis in that situation -- persons with immune deficiencies and those who might not respond to vaccination and finally unvaccinated staff and persons doing response to an outbreak in a close setting. Next slide, please.

So now a few words about antivirals for treatment or prevention of influenza -- next slide. The neuraminidase inhibitors are -- have been the mainstay of influenza treatment and prevention over the -- influenza chemoprophylaxis

rather over the last several seasons. The two ones that are in the U.S. are oseltamivir, trade name Tamiflu, and zanamivir, trade name Relenza.

And these are used for the treatment and prevention of seasonal influenza A and B infections. I mentioned treatment should begin as soon as possible, and that the benefits of treatment are only well show if it's started within 48 hours of onset. Next slide, please.

This is a cartoon. And I tried to break up all these tech slides I'm throwing at you with a visual. This shows that the mechanism of action of neuraminidase inhibitors. And what they do is they attach to the neuraminidase protein on the outside of the virus and make it so that it can't release itself from the cell that it's infected. And so it renders it unable to replicate further. Next slide, please.

So as far as the fact in this in treating seasonal influenza, it has been shown in several nicely done randomized control trials that there -- you can reduce the duration of symptoms by an average of 1 to 1.5 days if you give it within two days or 48 hours of illness onset.

There have been other observational studies -- again, not randomized controlled trials but observational studies. And it showed there was some benefit even when treatment started more than 48 hours after onset. We have less information about these drugs' ability to reduce the risk of lower respiratory tract complications or pneumonia for hospitalization. But we have seen reductions in some studies, not randomized control trials with some studies.

And in fact one recent trial -- sorry, one recent observational study that I refer to at the bottom of the side publishing clinical infectious diseases last year, indicated that oseltamivir use could reduce mortality in hospitalized patients

who had lab-confirmed influenza A even if it started -- sorry, I'll mention that in the next slide -- but even if started more than 48 hours after onset. And those results seem to be confirmed.

But I think people are a little bit more aggressive as you would expect in treating hospitalized patients, even if they have -- show up to the hospital more than 48 hours after onset. These inhibitors are effective in preventing seasonal influenza. And that's chemoprophylaxis I mentioned.

You want to start within 48 hours of exposure. Our randomized controlled trial shows 70 to 90% reductions in illness if it's started at that point. And these are sometimes used given daily persons at high risk for complications during the season such as in a nursing home setting. And they are quite effective when used that way.

Specifically talking about oseltamivir -- it's available as a capsule or a suspension. It's given by mouth. It's approved in the U.S. for persons one year of age and older. Treatment's for five days. The prevention regimen is for ten days. You have to change the dosage according to pediatric considerations of age and weight. And side effects include nausea and vomiting in some persons.

And the severe side effects that maybe occur in a few percentage of persons -- less than 10%. The most serious side effect that people have been worrying about most recently there were some reports of delirium in pediatric patients, particularly in adolescents. Most of these reports were from Japan.

It's not entirely clear at this point whether these symptoms were due to influenza virus infection itself or due to the drug. However, a warning was added to the U.S. label in 2007, warning clinicians to tell patients about this

potential side effect and to monitor patients who are getting oseltamivir in this age group. People with kidney disease need to get their dosage reduced.

I'm on the next slide -- oseltamivir is Slide 2 -- and pregnant or nursing women. The safety is unknown. There's not known to be any problem. But just the studies haven't been done. There is a resistance sometimes seen which can develop during treatment.

This is actually for the neuraminidase inhibitors including oseltamivir was quite low up until last season. And it typically was reported in persons safe who are immunosuppressed who are getting these long courses of treatment, so a little more about that in a minute.

Zanamivir is the other neuraminidase inhibitor available. This is delivered in a different way. It's an orderly, inhaled powder that's given by a special device that I've shown in this picture here. I'm on the next slide by the way -- the zanamivir slide. Sorry about that.

It's approved in the U.S. for treatment of seasonal influenza if you're over age seven or over and for prevention of -- sorry, treatment of seasonal influenza for seven and over, prevention for five and over. Now the dosages for treatment is two puffs in the morning and two at night. The prevention dosage is two puffs once a day.

And typically that's done for ten days. Side effects include a low risk of wheezing and breathing problems. Because of concerns about reports of delirium associated with oseltamivir and knowing that zanamivir is in the same class of drugs, there was a warning label added in 2008 with similar language as in the oseltamivir warning. There's a lot less data I think on delirium associated with zanamivir. But that does appear on the label.

The second zanamivir slide I've just moved to -- precautions include there's a chronic respiratory disease as you'd expect because of the delivery system. Pregnant or nursing women -- again, unknown of any problems just that there's not been enough studies to say it's safe in this group.

Resistance can develop during treatment though again rarely and in persons who are getting prolonged courses of treatment. And there are -- and I say this in the present tense now -- there are very low levels of resistance among influenza A H1 and H3 viruses. And in fact it's extremely rare.

The next slide is not one I think I'm going to go through. I'm just going to refer you to this. This is a table that gives the dosages and the weight-based dosing and son that appears in the annual recommendations. And you can download these from the CDC Web site if you'd like to look at them. They're a bit lengthy to go through. Next slide, please.

There are other antivirals active against influenza A viruses. And these are antivirals that many of you might remember were commonly used before about 2006. And they're amantadine and rimantadine, collectively known as a class of drugs called adamantanes.

They have a different mode of mechanism that they -- mode of operation rather. They inhibit the function of the M2 ion channel in the influenza A virus and B virus -- sorry, not B virus. They don't have activity against B. Sorry. Resistance develops rapidly within influenza A viruses.

These were effective drugs. But we were much more concerned when were using them about resistance developing over the course of treatment. At this

point and for the last several years, there's been a very high level of resistance among influenza A, H3 and 2 viruses to the adamantanes.

And for that reason they actually were no longer recommended starting in 2006. And they are not recommended every as a single agent for treatment. The important thing here at the bottom of the slide that I've mentioned is that there's no additional antivirals that are expected to be available in the new future. We have these four. And these are the four we'll have for this season and for the near term. Next slide, please.

I'm going to explain to you just in a couple slides where we get our antiviral resistance data from. This is a schematic of all the different ways and information about influenza feeds into the CDC surveillance system, and how we send it out to public health officials and divisions in the public and so on. The one I'm of course going to focus on is the laboratory part of it. And that's I've highlighted in red here. Next slide, please.

This is a schematic -- rather a graph showing the number of virus isolates that came in to CDC over the last season. And what you can see here is the virus isolation pattern mirrors what the season looks like. So Week 40 is in September. That's at the left side of the X axis there.

And it goes right up through the end of the year and into the first couple months of the following year. And so we do a lot of testing -- us in collaboration with all our WHO and NREVSS labs together tested 229,000 samples from persons with acute respiratory illness last year.

Nearly 40,000 of them were positive for influenza. And it's broken down on these bars here according to which type of influenza it was positive for. And

so you can see the red is influenza A H3. the blues are A H1. The Bs are green.

And a number of these specimens don't actually end up getting typed. They're just influenza, are you positive -- yes or no? The inset with the pie graph there shows the proportion of viruses over the course of the season that were according to type or subtype. And so you can see from here about 60% or so of the viruses were H3 and 2s. About 1/3 of them were B viruses and then a little less than a quarter were influenza A H1s. Next slide, please.

So during the season that I just showed you here, we saw the development of oseltamivir resistance among influenza A H1/N1 viruses. At the end of the season when all of it was all tallied up, we'd had 123 of the 1026 influenza A H1N viruses tested to have been resistant to oseltamivir. And that was almost 12% of viruses tested, and this compared to from the previous season only 0.7%, so quite a dramatic jump in resistance.

However, because of the fact that we had most of the H3N2 and B viruses circulating in this past season, we only think about 2% of all the influenza viruses circulating were resistant to oseltamivir, so from a clinical perspective a fairly low chance of you running into a patient with the resistant influenza A H1N1 last season.

Worldwide the prevalence of resistance was a little higher at the end of the Northern Hemisphere season. About 16% of the 7500 or so viruses tested were resistant to oseltamivir. And of all these viruses tested -- of all these influenza A H1N1s tested that were resistant, they all had the same genetic mutation which is called H274Y for the amino acid that's replaced in the neuraminidase gene. They were all the same looking virus.

We did go back and look at patients who had infection with these oseltamivir resistant viruses. In all cases, this was an incidental finding in the sense that the person that had for whatever reason a sample taken. It got sent to the lab. It got to us. It got antiviral resistance testing. And lo and behold it was resistant.

At that point, the patient had long since recovered from their illness. And their illness as best we could tell didn't look any different from the illness caused by oseltamivir sensitive viruses. So amongst the 99 patients with influenza that we were able to follow up on that had influenza A H1N1 that was resistant to oseltamivir, none of them had actually been taking oseltamivir before they got tested. And none of them had had contacts taking oseltamivir.

Now when we compare to the oseltamivir sensitive illnesses, the illness is caused by oseltamivir sensitive influenza A viruses. The clinical illness, the severity of the illness and the type of persons who are getting ill really looked about the same.

So for all intents and purposes, this looked like influenza A H1N1 infection just whether or not it was resistant or sensitive to oseltamivir. The European Union did some similar looking into their data. They also felt that oseltamivir use was not the cause of increases in resistance.

They saw in general the same clinical characteristics for persons with oseltamivir-sensitive viruses similar to our findings in the U.S. And you can see these summarized on the EU Web site. Next slide, please.

So where are we now? This is just getting to the start of the 2008-2009 season. I wanted to give you a summary of where we are with antiviral resistance and them summarize the guidelines. Next slide, please.

And at this point we actually do not have in most communities much in the way of influenza activity. It's been a pretty slow start to the season. As a result, we don't have a lot of viruses available for antiviral testing. Since October 1, we've been able to get viruses from 21 states including 73 influenza A H1N1s, 11 H3N2s and 33 Bs.

Fifty-eight percent of these influenza A viruses tested were only from three states, so a lot of activity from three states only. So we don't have a very good representative sample from across the U.S. at this point just because there hasn't been enough activity. Next slide, please.

Sorry. I've had a glitch in my computer here. I'm having trouble advancing my own slides. Okay. So here we are. We have moved to the next slide which has a map of the U.S. And this shows the influenza activity just underscoring what I was saying.

Local activity has been reported in it looks about six or seven states there scattered around. There is some regional activity the next level up of activity in three states. But most states either have no activity or sporadic activity. And you can see the key at the bottom.

And I've pulled this slide directly from the weekly update that CDC has on their Web site. So if you want to follow this yourself, you can go to that Web site I have listed at the bottom of the slide and look at the publication called FluView. And this will give you a lot of information about influenza there. This also can be obtained from FluView.

This is our surveillance where we look at influenza-like illnesses from a system of about 2500 sentinel providers -- that is providers who have agreed

to tell us how many persons come into their office each week with an influenza-like illness.

You can see the last two seasons in the green and the blue where you see a blip up above the national baseline, and late in the year and then at the beginning -- at the start of the next year a pretty good peak just as typical as the influenza season.

In the red there you see tracks what we have so far this year. And you can see we really haven't got up above the baseline this year, just again emphasizing we don't have a lot of influenza activity yet. And as a result we don't have a whole lot of viruses to test. Next slide, please.

Of the viruses we have tested though, here are the results. So of the influenza A H1N1s, we've had 73 viruses that have gotten antiviral testing. Seventy-two out of the 73 -- and I need to tell that that's going to be well over 95% -- were resistant to oseltamivir.

All of these oseltamivir resistant viruses were sensitive to zanamivir. In fact, all of the influenza A viruses were sensitive to zanamivir. Among the H3N2 viruses, we have very little H3N2 activity so far. All 11 tested were sensitive to both of the neuraminidase inhibitors as they have been in past seasons.

All the B viruses were also sensitive to both of the neuraminidase inhibitors -- oseltamivir and zanamivir. As far as adamantane resistance which we are quite interested in again of course, of the 73 H1N1s and H3N2 viruses that were tested, all the influenza A H1N viruses were sensitive to amantadine and rimantadine.

And I should note that H1N1s are not only sensitive to these drugs. It just happens that these viruses resistant to oseltamivir appear to be sensitive to the adamantanes. All of the H3N2s, however, were resistant to the adamantanes. And those adamantane drugs amantadine and rimantadine are not effective against influenza B. We don't even test them.

So here's a grid kind of summarizing these results. And what you can see if you look at the rows, there's really only zanamivir where you can reliably say that an influenza strain is susceptible. And you have resistance to oseltamivir and the H1N1s. You have resistance to the adamantanes in the H3N2s and the Bs. Next slide, please.

So in summary, resistance probably developed as part of the antigenic drift process and not driven by oseltamivir use. And in fact we have some indirect evidence for that. Japan uses a lot of oseltamivir, so sort of a different clinical way of practicing there in terms of influenza. And they have about 75% of the world's oseltamivir use. But oddly enough they have a low prevalence of resistance.

And in the converse is true in Norway which doesn't use a lot of oseltamivir but was the first country to report much resistance, and at the end of last season even already had 70% resistance to oseltamivir among their H1N1s. There is no evidence as I stated before just to summarize, there's no evidence that these oseltamivir resistant viruses are different in a clinically important way from the oseltamivir sensitive viruses, at least in data obtained in the U.S.

So there's implications for clinical management. And this is what led us to issue the interim guidelines. There's no test for antiviral resistance available to a person at the bedside. There are rapid tests that can distinguish influenza A from B. However, there's no rapid test that can distinguish H3N2 from H1N1.

That’s called subtyping, although some state health laboratories and reference labs can do it.

Empiric treatment is often used when influenza activity is high. And finally many clinicians don’t actually use antivirals. And that we know that from results of surveys, and from looking at medical records of patients who have had laboratory confirmed influenza.

There actually is not that much antiviral use going on out there among patients with influenza anyway. However, we were concerned going into the season clinicians who do use antivirals for treatments and chemoprophylaxis would want to be updated on resistance issues, and have some options if resistance developed as it turned out to have developed.

So we worked with the state health labs to enhance our viral surveillance system to try to get more representative samples of the viruses from across the U.S. We’ve worked on increasing our ability to do antiviral resistance testing. We discussed some of the response scenarios with consultants and with the ACIP workgroup.

During the season so far to date, we had an update in December 2008 of influenza activity. We have the FluView I mentioned earlier which is updated every week every Friday. We discussed these issues with the manufacturers the neuraminidase inhibitors. And we developed a draft health alert network advisory which we refer to as the HAN -- H-A-N -- that had these interim guidelines. Next slide, please.

And these last couple slides will run us through the interim guidelines and where they stand now. They look complicated. But I think if you think it

through that you actually can probably predict the choices that we are suggesting. Next slide, please.

So this is the first text slide here of the interim guidance. And then these are just kind of the three main points out of the guidance. First is that early season's data indicates that oseltamivir-resistant H1N1 is the most commonly isolated virus so far. I showed you the numbers before.

Not only are they almost all resistant, but H1N1 is also the most common virus at this point in the season. The clinicians need to know oseltamivir alone might not effectively prevent or treat influenza if there's a lot of H1N1 in the community.

And the Health Alert Network advisory or the HAN is the focus of the next few slides. The bottom line here is that treatment with zanamivir or a combination of oseltamivir and rimantadine might be preferable in some situations.

You can use local influenza surveillance data if you have it. You can use laboratory testing, the rapid antigen tests to help with decision making regarding the choice of antiviral agents for patients. And finally oseltamivir-resistant H1N1 strains are antigenically similar identical to the strains in the vaccine.

And the implication of this is that the vaccine should be capable of preventing illness with the oseltamivir resistant strains because it's very similar to the strain that's in the vaccine. And that's somewhat in contrast to what we saw last season where we had a lot of mismatch between the strains in the vaccine and the strains that were circulating.

We could still have that in the future. Again, we're early in the season. But thus far all signs are good in terms of having a year that has a good match to the circulating strains. Next slide, please.

So let's expand on these points a little bit more. You can use influenza virus testing to help with decision making. For example, a rapid test that can distinguish influenza A from influenza B is useful. If a patient tests positive for B, you don't have to worry about oseltamivir resistance.

You can use oseltamivir or zanamivir. And there's no preference and no change for treatment of influenza B infections because we haven't seen oseltamivir resistance among these viruses. Next slide, please.

So you can also review your local or your state influenza virus surveillance data during the influenza season, to see if you can get some sense of which viruses are circulating in the area. Again, state health laboratories do have the capacity and do subtyping of influenza viruses. And they could substantially provide this data. And it could be useful.

However, I mean realistically speaking because influenza is so variable, it can be variable across states and even within communities. There are going to be some instances in some communities where there's just not enough information available. You know, it's just not timely enough to be that useful to clinicians. We recognize that. But if that data is available you can put it to good use. Next slide, please.

So we have sort of laid out the various scenarios here in the next three slides in a grid form. And the four columns are the results of the rapid antigen or the other laboratory tests, the predominant viruses in the community, the preferred

medications and the alternative medication which is typically going to be combination treatment.

So this first slide here goes to the scenario if you've not been able to do testing or the testing's negative but you really think this might be influenza. Now suppose the predominant virus in the community is unknown to you or you happen to know it's H1N1. The best medication in that instance to use is probably going to be zanamivir.

But as we'll discuss in a minute, there are lots of people who can't take zanamivir. There may be issues with availability. In that case, an alternative combination - regimen would include a combination of two antivirals. That is oseltamivir which would be treating the H3N2s and the B viruses, and rimantadine which would be treating the H1N1 viruses.

So you need them both. They're not acting in a synergistic way. They're acting in sort of a complementary way with one of the, rimantadine, hitting the H1N1s and oseltamivir, the other hitting the Bs and H3N2s. The second row on this slide again goes to the scenario of no test available or a clinical suspicion of flu.

However, this time you have access to the information about viruses in the community. And it looks like it's a H3N2 or a B part of the season. In that case, it's reasonable to go with either oseltamivir or zanamivir. And in that case you don't need to worry about combination treatment.

That's important to know. And I've put a little footnote here. We don't have a lot of clinical experience with combination treatment. There's no reason to think there should be issues with safety. But it's just not well studied. And it's

important to keep in mind when you're using combination treatment. Next slide, please.

So here we have another scenario. And that is that you do have a rapid antigen test or some other laboratory test available to you that tells you that you have an influenza A virus. And remember you're not likely going to be able to get subtyping available at the bedside.

Now you look at your local surveillance data and you find you really can't tell or you know that you have H1N1. Here again you're going to want to look for zanamivir as the one drug -- if you want to use a single drug -- the one drug that would get all of the potential -- that would treat all the potential influenza viruses that might be circulating.

And again, combination treatment with oseltamivir or rimantadine is an alternative. Suppose you have a positive rapid antigen test for influenza A. But you know there's H3N2 or B in the community. Here is an instance where you might use oseltamivir or zanamivir without any preference. Next slide, please.

Okay. In the last three situations here, you have a rapid antigen test. And it's one of those tests that can't tell you the difference between A and B. If you know there's H1N1 or unknown in the community again -- and I'm sure you're going to be able to predict these pretty soon -- the preferred medication in that case is going be zanamivir with the alternative being the combination of oseltamivir or rimantadine.

If you have an A/B positive test and you have H3N2 or B, in that case oseltamivir or zanamivir could be used. Here of course as we've mentioned before if you have a positive influenza B test, then it really doesn't matter

what the viruses are in the community. You can use oseltamivir or zanamivir. Next slide, please.

So chemoprophylaxis issues are actually a little bit more complicated. And they can't really be easily kind of gamed out in these scenarios like treatment can. This is the kind of thing that you likely are going to want to consult with your local or state health department if you have an outbreak situation.

But here I've just listed a couple of key points about chemoprophylaxis in this era of antiviral resistance among H1N1s. Obviously you want to use chemoprophylaxis that's the most likely to be effective against -- in preventing treatment if the influenza viruses that are the cause of the outbreak if you know it.

If you have an institutional outbreak it's great to -- you have perhaps a little bit more time in the situation. And you have a lot more people that you're talking about putting on chemoprophylaxis.

So you would do well to get -- do your best efforts to get a respiratory specimen and see if you can't get the type and subtype of influenza A, so that you can specifically tailor chemoprophylaxis and specifically tailor treatment if anybody has a breakthrough infection.

If the person who needs chemoprophylaxis has an exposure the a person that you know had lab-confirmed H3N2 or influenza B, you can oseltamivir or zanamivir -- no preference. You suspect you know what that person is -- what you're trying to prevent in that person in that case. You can use zanamivir. It can be used for chemoprophylaxis when a person needs chemoprophylaxis against exposure to influenza A H1N1.

Rimantadine is a potential alternative if the person can't take zanamivir. There might be some situations where you need to use oseltamivir and rimantadine for chemoprophylaxis. To reduce the need for combination therapy and rather prophylaxis -- and as I mentioned we don't have a lot of clinical experience with this.

It's a good idea to look for subtyping and determine if it's an influenza A H3N2 or H1N1. And if it's an H1N1, you might even be able to get your state lab or have your state lab send the CDC the virus isolate for antiviral testing. Next slide, please.

Now I mentioned some challenges associated with zanamivir use. And there are three main ones. One is this method of administration. It's an inhaled medication. Severely ill patients might not be able to take it. The age limitations I mentioned it can't be given small children. It's contraindicated for patients with pulmonary disease. And it's hard to administer to a hospitalized patient.

Clinicians have not used a lot of zanamivir in the past probably partly due to this third reason here, because of relatively reduced availability to clinicians that might not be familiar with zanamivir. But this would be a good season to develop familiarity.

We have spoken to the manufacturer of zanamivir. They have greatly increased the supply available for 2008-2009. Of course, we haven't had much activity yet to really test this. But we have not heard about people having trouble getting zanamivir at this point. Next slide, please.

So just the last few slides to wrap this up -- to sum up and also describe to you what you might see from CDC or elsewhere regarding antiviral resistance over the course of the next few months. Next slide, please.

So I mentioned that during the season so far, we've enhanced our viral surveillance. We have the MMWR that came out December 2008. We have the HAN that came out. We've had discussions ongoing discussions with the manufacturers. And we've developed a communication strategy.

And there's lots of information on antiviral resistance now available on the CDC Web. And those Web sites I think were -- appeared in earlier slides. Now what you might expect coming up you're going to keep seeing the FluView every week every Friday. We'll update it with all sorts of different data about influenza activity, including antiviral resistance.

There's a scheduled MMWR in February 2009. There always is one in February 2009. But this is -- this will of course cover influenza activity. But we're obviously going to need to devote some time to the issue of resistance, another one coming out in April 2009 is the potential for additional guidelines based on emerging surveillance data.

There's going to be a full HCIP meeting, a previously scheduled meeting. It's their thrice yearly meeting. And the next one's in February 2009 where there will be some discussion of antiviral resistance. The annual recommendations which are voted on at that meeting typically contain information about recommendations for antivirals.

It's possible this year they might split off that piece of the recommendations awaiting to see what happens with the rest of the influenza season. And of course CDC and the health departments will be monitoring for severe

infections or for outbreaks. Unusual outbreaks involve oseltamivir resistant viruses.

So just to leave you with a little bit of good news though, so far we've -- we also here at CDC do antigenic characterization. And what this means is we look at the similarity between the circulating strains in the communities and the similarity to the strains represented in the vaccine.

And as I mentioned so far this season the influenza A H1N1s that have been antigenically characterized are very similar. In fact, all of them are 100% similar -- 100% of them are similar rather to the vaccine strain that's called A/Brisbane/59. We don't have many H3s characterized yet -- only seven of them.

However, all of them are similar to the vaccine strain. B viruses are always problematic because there are two distinct types of influenza B viruses that circulate. And there's only one type represented in the vaccine. This year 33% of the 27 B viruses characterized are similar to the vaccine strain. Next slide, please.

So just to sum it up we are continuing to actively test viruses to monitor antiviral resistance through the season. Viruses that are sensitive -- that are resistant to oseltamivir are sensitive to zanamivir and adamantanes. That is the influenza A H1N1s we've been talking about.

That is influenza A H1N1 viruses that are resistant to oseltamivir do not appear to be more dangerous or infectious in any way. They look just like a regular flu virus in terms of the clinical appearance. Next slide, please.

You're going to need to -- it's going to be a little complicated making decisions about antiviral treatment this season. You're going to need to look at if you have it available to you local surveillance data. Use your clinical judgment and rapid antigen testing to guide your choice of antiviral regimen. Be alert for changes in antiviral recommendations. We'll update these as we need to. I don't foresee any updates in the future. And as I mentioned, we have a fairly limited armamentarium available to us to change antiviral recommendations at this point.

But keep alert. We'll try to release any information we think might be useful to clinicians and public health officials as soon as we get it. And finally the final bullet here is that vaccination prevents influenza. And as far as we can tell, vaccination should prevent, you know, infections due to the oseltamivir resistant strains.

And the last slide -- and this is just a recap of what happened last season. Just to help you keep in mind that the viruses that are most common in the communities change over the course of time. So right now we are seeing a lot of H1N1. And almost all that H1N1 is resistant to oseltamivir.

Well let's go back in time and look at the previous influenza season -- the 2007-8 season. And I'm going into January. H1N1s were most common last season also. And they're represented here in the red blocks. However by February, the H1N1s had kind of faded out. And the other two viruses had overtaken them in terms of prevalence.

So the B viruses here are represented by the green blocks. And the H3N2 viruses are represented by the yellow blocks. And as I showed you earlier in the slide presentation, we really had an H3N2 and a B year. So it might be that in a few weeks from now H1N1s could reduce in prevalence. And this issue of

antiviral resistance might become less of a pressing issue. But let's see what happens. And the season's just getting underway.

And with that, I'll wrap up the talk and take questions. And please do let me know about issues you have with the interim guidelines, or any sources of confusion in particular I'd be interested to know about. Thanks very much.

Coordinator: Yes. Thank you. To ask a question, please press star 1. When prompted, clearly record your first and last name. To withdraw your question, please press star 2. We'll now take a moment for questions.

Our first question comes from Doctor. Sir, your line is open.

Question: Yes. Healthcare workers -- direct healthcare workers who have not taken some vaccine yet, if they are exposed to a patient with flu A, is the recommendation to use the antivirals for 10 or 14 days, assuming you can get them to take a vaccination at the same time you start them on the antivirals?

Anthony Fiore: Sorry. I think you can just use them for ten days as the typical regimen, just given the incubation period. Are you talking about specific exposure or just the community outbreak started and you think they're getting exposed everyday in the clinic potentially?

Question cont'd: Specific exposure.

Anthony Fiore: Okay.

Question cont'd: Starting them within 48 hours but also trying to get them then those who have not taken it yet to take a vaccine. So you would use ten days of the antiviral, get them vaccinated...

Anthony Fiore: Right.

Question cont'd: ...and so okay. That's the question. Okay.

Anthony Fiore: Yes.

Question cont'd: Thank you.

Coordinator: Our next question. Sir, your line is open.

Question: I had a question regarding the availability of rapid typing. There was a paper in I think the Journal of Virologic Methods regarding rapid typing to tell the neuraminidase type. And I was wondering if CDC has any plans to trial that in emergency rooms or clinics so that we would have real time resistance data.

Anthony Fiore: Well we have -- there are two PCR-based tests first that can do subtyping that are become available in this last year. One of them is the (lumenex) platform and the other is the platform I'm actually not even sure what the trade name of it is. But CDC helped develop it. And the state health labs have these. And some reference labs do have these at this point.

In fact, we actually don't really know how many labs might have the capacity to do this. It might be that some of your bigger academic centers might have a (lumenex) platform and be able give you subtype information. As far as the rapid antiviral resistance testing goes, I don't see that -- I don't know the plans for trying to get that out into the community at this point.

I think it's thought to not be ready yet from our perspective. But I'm not one of the virologists. So it's not going to help you this season. I guess I could put

it that way. But obviously with this level of resistance arising so suddenly like this, there certainly will be an increasing pressure to see such a test get out there more quickly perhaps than it had been planned.

Question cont'd: But then technically all you need to know is the N1 or the N2 type. And then you could make your decision based upon that on your antiviral treatment. You wouldn't need to know if it was actually resistant or not based on the data from this season.

Anthony Fiore: Yes. Right. And so for those two tests that can give you H3N2 versus H1N1, I think you might actually be referring to a specific neuraminidase test. I don't know much about. But it's sort of the same situation. Yes. If you can a hold of that, that's great. I don't think a specific neuraminidase typing test is commercially available. I don't know that the timeline for getting it out there.

Coordinator: Our next question. Sir, your line is open.

Question: Hello. There were a couple reports that just came out of the NIH in Japan regarding outbreaks in elementary schools. One I think closed ten schools in Tendai. And they released some of the sequence data. They were oseltamivir resistant.

And in fact they had the identical changes that were seen in Hawaii, Pennsylvania and Texas here in the United States. And I was wondering if the CDC would have a good representation in their surveillance for elementary school students.

Anthony Fiore: Well we do worry about a representation amongst children, because I think our virus surveillance is based on a person going to a doctor who submits a specimen to one of the collaborating labs. And if kids tend to get less severe

infection which, you know, which sometimes they do compared to the elderly for example, we might not get as many specimens from children.

Yes. So it's a concern. When we say we have, you know, X percent of resistance I think you just have to keep in mind that we may not -- well two things. One is we may not have as broad a swath of the population represented in our viral surveillance.

But the second thing is from community to community the variation is great. And so there may be communities out there that for example, I'm sure there would be communities out there that don't see any H1N1 this year at all. That's just how -- they will just see B and H3N2 or just how it works out.

So we don't have a specific system for getting to -- the short answer to your question is we don't have a specific system for linking in with outbreaks particularly with elementary schools, with the exception if the state health department is interested and goes out and swabs some throats and sends it in, in which case we do get it.

Coordinator: Our next question. Your line is open.

Question: Great. Thanks for taking my phone call. One of your slides titled Challenges Associated with Zanamivir Use -- it stated that it was contraindicated for patients with pulmonary disease. And we see a lot of students with asthma or -- so I just wanted to clarify that we don't give zanamivir to patients with asthma.

And also there -- even some students that come in without a diagnosis of asthma in the past. And I hear wheezing. So for those individuals, I would not prescribe zanamivir if their test was positive for flu. Is that right?

Anthony Fiore: Yes. It could be problematic. I mean if you're spraying a powder into their upper airways and it definitely could elicit some bronchial spasm, so most of the bronchial spasm instances in the trials at least were pretty minor. So this is sort of a judgment call.

If you really would rather not give the child combination therapy if you have positive flu test, you know, with caution you try the zanamivir. But in general people shy away from using zanamivir in persons with bronchial spasm.

Question cont'd: Okay. Great. Thank you.

Coordinator: Our next question. Ma'am, your line is open.

Question: Yes. I'm fortunate to live in a community -- we're actually part of a surveillance system to send samples to you which fortunately we have pediatric samples, too. And I'm also in a community where viral subtyping is likely to be available, you know, within a week or two of the epidemic reaching its peak anyway.

So my question is on your chart, you have positive A H1N1 or unknown. And the alternative treatment for pediatric patients who can't take zanamivir for age or bronchial spasm is combination.

And I'm wondering if we are pretty certain that H1N1 is what's circulating, can we just use rimantadine because both of those medications have CNS effects that can be pretty remarkable in pediatric patients. So using a combination that, you know, might both cause hallucinations or whatever would be pretty unpopular for families.

Anthony Fiore: Right. Yes. We struggle with this. I mean I think there is a real lack of enthusiasm about using rimantadine alone as treatment because of the fairly rapid development of resistance that's seen. It's different from the resistance you see to neuraminidase inhibitors after a sort of a prolonged treatment.

This is -- you can pretty quickly see resistant viruses in persons that get rimantadine. But, you know, here's a good -- you actually have sort of the Cadillac version of surveillance it sounds like.

Question cont'd: Right.

Anthony Fiore: And, you know, it might -- I think there's a lot of leeway for clinical judgment here. And I think, you know, rimantadine might be a reasonable choice if you're quite certain that your -- well not quite certain but reasonably certain that you have H1N1 that you're dealing with.

But I think the important thing though also to keep in mind is that H1N1s have been resistant in past seasons to rimantadine. It's not nearly the high level you see in H3N2s. But, you know, 10 to 20% of H1N1s in most of the past couple of seasons have been resistant. It just so happens this H1N1 we're seeing now is sensitive.

But one could easily imagine this -- the resistance pattern flipping if a new H1N1 comes through, it might be then sensitive to oseltamivir and yet resistant to rimantadine. So if you do elect to go with rimantadine alone, I think you'll need to keep on top of the antiviral resistance data also, which might be a little harder to do.

Question cont'd: Thank you.

Anthony Fiore: That make sense? Okay.

Coordinator: Our next question.. Sir, your line is open.

Question: Hi, Tony. Jim Turner from the University of Virginia. Thank you very much for an excellent presentation. I was curious to know of the 99 patients you cited earlier who had influenza from the oseltamivir resistant strains, did any of them get treated with oseltamivir? And was there evidence that the resistance really was -- impacted their ability to respond to the drug or their clinical outcome?

Anthony Fiore: Jim, thanks for that question. I wish I had the paper in front of me right now or at least the draft of the paper. As I recall, I mean a handful of folks got oseltamivir treatment. This was the resistant -- the fact that the virus was resistant was discovered, you know, weeks after the person got ill.

And a number of these were young persons, children who often don't get treatment at all. So I'm pretty confident that only a few of them got oseltamivir resistant -- got oseltamivir treatment rather. So I don't think we have enough to say that the drug might have actually helped them despite the in vitro finding of resistance.

Question cont'd: Okay. Thank you.

Coordinator: Our next question. Sir, your line is open.

Question: Thank you. Another question about chemoprophylaxis and healthcare workers who still choose not to take a vaccine -- if you can get them on to the antiviral within 48 hours of exposure, how long would you have to continue to prevent

that specific exposure? Is five days adequate? Seven days adequate? Or would you have to still use that ten day protocol?

Anthony Fiore: I think that -- sorry. I think the ten day protocol is what I would use.

Question cont'd: Thank you.

Coordinator: Our next question. Sir, your line is open.

Question: Hi. I just wanted to make a comment regarding the adamantane resistance, and the likelihood that that's going to appear in the United States this season. Last season the resistance really segregated out. And there's a class 2B and a class 2C. The Brisbane is 2B. And that was sensitive and the 2C was 100% resistant. Most of the 2C was in Asia. And in the United States it was mostly in the western states like Hawaii or California.

This season there does not seem to be any of that circulating here. And it also doesn't seem to be circulating in Asia. Japan just has the 2B. And so the 2B with the oseltamivir resistance seems to have taken over. And the 2C is fading away. So the chance that there be rimantadine resistance this season is probably pretty low.

Anthony Fiore: Okay. Thanks. You sound like you're well informed in the virology of this, probably more than me. Yes, it's a good -- you're likely right. It might be not till next season if at all that we see those H1N1s that are resistant to rimantadine show back up. I bet it'll happen eventually. But yes. Thanks for the comment. I think it's -- we're both speculating. It sounds like you have a good basis for speculation.

Question cont'd: Great. Thank you.

Coordinator: I show no further questions in queue at this time.

Alycia Downs: Well I want to thank Doctor Fiore for this very timely update and for providing our listeners with this information. So if you have another question or if you think of one later, please always feel free to e-mail COCA at coca@cdc.gov. And we'll try to get an answer to you as soon as possible.

The recording of this call and the transcript will be posted to the COCA Web site at www.emergency.cdc.gov/coca within the next week. You have one year to obtain continuing education credits for this call.

All continuing education credits for COCA conference calls are issued online, through the CDC Training and Continuing Education Online system at www.2a.cdc.gov/tceonline . Thanks again for participating.and have a wonderful day.

Coordinator: That concludes today's conference. You may disconnect at this time.

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