FTS – CDC - EPO

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1:00 p.m. CST

Coordinator Good afternoon, everyone. Thank you for standing by and welcome to today's conference. At this time all participants are in a listen-only mode for today's call. During the question and answer session you will be prompted to press star one on your touchtone phone. Today's conference is also being recorded. If you have any objections you may disconnect at this time. I would now like to turn today's conference over to Miss Denise Korzeniowski. Miss Korzeniowski, you may begin.

D. Korzeniowski Welcome to our teleconference: Influenza 2005: The Laboratory's Role in Pandemic Preparedness and Response. This is Denise Korzeniowski training associates at the National Laboratory Training Network, Boston Office located in the state lab institute in Boston, Massachusetts. This program has been made possible in part by an unrestricted educational grant from BD Diagnostic Systems.

A few notes before we begin. CDC, our planners and our presenters wish to disclose they have no financial interest or relationship with the manufacturers of commercial products, suppliers of commercial services or commercial supporters. Presenters will not include any discussion of the unlabeled use of a product or a product under investigational use.

Also, after the program each participant needs to register and complete an evaluation form. Documenting your participation helps us to continue to bring high quality training programs in a variety of … I think somebody is not on mute. To do this, after the program go to www.cdc.gov/thtnonline. The verification code is flu. Again, the Internet address is www.cdc.gov/thtnonline. The verification code is flu.

When you have completed the registration and evaluation form you will be able to print your CEU certificate. Florida and California CEU's are also available. You have until January 9, 2006 to complete this process. These instructions are on your original confirmation letter in the general handout. They were also e-mailed to each site representative this morning.

If time permits at the end of the program we will open up for questions. You are on a listen-only line. We cannot hear you; you can hear us. If you experience any problems with the line during the conference, please press star zero. This will signal the attendant that you are having a problem.

Again, welcome and thanks for joining us. We have over 900 sites from across the United States and Canada listening to this teleconference. Today's speakers are Carol Kirk and Peter Schultz to speak to us from the Wisconsin State Laboratory of Hygiene in Madison, Wisconsin. For little introductions, Pete Schultz serves as the Director of the Communicable Disease Division in Emergency Laboratory Response for the Wisconsin State Laboratory of Hygiene. He received his PhD in medical microbiology from the University of Wisconsin Madison and has more than 25 years of experience in clinical microbiology and public health. Doctor Schultz leads the whole laboratory-related emergency preparedness and response activities in Wisconsin.

Carol Kirk, our resident speaker, is the Laboratory Network Coordinator at the Wisconsin State Laboratory of Hygiene. She is responsible for the development and coordination of the state-wide laboratory network for

public health and emergency response and has worked extensively to establish communications with contacts at Sentinel Laboratories, a statewide laboratory messaging system and assessments of clinical laboratory capabilities. Carol also manages the laboratory network for influenza and virus surveillance in Wisconsin. It is my pleasure to introduce to you and to welcome our first speaker, Carol Kirk.

C. Kirk Thank you, Denise. I want to also thank Denise and her colleagues at National Laboratory Training Network for providing us the opportunity to speak with you today on a topic that certainly is an exciting one for us. If you would go on to slide two, what I want to do is just give you a brief overview of our agenda, the material that we intend to cover today. Obviously, initially we want to provide you with an overview of the antigenic characteristics of influenza and an overview of the diagnostic methods that are available for laboratories. These are going to be really very brief overviews because we've discussed these at length in previous teleconferences. This is going to be a brief review.

We'll then go on with surveillance for new strains of influenza viruses, pandemic concerns and the laboratory's role in pandemic preparedness response and activities. Now, these are the topics that really are going to

be the major focus of today's presentations, so we'll be spending more time on those.

The next three slides, slides three, four and five really provide you with a list of resources that we certainly encourage you to refer to, the CDC resources. Among those is included the weekly updates of influenza activity. There's also a resource on the United States pandemic influenza planning, the World Health Organization and then on slide four some information about the performance characteristics by the Food and Drug Administration and also by Dr. … and also the information on accessing ProMed, which is actually a communications mechanism that really does allow you to stay current with whatever is going on with infectious diseases in the world.

Slide five really provides a couple of references for safety and bio-safety. Again, we would recommend that you certainly check out these references and we may refer back to them periodically today.

Now what I'm going to do is turn the presentation over to Pete, who's going to talk to you about the overview of the influenza and antigenic characteristics.

P. Schultz Thank you, Carol, and welcome to all the attendees of the teleconference. Slide six provides the title slide overview of influenza and antigenic characteristics. Now, as Carol mentioned, in past teleconferences we've gone over this at some length. What I would like to do today is just again provide a brief review because our audience does change. I'd also like to touch on a number of the highlights and new information, particularly as it pertains to pandemic influenza.

If you go to slide seven, I just want to start with some review information about influenza, the virus. Basically, this is as segmented R&A virus and by virtue of the fact that it is an R&A virus it is subjected to very high rates of mutation and has very little in the way of proofreading mechanisms, so inherently, influenza, as many other R&A viruses, are going to be subject to very high rates of mutation.

You can see the little cartoon in the upper right hand corner. It also points out a couple of the other key features that we'll be discussing today. The first of these is it's well known segmented genome. Influenza A has eight discreet gene segments, each which code for a key element of the infectious … or products necessary for the replication process. We'll talk about the importance of the segmented genome a little later on.

You can also see illustrated three key surface antigens. The first of these is the hemagglutinin, which is a glycoprotein responsible for initiating, for binding to specific receptors on the host cell and initiating the replication process. It is against the neuraminidase that a very major share of the immune response to an influenza infection is directed. You can also see the neuraminidase, which is a glycoprotein responsible primarily for helping release infectious variants from the infected cell, so it's a very important pathogenetic mechanism or glycoprotein and a portion of our immune response is directed toward it as well.

A third surface antigen, the M2 protein, which is a transmembrane protein, is important. It functions as an ion channel. It is instrumental in helping the encoding early on in the infection process, encoding of the influenza virus to begin an early step in the replication process. As mentioned here, because one of the key classes of antivirals, the adamantines, is directed toward this protein.

Moving down, I have listed there the family influenza belongs to. I think we're all familiar with the fact that there are three types of influenza. The two highlighted, influenza A and B, are the ones that have greatest clinical significance and certainly greatest public health significance. Type A

influenza viruses infect humans and birds and a variety of other mammals. Influenza B infects only humans. Influenza C has been detected both in humans and swine; it's been found mainly in a research setting as a cause of only mild illness with no real seasonality. We're not really going to discuss influenza C anymore.

We're only going to focus on influenza A. The natural reservoir for influenza A is actually wild waterfowl; many, many species of wild birds. If you go down on the slide you can see that influenza A is defined as having subtypes based on the antigenic characteristic of the hemagglutinin and the neuraminidase. You can see that birds contain or carry the entire genetic repertoire of influenza viruses; 16 hemagglutinin and subtypes, nine neuraminidase subtypes, and they really are the natural reservoir for all the possible influenza viruses that can infect humans.

You'll notice, and it's interesting that when you look historically, very few subtypes really have established in the human host. Currently circulating we have predominantly and have been for about the last 15 years H3N2. We see sporadic H1N1. Wisconsin, in fact, isolated its first H1N1 of the year along with H3N2 this year. We've seen H1N2, which was a re-assortment between the H1N1 and the H3N2 and then I have listed the

H2N2, which, when H3N2 emerged, supplanted that as the predominant subtype. We've really, in our history here, have only had four subtypes that have adapted to the human host.

If you go down further and where we're going to focus a lot of our talk today, you can see more and more over the last eight or nine years there have been incursions of novel subtypes from avian populations into the humans. The one we're going to spend most of our time with today is the H5N1. However, and I'll show a slide on this a little later, there have been, in human infections recently, fairly recently, with a number of other subtypes again that are known to widely circulate in avian populations. We'll come back and revisit these a little later on.

If you go to slide eight, I just want to review some feature about the nomenclature. I think most are familiar with this. In terms of the naming of influenza, the scientific naming, you'll see the virus listed by its type, either A or B, location of the original isolation as well as the original lab identification number, the year of initial isolation and then a subtype for influenza A. I didn't mention before that influenza B in fact does not have subtypes. Further down on the slide you see the strains using that nomenclature that have been included in this year's vaccine.

Now, a couple other points I want to make about the nomenclature, particularly in the last year or so we're hearing the term and, in fact, using the term avian influenza or you'll read and hear about bird flu. Over the last year or so it's really been in the context of H5N1. The fact is, as I pointed out before, there are many, many other avian subtypes of influenza, including some that have gotten into the human population, so I think that depending on how things happen in the future, we'll have to be a little rigorous or more precise in how we refer to these influenza viruses, something a little more specific than just avian influenza.

Another point, fairly minor point, for the laboratory is we tend to talk about H3N2 viruses, but the reality is, at least to the level of testing that we do in the public health laboratory, our subtyping is really subtyping the hemagglutinin and the presumption is that when we see an H3 that we're dealing with the N2. A little caution here, I think we have to pay a little attention to this because we're seeing H5 as N1. The fact is we really are only going to be able to, at least in the public health lab, identify it to the H5 level, keeping in mind that there have been other neuraminidase types, N2, N3, that have been found in avian populations fairly recently.

Going on to slide nine then, a real hallmark of influenza is its ability to change antigenically and there are two major ways that this occurs. The first of these is called antigenic drift. This is a process of gradual and continuous change in the hemagglutinin and/or neuraminidase glycoproteins. Basically, antigenic drift occurs because of an evolutionary pressure that's exerted by the host population and immune response, always selecting for new strains of virus. Keeping in mind what I mentioned before, that influenza, being an R&A virus, it's highly prone to mutation.

Now, antigenic drift will occur with both influenza A and B. We refer to the new variants that arise as viral strains, so we can see in the makeup of vaccine every year that, in fact, it represents the viral strains that we feel are going to be circulating in that particular year. The fact that the virus continually is going through this antigenic change, this is going to allow for repeated infections over a lifetime in the individual and it's also going to be responsible for the annual epidemic that we see and are quite familiar with.

I might point out although most of the talk we're going to be talking about influenza A, influenza B can also go through antigenic drift, but when

looked at historically it seems to be much more genetically stable. The changes aren't as great and they don't occur as frequently.

One final point to make on this slide: We do have these annual epidemics. Since we're dealing with talking about it, pandemic influenza now, we need to be distinguishing between the influenza that we see on the year-to-year basis. With that, that might arise and become a pandemic strain. Therefore, the terminology that's been used is either seasonal influenza or, if you look at some of the influenza plans, inter-pandemic influenza. Just a little note on nomenclature.

Go on to slide ten then. The next couple of slides I just want to discuss a little about the impact, what occurs after an antigenic drift has occurred. As I mentioned, antigenic drift is responsible for the annual epidemic that we see of influenza of varying severity. What I have on slide ten is just the history of influenza in Wisconsin, the epidemics that we've had for roughly the last ten years. You can see, and this is reproduced pretty much in every state and pretty much throughout the world, we have our characteristic epidemics of either influenza A or influenza B in combination. We see that very characteristic sharp epidemic peak. You'll see this type of presentation. Either these are data that are statewide data,

but if you looked at a locale in the state or if you even look in an institution suffering an epidemic, you're going to see this very sharp epidemic peak.

You'll also notice the very striking seasonality, which in Wisconsin the influenza season typically is November to April or May, although we'll start to see our first sporadic cases throughout communities as early as October, sometimes even earlier than that. It's very rare that we see off-season influenza during the summer months unless we have seen occasional cases associated with overseas travel.

Now, we would presume that we're going to see the same epidemic characteristics of influenza should a pandemic subtype emerge, again this very characteristic sharp epidemic peak. The seasonality, particularly of the first waves of influenza, might be different. In 1957 when the H2N2 first emerged, in fact the first cases were seen in the middle of summer and the actual peak of the first wave occurred in October, so we're going to have to be prepared for perhaps recognizing an earlier seasonality.

If you go to slide 11, I just want to review a little of the annual impact of influenza. I think all of us would agree that seasonal influenza in its own

right is a public health problem. It's one of those things to be careful what one wishes for. I've been talking about influenza for 20 years and you go out into the public and talk about it and no one cared about it, no one really recognized it was an issue. Things have certainly changed in the last few years, and for good reason.

If you follow this diagram, in a typical influenza year season we might have 10%, 15%, up to 20% of individuals affected, infected. At least half of these are going to be symptomatic and at least over the last ten to 15 years a very significant number are going to be hospitalized and the now very widely quoted figure of mortality of in excess of 36,000 deaths in the United States alone.

When you look into the impact a little more, not shown on this slide, we know that the highest incidence of infection is going to occur in children. They suffer very significant morbidity, which is a fact we're more and more recognizing in recent years. In fact, this age group, less than five, that suffers the highest rate of infection, of hospitalization, second only to the elderly. There's a significant clinical impact on young children; preschool and school age children as well. This age group or these age groups are also critical in the transmission of influenza in our

communities. Therefore, when we're talking about the pandemic influenza we're not only going to have to worry about focusing on that age group to mitigate the morbidity that's going to occur, but we have to recognize the fact that they may be significant. These age groups may be significant in the spread of a pandemic strain or even seasonal influenza in our communities each and every year.

Of course, the highest mortality in seasonal influenza occurs in the elderly and those with underlying illness. It is against or towards these populations that many of our preventative measures have been directed.

There's also a couple of confounders that I want to mention in terms of how influenza presents clinically and we have to take these into account when we're talking about prevention and control. Influenza has a very short incubation period; usually cited one to three days, which helps account for those very sharp epidemic peaks. We also know that as many as 50% of individuals may be asymptomatically infected and capable of transmitting the virus, although not necessarily shedding it in as high amounts or as efficiently or effectively as they would if they were clinically effected by influenza, but being a source of infectious virus in the community nevertheless.

To further complicate things, in those individuals who turn out to go on to have clinical disease, virus may be shed in amounts enough to be allowed transmission in the community as early as a half day or a day prior to symptoms. Finally, influenza is just a very communicable disease and can be spread by a number of mechanisms; large particle droplets, smaller particle aerosols and direct contact.

Finally, we have to recognize or keep in mind when we're looking at seasonal influenza or as we worry about the emergence of a pandemic strain that we have the backdrop of many, many other respiratory illnesses, both viral and bacterial, many of which, if not all of which are going to present early on as influenza-like illness. It'll be very difficult for the clinician to determine when … influenza or any influenza is affecting his patient population. There's going to be a heavy reliance on the laboratory to support the clinician.

Going on to slide 12, the real key antigenic change that occurs with influenza and the contacts of pandemic influenza and most relevant to today's discussion is antigenic shift. It is actually our study of what's been happening with the avian influenza, the H5N1 might be redefining some of the mechanisms of the antigenic shift. Basically, shift is a process

whereby existing surface hemagglutinin and neuraminidase proteins are replaced by an … or neuraminidase protein that is significantly different. The term now being used is novel, a novel subtype of hemagglutinin and neuraminidase. Antigenic shift occurs only with influenza A and leads to new viral subtypes. The change will be abrupt, infrequent and unpredictable. We're learning that very well over the last few years. It is, in fact, the processes of antigenic shift that can result in a pandemic of influenza.

Slide 13 basically defines the characteristics of a pandemic. What is pandemic influenza? It is essentially a worldwide epidemic which is due to the emergence of a novel subtype of influenza A that gains the ability to spread easily and efficiently from person to person. Some of its characteristics known from past observance of pandemics: It's likely to occur in multiple or widespread geographic areas worldwide, so that's a key. This is going to be a global event. However, within each locale where it occurs there's going to be the typical locally explosive epidemics much like we deal with on a seasonal basis. We'd expect it to be associated with unusually high rates of morbidity and mortality largely because it's coming into a population that probably has little or no

immunity to the particular subtype of at least hemagglutinin and possibly a hemagglutinin and neuraminidase.

It'll be notable for extremely rapid global spread, owing to the fact that, and we tend to compare these to past pandemics, but right now with air transport and the fact that we have air transport between very large population centers and the fact that influenza is an inherently infectious virus, one would anticipate that if a pandemic subtype does in fact emerge, we would anticipate that there is going to be extremely rapid global spread.

This might be, perhaps, quite a bit different than what was experienced with SARS or, in fact, in that regard it'll probably be similar. SARS went global fairly quickly despite the fact that it did not share the same transmissibility as influenza and had quite a bit longer incubation period. Nevertheless, it circulated globally largely because of air travel over a matter of weeks. We'd also anticipate that there are going to be multiple waves of disease. Again, this makes sense immunologically and this has been seen in past pandemics.

If we go to slide 14, we have had three pandemics during the 20th Century. These are highlighted at the bottom of the slide, a slide which I borrowed from the CDC. The most now famous pandemic was the Spanish Influenza or the Great Influenza Pandemic of 1918-1919, which is really serving as a benchmark, as a worst possible case if there is an emergence of a pandemic subtype.

We had the H2N2 or Asian influenza emerge in 1957 and remain dominant until 1968 when it was replaced by Hong Kong influenza, H3N2, which has been amazingly tenacious in the human host and having been with us now even as we speak. When you look at the cumulative effect of the H3N2 in terms of morbidity and mortality since it translates over a period of almost 40 years, 38 years, it's had a huge, huge public health impact.

There was also essentially a reemergence of H1, the so-called Russian influenza in 1977, which many sources now don't even consider a pandemic just because of the mildness of the overall global outbreak and its association with milder diseases and less impact of the epidemics on a year-to-year basis. We do see isolates of H1. It's been some time and I

can't remember when we've had just a predominantly major epidemic of H1, at least in Wisconsin.

If you go to the top of the slide the concern now, of course, over about the last eight or nine years has been the repeated emergence of avian influenza subtypes in the host population. That's what we're going to look at in a little more detail.

If we go to slide 15, I mentioned that there has been some evolution in the thinking on how pandemics, influenza subtypes will be generated, what is the mechanism of antigenic shift. We've known for many years, the duration of my career, that influenza A is a natural infection of wild waterfowl depicted on the left. I think up until fairly recently the standard wisdom was it was very difficult for avian viruses and fairly rare for avian viruses to directly affect and have a major impact on the human host population, although it was recognized for some time that the H2N2 and H3N2 or at least portions of those viruses had an avian origin.

The preferred model was a re-assortment event between a circulating human virus and a novel bird virus, avian virus, and the pig being described as a mixing vessel, which would then kind of bridge the species

gap, at least as influenza infection virus goes, between birds and humans. The emergence would occur via swine population. In fact, this is the model that is likely to be still in operation.

However, if you go to the top of the slide, the events over the last several years and also really remarkable molecular studies of the 1918-1919 viruses really is causing us to redefine how a pandemic subtype might emerge. What's depicted up there is an avian virus going through perhaps intermediate hosts, but however getting into the domestic poultry population where it can transform into a highly pathogenic form that causes significant morbidity and mortality in domestic fowl populations, keeping in mind typically in the normal avian host, that is the wild waterfowl. Influenza is largely an asymptomatic infection, although they will shed very large amounts of virus in feces and respiratory secretions.

Then once it's gotten into the domestic waterfowl, direct transmission into the human host population. Now, two things could be occurring here: Either a re-assortment between an avian virus and a circulating human virus could occur in the human host population, but I think a more direct route now based on the data and the studies of the 1918 virus, the molecular studies, suggests that possibly there could be an adaptive

mutation of the avian virus so that it gains the ability to directly infect, cause illness and possibly lead to a pandemic in humans. There is, in essence, at least three possible models here how avian viruses normally circulating asymptomatically in wild waterfowl can make it into the human host population.

So, that's an overview on some of the basic theorology and basic epidemiology. At this point I want to turn the talk back to Carol and she'll provide an overview of laboratory diagnostic methods and build on this basic information that we want to share.

C. Kirk Thank you, Pete. As Pete said, I'm going to talk to you about the laboratory diagnostic methods. As I mentioned earlier, what we're really going to do is go through this much more briefly because we've covered that extensively in previous audio conferences, so this is really going to be a brief review.

If we move onto slide 17, which you'll know because it doesn't have the number visible on the slide, it's titled Laboratory Diagnosis of Influenza. Really, this is just a summary slide of the main test methods that are available in the laboratory. I certainly don't intend to read the slide to

you, but just comment on a few of the test methods there. Culture really is still considered the gold standard because it indicates the presence of infectious virus, but also partly because it provides an islet for characterization and other studies, which is really important in influenza viruses.

Molecular testing methods, particularly real-time PCR, in our opinion are becoming a gold standard because of their speed, their sensitivity specificity. It may reach a point where actually we may end up with a dual gold standard for influenza testing shared between culture and molecular.

Moving on, I do want to comment in terms of serology. It's really not useful for patient diagnosis for the most part. It is useful for epidemiologic studies, but because of a need for paired sera for a definitive test result, it's not particularly useful for direct patient diagnosis. It has been suggested in the current pandemic plan that public health labs may want to consider usefulness of serology and having the capability for serologic testing in the event of a pandemic.

The other comment that I want to make is that on the rapid EIA-like test listed on the bottom of the slide, and if you look from top to bottom it is interesting if you see that we're talking anywhere from weeks, days, hours to minutes in terms of the turnaround time on any of these test methods. The EIA-type or rapid test really have allowed widespread use of testing and they're available from physician office, laboratories to emergency departments to the large laboratories. They really have found some widespread use.

Moving on then to slide 18, actually slide 18 and 19, I really have a listing of the rapid tests that are available for laboratories there, their … status and the antigen that's detected. Obviously, they range from wave to non-wave in terms of … status. The antigen detected can be only A or B. It can be both A and B without differentiating between them or it may be A and B with differentiation between the two viruses.

I should also mention now we've presented on this in previous years, so I didn't provide the data here, that there's also, in addition to the … status and the antigen detection, there's also a range in terms of the sensitivity and specificity of these tests from roughly 60% to more than 90%. There's also a range in terms of the specimen type that's allowed. There

are additional factors that are going to influence its usefulness and its sensitivity specificity in any specific laboratory including the age of the patients that are being tested. We all know that children shed virus, generally speaking, in larger amounts, in greater concentrations than the elderly do, so therefore, most tests are more sensitive if you're looking at children specimens.

As with any laboratory test, the quality of the specimen being collected is absolutely critical. It's going to make a huge difference potentially in any given laboratory's results.

Moving on then to slide 20, I really just wanted to provide more detail in terms of the advantages and disadvantages or concerns with rapid tests. The advantages that the rapid influenza tests have I think are largely self-explanatory. The rapid tests really provide a rapid turnaround time. They allow you to provide STAT testing, they allow you to identify outbreaks rapidly. You have a result soon enough that it can impact the antibiotic and antiviral usage. There's really less expertise required and therefore, they can be used in widespread areas.

Concerns that have been detailed in the past are the performance characteristics. Early and late in the season when influenza prevalence is low, the predictive value positive is going to be relatively poor. It would be recommended that positive results be confirmed. At peak season, we've not emphasized this in the past, but I know in Wisconsin several laboratories had noticed a real significant problem with the lack of predictive value negative at peak season. At peak season, if it's going to be relevant to your patient care, patient management, you may want to perform confirmatory testing of the rapid test negative specimens.

One comment that I do want to make is that anytime you're performing confirmatory testing you may require a second specimen even for PCR confirmation depending upon what that rapid test procedure initial steps are. It may make the specimen not viable for additional confirmatory testing.

Biosafety issues I'm going to talk a little bit more about in a minute and the concerns about islets and surveillance data also. Obviously, through the last several years it seems as though every year there's a problem with at least one if not more of the rapid test kids, with the supplies being

available and backordered. So this is something that I think also is a concern every year with the rapid test.

Moving on then to slide 21, this is also something that we've talked about in previous teleconferences, but I really want to reiterate it in terms of optimizing rapid test use. I frankly think that we need to really make a point of educating clinicians on predictive values and limitations of the test results. This is something that's really critical, they do need to understand and quite frankly, it's sometimes painful for us in the laboratory to admit that there is no perfect laboratory test. They all have advantages, disadvantages and limitations. We really need to help clinicians understand that a positive may not be a true positive in September, that the negative may not be a true negative at peak season, etc, and that it's simply the nature of the test and the impact of prevalence on the test.

By doing that, educating them, they can understand that we really do need to confirm those early and late season or out of season positives when the prevalence is low. We may need to confirm peak season negatives if it's going to impact the patient. We also need to, for much of the year when influenza really is a rare occurrence, certainly in Wisconsin, we need to

recognize the value of that negative result. We tend to look for the positive result, but really, in June, July, August, September, certainly in Wisconsin, a negative result has a remarkable predictive value, again because the prevalence is just about zero at that time.

One of the recommendations that we've made in the past is that laboratories or rapid test sites should use prevalence indicators to decide when they should test, when to qualify a result and when they need to confirm results. What we've suggested in the past is you can use just about, frankly, anything as a prevalence indicator. You can use national laboratory data that CDC provides on a weekly basis. You can use the influenza-like illness or ILI indicator CDC provides, you may have statewide data, either lab or epidemiologic data, you may have in hospital data that tells you when influenza prevalence is low, increasing or near peak time. Any of those things really will give you a little better sense of how to interpret that test result.

One of the comments that I do want to go back to in terms of the concerns I had mentioned on the previous slide is some of the concerns were the loss of islets for further characterization and loss of surveillance data. I neglected to say I frankly feel like those have been concerns since the

beginning with these tests, but I believe that they can be compensated for simply by engaging rapid test sites in our surveillance. I'll be talking about that later, also.

Now, moving on to slide 22, talking a little bit more about the biosafety concerns I had mentioned, this really came to light I think or started increasing in our awareness a few years ago when SARS came on the scene and there were additional biosafety recommendations for handling SARS specimens in the laboratory. It popped up again last year with the inadvertent use of influenza A H2N2 in the proficiency testing sample.

The real concern is potential exposures of laboratory staff to new or exotic, certainly unusual viruses in the laboratory. Some of those concerns can be dealt with by improving our communication with infectious disease doctors or infection control. It seems as though getting the information you need in the laboratory for specimens has always been an issue, but I think with the concern recently with, again, SARS, with avian flu currently, with H2N2 last winter or other exotic viruses, essentially we're at the point where we really do need to get specific information. It's at the point where travel history of the patient or other

relevant exposure information like if there's been an exposure to swine, etc, really is critical for the laboratory staff's protection and safety.

Some of the other ways that you can address concerns is enhancing your safety in the laboratory if possible when using a rapid influenza test. You can certainly perform the test in a biosafety cabinet if you have one and if the procedure is such that it is adaptable to that. In cases where you don't have a biosafety cabinet or it's not going to work in the BSE, consider using additional personal protective equipment, whether certainly you want to wear gloves and a lab coat, but perhaps you'll want to also put on a mask, wear a face shield. You might want to also think about sequestering the work in the laboratory so that if the testing is being performed outside of BSE you're at least not performing it in a real high traffic area, so you can at least minimize exposure. You could perhaps also use a bench guard or bench shield to protect from some aerosol.

I think one of the other things you can certainly consider is contacting your public health laboratory and consulting with them and weighing if there's truly a known travel history or an additional exposure risk on a specimen. Is this something you really want to test in your laboratory or is

it something that would be better forwarded onto another laboratory because of its increased risk?

Really, what all of this boils down to is performing a risk assessment in your laboratory overall and then doing a risk assessment with each of the specimens you receive based on the information that you receive with them.

Moving on to slide 23, this is an outline of a map of Wisconsin, for those of you who don't recognize it. I really wanted to point out that I had commented earlier that the rapid tests can really … widespread use. That's really the only reason that I wanted to show this map. This is rapid test sites that we identified in Wisconsin last year. This does not include any physician office laboratories that might be using rapid tests. These are just rapid test sites that reported to us. There were about 100 of them that reported to us in Wisconsin last year. By comparison, there are about 10 virus labs in Wisconsin that actually perform culture. This is particularly significant if you think in terms of coverage of your state for surveillance purposes.

Moving on them to slide 24, this is another visual to demonstrate widespread use. Again, this is that same data in terms of these rapid test sites that reported to us last year and have been reporting to us over the last several years. If you look at last year's, the 2004-2005 season, you'll see that these sites actually tested about 50,000 specimens in Wisconsin.

Really, these last two slides together really I think make a real strong point in terms of the need to engage rapid sites to get the most widespread geographic coverage, but also to get the most sensitive detection of influenza in the state. You might want to note also that certainly in Wisconsin for the last four to five years, our first influenza in the state has been from confirmatory testing of a rapid test positive.

Touching now to slide 25, I want to talk a little bit about influenza surveillance. Moving on to slide 26, what we're going to, just as a reminder of the objectives of influenza surveillance, point of influenza surveillance isn't to diagnose every case out there. It isn't necessarily to develop numbers of the absolute number of cases of influenza that occur, but to really define when, where, how much and what kind of influenza viruses are circulating. It's also to look for unusual viruses or unusual illnesses that are caused by influenza viruses.

Really, I want to highlight or I want to draw your attention to those, if you have those in color, the lines that are printed in yellow or have the asterisk after them really highlight what the laboratory's contributions are toward influenza surveillance. There's an awful lot of influenza surveillance that really depends upon laboratory contribution.

Moving on then to the next slide, it also makes a point that influenza is really a global concern, regardless of whether there's a pandemic or not. Even in terms of its seasonal nature, it's a global issue and therefore, surveillance is really a global issue, also. Surveillance for influenza can occur at local, state, national and international levels. This is really a graphic just to represent international surveillance, which is coordinated by the World Health Organization.

Again, I refer you to that resource in one of the early slides. If you go to the WHO Web site you can find much more information about a very active influenza surveillance program that they have. They are dependant on national influenza centers and right now there are about 112 of those in 83 countries. The collaborating centers for influenza, there are four of those, one of which is CDC.

Moving on then, and I recognize that there are other groups. There is a Canadian surveillance network, there's a European influenza surveillance scheme, etc. What I'm going to do, though, in terms of national surveillance is focus briefly on the U.S. influenza surveillance. I mentioned earlier the CDC has a resource on one of the early slides and there are weekly updates of influenza activity available at their Web site.

Really, in the U.S. surveillance is coordinated by the CDC. There are really several components to the surveillance, influenza surveillance in the U.S. These are complimentary components. If you look at this slide, which we also borrowed from CDC, slide 28, there are reports from laboratories, there are islets from laboratories, and these are World Health Organization and National Respiratory and Interic Virus Surveillance System collaborating laboratories.

There are about 1,000 clinicians or healthcare providers in the country who are the sentinel providers and provide weekly estimates of influenza-like illness, or ILI. There's the Pediatric Hospitalization Surveillance, which really is something that's only been implemented the last few years. There are anecdotal reports from state and territorial epidemiologists. Then there are the vital statistics registrars, where really, from 122 cities

they collect data on the number of deaths or percentage of deaths which are caused by pneumonia or influenza.

I want to make a comment about it. It's probably obvious to you, but the arrows in and arrows out have to do with the information and data flow coming into CDC and then flowing out to public health, physicians, media, etc. Really, the U.S. influenza surveillance is a series of checks and balances between laboratory epidemiologic death reporting, etc, so that there's really a very comprehensive system.

Moving on then to slide 29, this is presented. Influenza surveillance in Wisconsin is presented as an example of statewide or state level surveillance, and we're using Wisconsin probably pretty obviously, because it's the state that we're familiar with. In Wisconsin, influenza surveillance tends to be somewhat comprehensive. We're collecting information from the sentinel providers, from laboratories, from institution and other reporters who have outbreaks. We're trying to share that information back out with clinicians, with the public, etc.

Moving on to slide 30, I want to focus down to laboratory-based influenza surveillance. Again, we're using Wisconsin because that's the state that

we're familiar with. What I want to focus on here is the laboratory surveillance in Wisconsin really depends upon direct submissions from some of those clinicians out there who are sentinel submitters, send specimens direct to the state lab. It also depends on virology laboratories and the rapid test sites. In Wisconsin we consider that really, lab-based surveillance is a critical element of surveillance and we do share that information again.

On slide 31, the elements of lab-based surveillance, it's really, as I mentioned earlier, we're getting direct patient samples and islets for testing at the state laboratory. We're also getting weekly reports of testing from both the virus labs and the rapid sites. Obviously, there's communication information about any unusual occurrences that are occurring. Then there's really an education for clinicians and test sites. This is almost a cascade or web system, where we are communicating as much as we can about prevalence, use and interpretation of tests, but then the laboratories out there are also communicating that onto their clients.

Moving on to slide 32, just some recommendations that we would have that would improve lab-based surveillance. Really, we need to develop algorithms for use of PCR in the state public health laboratories. A real-

time PCR I think is probably critical for rapid test confirmation and ruling out unusual subtypes like suspect avian influenza cases. There really isn't time for the multi-day culture that's required, so really, the best test that immediately meets that need is a real-time PCR.

We need to continue to work to incorporate rapid test sites as key partners. Those slide I showed earlier about the volume of testing and just geographic location in terms of rapid test sites really make the point, as far as I'm concerned, that if you want earliest detection and you want the greatest coverage, we really need to continue to engage them in surveillance.

The next challenge, however, is we often need to figure out how to incorporate molecular site in influenza surveillance. As molecular tests become more and more widely used, and right now there are no FDA approved molecular tests out there for influenza, but as more of them, more labs either develop or work with some of the commercial kits that are available or develop their own in-house assays, we need to work just as we did with the rapid sites to gather their data and incorporate it into our surveillance and establish procedures to capture at least selected specimens for culture and/or subtyping.

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The other obvious thing for enhancing influenza surveillance is expanding it to year-round. All of these enhancements I think are really vitally important in pandemic preparedness. And now I'm going to turn the microphone back to Pete.

P. Schultz If you change to slide 33, I want to talk a little briefly about the current pandemic concerns and then get down to the real substance, what are we going to have to do about this as laboratories? I think we're all aware that there's been a hyper-awareness in the scientific community and the general public about pandemic influenza. Remember by "Be careful what you wish for" comment.

We know politicians have gotten onto the bandwagon, particularly now in the aftermath of Hurricane Katrina and some of the other disasters where there are really questions being posed about how effectively could we respond to any public health emergency. Because of these pressures, it is very incumbent on all of us to keep up to speed with the current pandemic concerns and what we're going to need to do about it. For this reason, I strongly urge you to—again, going back to the references we've given you—follow the up-to-date information provided at the CDC, WHO Web sites and also ProMED, so you can see the events. They definitely are unfolding essentially on a day-to-day basis.

If you go to slide 34, I'm just going to have a series of slides here to briefly go through the situation where we are now. Basically what this slide shows you is that the story has really been unfolding over the last eight years, beginning in 1997 with the first emergence of the H5N1 in the human population with the 18 very well documented cases of respiratory illness and 6 deaths in Hong Kong. You can see then, over the ensuing seven to eight years, there has been emergence of several other avian subtypes with less dramatic effects in the human population, including, again in 2003, a couple other H5N1 cases that sort of slipped in under the

radar, because we were a bit busy with SARS, leading up to the events over the last two years with a very large-scale emergence of H5N1.

I didn't get all the things on this slide, but there was another in H7 and two isolated cases in Virginia and New York in 2002 and 2003. I think we all, of course, remember last year with the inadvertent release of the H2N2 into proficiency test and, for good measure, another species crossover, the H3N8, which went from horses to dogs and causes considerable veterinary concern and then, kind of in the cascade effect, what effect does this have on the human population?

If you go to slide 35, it's a nice summary map taken from the World Health Organization Web site. It shows that there are essentially two things going on concurrently. The widespread dissemination and now establishment endemically of H5N1 in avian populations, both wild waterfowl, many other bird species, and domestic fowl. You can see the extent colored in gray.

Concomitant with that then, three distinct waves of human cases have occurred since December of '03. If you look at the blue dots, the first cases/clusters were described in Vietnam and Thailand, a second wave

from July ’04 to October ’04, again, which occurred in Vietnam and Thailand, and then, most recently, the events unfolding since December of ’04 and recognition of human cases now in Vietnam, Cambodia, Indonesia, Thailand and, most recently, China. Throughout this time period and throughout these areas, very extensive outbreaks in domestic poultry are having a dramatic impact on the population of these birds and economies surrounding these birds throughout that part of the world.

If you go to slide 36 then, it only gets better with now the spread, via wild waterfowl, of the H5N1 west to include further reaches of China, Mongolia, Russian Federation, Kazakhstan and on into Eastern Europe, as far west as Croatia, reports in recent days in the Ukraine and so on. The concern being it appears to be spreading in wild waterfowl. There’s some now evidence that the wild waterfowl are quite capable of spreading the highly pathogenic H5N1. The problem is, wherever it spreads and gets into the domestic poultry populations, this puts the human populations in contact with them at greater risk for infection.

Then, of course, the concern is for further spread as the numbers of these virus outbreaks in birds have been identified along major flyways, which could, in fact, spread the virus to the Middle East, to Africa and, in fact,

back toward the east to Canada and possibly to the United States. So a lot is happening quickly, particularly in the last year and really bears close watching.

If you go to slide 37, this is a summary as of November 17th. It's sort of a bit of a challenge to keep up with the case counts, because they seem to be changing essentially daily. I think the real emphasis now isn't so much on the number of cases that are occurring, but looking for certain indicators that this threat is going to go to another level. Basically more and more, we're looking for clusters of illness or evidence of human-to-human transmission, particularly that which would be sustained, which may be a much stronger indicator that we're getting very close to a pandemic.

Something to note from the table, though, is the very high case fatality rate. What isn't illustrated in the table is that most of these cases have been in children and young adults. The disease has had very aggressive clinical course with primary viral pneumonia a likely outcome, multi-organ failure common and acute respiratory distress syndrome. It's a very bad disease and, of course, that also raises the concern that this might be sort of the iceberg where a lot of less-severe disease is not being detected.

In slide 38, there's just a quick situation update. Basically I already discussed the geographic and host range expanding, continuing very large outbreaks in domestic fowl. The good news, or a bit of good news, in human isolates so far, all genes have been of avian origin. On the other hand, based on that really remarkable research on the 1918 pandemic flu strain, that doesn't give us as much comfort as it might have some time ago.

Viral resistance to the adamantines, however, we still appear to be okay for the most part with the neuraminidase inhibitors. Concern has been the continued evolution of pathogenicity and antigenicity; the virus, H5N1, getting into non-typical mammalian hosts, such as several outbreaks described in big cats (lions, leopards, so on); experimental infection of domestic cats and other experimentally infected rodents, very severe disease being caused; documentation that the virus has, in fact, gotten in pigs, which would then possibly invoke the more traditional mechanism for reassortment with a human subtype.

They're looking at human indicators as well. As I mentioned, very close attention being paid to clusters in family, which would indicate a greater likelihood of person-to-person transmission and also, somewhat

paradoxically, looking for milder illness or some evidence that there are cases of milder illness, which might be another indicator that the virus is, in fact, adapting better to the human host population. It really isn't in the virus' best interest to kill off 50% of its host. If it starts better to cohabitate with a human host population, that's not necessarily good news for us in the context of pandemic.

Slide 39, we're essentially dealing with a recipe for a human pandemic, and two of the ingredients are already present. We've had the emergence of a novel subtype of influenza, the H5N1. It is replicated. In fact, causes severe disease in humans, and what we're waiting on right now is the possibility that there would be efficient and sustained human-to-human transmission. Really in terms of monitoring and when we would invoke our pandemic planning, this is the event that we would probably be reacting to.

If you go to slide 40; I'm not going to spend a lot of time going through the kind of doom and gloom numbers. You can find them in many, many publications right now. But the fact is, if a pandemic does occur, it very much is going to be unlike many other events. I do have highlighted the first bullet. "Inevitable, yet unpredictable" I think really does well

describe the possibility that we'll have a pandemic. What we're seeing more and more, particularly in the popular press, is that it's imminent, that it's overdue and frankly, with what we're seeing, I don't think we're in the position to be able to say that. So we have to exercise some care in the terminology we use and take with a grain of salt some of the dire threats that we're reading about.

Having said that, I don't want to minimize the threat that does exist. We've spent a lot of time preparing for bioterrorism, but for a lot of reasons, pandemic influenza will be a much, much greater event, much greater public health impact. I've given some of the characteristics that we'd anticipate.

Finally, just to complete the thought, on slide 41, we in public health, in fact, are walking a fine line between appropriately sounding the alarm and causing panic or, worse yet, so dulling people to the threat of pandemic just by hammering them with these incredible numbers of impact in terms of morbidity and mortality. We have to continue to walk that fine line, because this presents a serious public health threat.

If we go to slide 42, it was an attempt at humor. It's a toned-down attempt at humor. I can't give detail, but I didn't want to risk getting sued by one or other institutions in the United States, so we put this in here kind of as a spacer and to lead into really a couple of the key topics we want to finish up with and that's pandemic influenza planning and what we need to be doing.

If you look on slide 43, just like there is influenza surveillance at many levels in the world, there's influenza pandemic preparedness going on as well. It's an international priority. You can access the WHO preparedness plan and checklist for pandemic planning at their Web site. Frankly, it doesn't give a lot of specific information for the laboratories. However, if you go to slide 44, particularly the national pandemic influenza plan is a document all of us in public health and in the clinical laboratories need to become very familiar with right away. It's a rather imposing document. You can download it in its entirety. I will give you some indication to help focus where you'd want to put your attention in reviewing it. Part two of the plan actually gives the public health guidance for state and local partners and supplements one, two and five within part two really have a lot of important information that relates to the laboratory and laboratory preparedness and response to pandemics.

If you go to slide 45, this is just to point out that all of our states should be well down the road with pandemic preparedness plans. In fact, we're now having to revisit those plans in the context of the new HHS pandemic influenza plan that was just released in early November. So we're having to modify our plans to get our terminology right and to make sure the preparedness planning that had gone into our planning early on now meshes with the new national plan.

Slides 46 and 47 just point out that critical to preparedness planning in response to a pandemic is familiarization with the WHO pandemic classification scheme. The HHS plan and all our plans should fit into this framework. Therefore, we need to be familiar with the terminology in terms of the different interpandemic, pandemic alert period and pandemic period and the different phases. We currently are in Phase Three. You'll note, for us to progress further really hinges on whether there's going to be human-to-human transmission of the virus. Again, this is what we're really looking for on a global level.

Now, going on to slide 48, I really want to touch on some of the laboratory's role in the pandemic preparedness response. This is kind of the punch line of the presentation. You'll recognize it is the title slide. In

fact, our purpose in the following slides—and you'll have these as resources when the talk is done—is really to help you define your roles in pandemic preparedness and response. We can offer our suggestion or insights and also take information from the HHS plan and public health conversations that we've had, but it's going to be up to each individual laboratory to put together their own plans. Hopefully what we're presenting here rather briefly, although not exhaustive, is really going to give you something to build on.

I like the diagram on slide 49. Just to give you a little idea, in the context of the different pandemic preparedness and response phases, interpandemic, pandemic alert, pandemic period and post-pandemic, right now we're in the pandemic alert period. We should be well underway with our planning or, put another way, our preparedness. By the time we make it to the pandemic alert period and certainly a pandemic period, we need to be implementing and responding. The final diagram, for those of you who have taken management theory and so on, recognizes the PDCA cycle (Plan, Do, Check, Act). In fact, if we come out of a pandemic, we're going to have likely sometime before the next wave comes, so we're going to have to continue to update our plans.

One slide 50, what I did is took some basic information that you can more detail by going to the HHS plan, supplement number two, just to review some of the lab responsibilities. The way they group this in the pandemic plan was to link interpandemic and pandemic alert influenza together. When you look at the laboratory responsibilities, there's nothing too surprising here. First is to perform diagnostic testing, although the reason for testing might be different in the clinical laboratory or the public health laboratory.

In the clinical laboratory during this period, it is important that you have a mechanism for suspecting cases of avian influenza and getting those specimens to the public health lab. If you find that you might, in fact, be culturing an avian influenza, you need to proceed with caution or stop the culture, because you are supposed to be working with this under biosafety level three enhanced conditions. Also keep in mind use of the rapid tests to detect novel influenza viruses. We're not sure how they're going to behave with all novel influenza viruses, and you're certainly not going to be able to tell the difference between a novel virus and what might be the seasonal influenza subtype.

We need to continue our surveillance activities, and Carol gave a description of what some of these are. However, in public health labs now, we've had to ramp up to look for novel subtypes, relying heavily on RTPCR technology, critical to participating in pandemic planning and exercises despite the drain on our time and resources, because this is how we get to know our response partners. Carol, in a few minutes, is going to quickly go over the concept of having some checklists. Then basically we need to continue that education of clinicians and laboratorians.

On slide 51, when the pandemic occurs, when we enter the pandemic period, we do delineate a little the laboratory's responsibilities based on whether they're a clinical lab or a public health laboratory. Clinical laboratory is going to bear a brunt here, because of the huge demand on diagnostic testing. One of the issues you need to be thinking about now is at what point do you scale back the testing and rely perhaps on a call on the basis of the clinician whether the person may have influenza or not. While this is going on, you're going to have to maintain your other diagnostic services. The public health lab and public health community are still going to look to you to support our surveillance activities, because you're frontline diagnostic entities. Again, we're going to need to continue the clinician education.

The public health laboratories are going to have to maintain the surveillance activities very early on in the pandemic really to define the scale of the outbreak as well as look for antigenic changes and see how maybe the new emergent subtype is either supplanting and co-existing with the existing subtype. We presume CDC will provide advice for subtyping, isolate referral and so on. This is described in the HHS plan.

Public health labs may be called on to conduct special studies related to serological studies in the community and also testing for antiviral resistance. We may have to be prepared for that or come up with maybe regional strategies. Yet a public health lab has to maintain our emergency response capabilities, because food borne outbreaks and so on are going to continue.

So that's kind of a thumbnail. We're going to maintain our responsibilities and gain new responsibilities. What I want to do now is turn it over to Carol to go over and really discuss what's going to be the impact of the pandemic on the lab and what are some of the issues and options that you're going to have.

C. Kirk Thank you, Pete. We're nearing the home stretch here now. The impact on the laboratory; these are some ideas that seemed obvious to us. You may have additional ideas of what would be the impact on the laboratory. It's fairly obvious to us that there are going to be staff shortages. The truth of the matter is some of this laboratory staff may be among those mortality statistics. Other laboratory staff may be ill. They may be home with ill family members. They may be home frankly just because of fear in the family of possible exposure to the virus. We can expect that there will be supply shortages. We've talked about there are backorders of various kits every season. You can imagine that there's potentially going to be a real shortage of testing kits. I think we can also assume that there's a potential for a shortage of gloves. There's a potential for a shortage of swabs. All of the things that we tend to sort of take for granted quite frankly in the laboratory could suddenly become short supply.

I think we can also expect, at the same time, there's going to be a very high demand for diagnostic testing as the concern mounts and the virus arrives and the illness statistics mount. Pete mentioned earlier a continued need for the routine or the non-pandemic work. It's not like we can just stop doing everything else and focus on influenza. There are going to be all the other laboratory responsibilities still going on.

We can expect disruptions of the medical community as a whole. We mentioned staff earlier, but we can expect that, if there's going to be a significant influx of patients, you can expect that we're going to have other supply issues. We're going to have facilities issues that the community of healthcare as a whole is going to be disrupted. The community infrastructure that you work in, law enforcement, utilities, transportation is going to be disrupted. All of those things quite frankly that we take for granted on a day-to-day basis, there's a good chance that there will be some disruption due to staff shortages or supply shortages on down the line. Then, also, there's going to be a real possibility of high visibility for the laboratory.

Now moving on to slide 53, our idea over the next several slides to lessen the impact really is to develop a checklist for laboratories. Laboratories really need to start planning now, if they haven't already started planning, and they need to develop their continuity of operations plans. Many of the elements are included here. In terms of staffing shortages, on slide 53, you need to think in terms of what other options are there. Can you cross-train staff? Can you pull staff in from other areas to provide perhaps some pre-analytic/post-analytic specimen management responsibilities? Can you identify search testing laboratories? Who are they?

Do you think there will be any search testing laboratory capability in a pandemic? Do you have access to temporary employment agencies who may be able to help you out? Can you prioritize your testing, both influenza and non-influenza testing? At what point is a clinical diagnosis sufficient and in what cases is that sufficient, and maybe the lab testing isn't required? Are there staff capabilities where they're going to be expected to help out in other areas of your institution?

As Pete said, there are still going to be the other outbreaks occurring. Can you prioritize some of that testing? We mentioned the supply shortages. Obviously is there a possibility of developing stockpiles? Are there stockpiles already out there? Can you use multiple vendors? Are there buyer's groups you can take advantage of?

On slide 54, biosafety; by definition, the pandemic strain is going to be easily transmissible between people. So you're going to perhaps want to consider enhanced biosafety not because it's an exotic disease at that point, but because you really need to protect the staff that you have to be able to keep functioning. You're going to want to think in terms of a risk assessment and how best to enhance biosafety of the staff. Think in terms of developing additional protocols of, if you are going to have to change

perhaps your testing prioritization or your schedule and your capabilities change, how are you going to communicate that to your clients?

I mentioned earlier, when is clinical diagnosis sufficient? Specimen management, you're going to be presumably dealing with a large influx of specimens. What are the gaps in terms of your handling that that you need to identify and figure out? If you are going to refer specimens to the public health laboratory, who is going to be packaging them? Where are you going to get the supplies? How are you going to transport them?

Employee health is going to be an issue obviously in terms of staff shortage, but what do you know about vaccine availability for lab staff, antivirals, family health plans in terms of being able to cover ill family members, shift adjustments. Are there plans in terms of whether it would be acceptable for staff members to be staying home with ill family members? On top of it all, unless something changes, this is still a select agent, assuming that it's avian influenza that there are going to be additional documentation and compliance rules that we may need to comply with.

Moving on then to slide 55, again, part of the planning that you can start putting in place now; training and education. Who can you cross-train, your staff on test procedures? Are there other people to bring in? I mentioned that earlier. Can you develop accelerated training protocol so that, if there is a need, you can provide someone with explicit instructions and provide a shortened training period for them? Communications; you really need to integrate your lab planning with the institutional plans and work with your institution, your hospital to develop a prioritization plan so that everybody is on the same page. There really needs to be some real-time information sharing.

Slide 56, in summary, basically you need to develop that continuity of operations plan develop checklist. We don't need a lot of pros, but just a real bullet-point checklist of what you need to do. Practice; exercise either within your lab, within your institution, within your community. Just try to find out where the gaps are.

We mentioned supporting surveillance earlier, but two of the main points that I really, really want to mention is that you really need to integrate your plans with your institution; your institution needs to integrate within the community and so on and so forth. None of us is operating in a

vacuum. What our communities around us are going to be doing is certainly going to impact us, and we may be impacting them, so we really need to reaffirm those contacts. Public health laboratories really have to continue to accept responsibility for providing leadership in pandemic planning and laboratory planning and response. Now for the last word, I'm going to turn it back to Pete.

P. Schultz We've been building an emergency lab response network for bioterrorism, and the public health lab has taken the lead in each state. We now need to exercise what we've been building for the much greater risk of pandemic influenza. The fact is we have a window of opportunity, possibly a small one, but a window nevertheless, to make sure we can be as prepared as possible for the next pandemic. We need to take advantage of that opportunity. So I want to thank you all for your attention, and wish us all luck in the coming season. I'll turn this back to Denise now.

D. Korzeniowski Thank you, Pete and Carol. That was very informative. Operator, we now have time for questions. As we wait, I wanted to ask both of you; how close are we to a pandemic?

P. Schultz I think when you see the events unfolding in the Far East and you see the messages coming across World Health Organization and CDC, the threat is out there. I go back to the slide; is it imminent, are we overdue? I don't think we can say that, but I think the threat is there and it is serious enough that we have to get serious about strengthening our planning in response to the pandemic. It's kind of an evasive answer. We could be close, maybe not, but we need to prepare now regardless, even if we're preparing for something that won't, in fact, happen for another four or five years.

D. Korzeniowski Operator, do we have anybody with a question? While we're waiting, I do have another question. How do you go about identifying rapid test sites for surveillance?

C. Kirk This is Carol. I'll take that one. Actually there isn't one standard step one, step two, step three way to do that, in our opinion. What we did in Wisconsin to identify rapid test sites is we basically compiled lists of places that were interested in rapid test, whether through phone calls with us or attending workshops, etc. We did some word of mouth. We identified the larger labs in the state, called them up and asked them if they were doing rapid tests and if they knew others in the area that were

doing it, so they self-identified. We did mailings to those that we thought might be and allowed them to self identify.

Another option that we didn't take advantage of, but I think is a viable option, is identifying the sales reps and the manufacturers and asking them "Can you get lists of the laboratories in your state or take advantage of that situation?" But there really isn't one standard way. You really have to basically use a lot of different directions. Then what you find is laboratories start identifying other laboratories that might also want this information or want to participate.

D. Korzeniowski Operator, do we have any questions? Well, then I guess I'll ask another question. How do labs get involved in pandemic planning?

P. Schultz There are going to be different levels of pandemic planning and not just pandemic, any emergency response planning. In the clinical laboratory, you need to make sure that you plug into your institutional planning. We have found throughout many labs in Wisconsin that they really aren't plugged in to their institution's planning, so I think it is up to the laboratory director to kind of impose themselves.

I think public health laboratories are more apt to be engaged, just by the way that the pandemic plans are being set up, but then we have an opportunity there to reach out to the clinical lab partners and bring them into the planning process via that direction and then maybe they can take that part back to their institution and kind of drive it there. So there are several ways, and part of it is just making yourself available and forcing yourself essentially onto people who are responsible for the planning, because the laboratory is going to be a critical part to any response to any public health emergency.

D. Korzeniowski Operator, do we have any questions? If anybody can think of any questions, you can always e-mail your question to neoffice@nltn.org. The speakers will be happy to answer your question by e-mail.

Coordinator We have a question from Mike in Connecticut. Sir, your line is open.

D. Korzeniowski Okay, good. Mike.

Mike I actually have a couple, but I'll start with the one that I think is most pressing. I went to a meeting of Northeastern Epidemiologists a couple weeks ago and was told that there is very little genetic difference between

high-path and low-path H5. The question is the LRN test that's coming out, I was told by an LRN lab member, will distinguish between these two. So there's conflicting information. Veterinarians are saying it's not possible at the PCR level, and the guidance from the CDC says that it is.

P. Schultz I can address it insofar as I'm able. About the only thing, and this isn't going to offer you too much, is it's up to us when those issues come up to discuss this with the CDC. I know the CDC has had teleconferences, and APHL has periodically coordinated teleconferences. That's about the only way to resolve these. I don't have an insight or an answer for you, but I suspect that more than you may be running into this issue, so we need to talk to the CDC flu branch. I'm sorry; I didn't hear. Are you from a public health lab?

Mike Yes, I am, from the state of Connecticut.

P. Schultz Then engaging the APHL and perhaps posing that to the Infection Disease Committee and see if we can kind of pursue that with the CDC.

Mike Okay, and then I had one other question, which is the extent to which recombination is likely to affect drift or shift to sort of middle ground, and how do you think that's going to affect the molecular testing?

P. Schultz Again, I don't have a real good handle on that in terms of those molecular level questions. I think the people at the CDC or some of the current researchers are probably in a lot better position than I am to answer that.

Mike Okay, thanks.

Coordinator We have a question from Sandy in Georgia. Sir, your line is open.

S. Tarleton Hi. My name is Sandy Tarleton from Athens Regional in Athens, Georgia. I have a question on the use of prevalence in optimizing the rapid testing. Has there ever been or are there any suggestions on the prevalence of the disease in the oncoming of the season, also as the season is winding down, where you find that the use of the rapid testing is most optimized to get your best predictive value positive?

C. Kirk If I'm understanding your question correctly, what you're asking is: is there a point of prevalence where you really get your maximum predictive value positive.

S. Tarleton Right. Has that ever been looked at? I know it will differ for the sensitivity and specificity of your test kit. But if you were going to try to implement something using the prevalence data available on the CDC Web site, etc., would there be a suggestion for that prevalence that would probably make this a workable way to use the testing?

C. Kirk I don't think there is at this point. Really all you have is surrogates for prevalence out there. Whether you're using the ILI or laboratory test data, whatever you're using, it's a surrogate that you can use as an indicator that prevalence is low, prevalence is high or prevalence is increasing or decreasing. There isn't an absolute number that you can use.

We tried using some data as indicators, and we made a really complex calculation several years ago and found out that really you do just as well by looking at the graph and saying, "Okay, it's really low. It's really high. It's increasing, decreasing," and, therefore, your positive predictive value or predictive value positive would be low, would be high, would be

increasing to moderate levels, but we haven't found a way to define it and I haven't seen anybody else representing a real absolute number either.

S. Tarleton Okay, thanks.

C. Kirk Sorry to disappoint you. If you do come up with one, I think we'd all like to hear it.

S. Tarleton I'll work on that.

C. Kirk I'd appreciate it.

D. Korzeniowski Operator, we have time for one more question.

Coordinator This is from Rebecca in Hawaii. Ma'am, your line is open.

Rebecca This question is for Pete. Hi, Pete.

P. Schultz Hi, Becky.

Rebecca And for Carol. My number one question is regarding the biosafety. Because we don't have a biosafety level three enhanced lab, what do you think about testing a laboratory's specimen that has like a leaking specimen that is possibly contaminated? We have to strike a balance between loss of the surveillance data or loss of the specimen versus the safety of the employee. Which one do you do?

P. Schultz Becky, you faded out toward the end, but I definitely would choose the safety of the employee over the surveillance. I know there's been a big push for the public health labs now to rely on real-time PCR where we can do the preparation of those specimens, the processing and so on, in a biological safety cabinet and then safely do the testing. I know that's pretty much the method of choice for us now in Wisconsin for all of our surveillance.

Keep in mind this is going to be a real big issue. Currently right now, as we're looking for novel strains of influenza, it would be an issue probably early on after an emergence of a novel strain. But if the pandemic does occur, I suspect that issue is going to go away, because it is going to be a predominant virus there. I would suspect it's going to come back to

biosafety level two. Right now I think the best thing we can do is rely on the RTPCR, which inherently is going to be safer for our staff.

Rebecca Thank you. My second question is do you think there is a potential for sentinel laboratories to be performing the real-time PCR, so the impact on the public health in doing all this real-time PCR testing will be less?

P. Schultz There are private laboratories who are doing real-time PCR for influenza and other respiratory pathogens. It was kind of buried in one of Carol's slides, but I'm of the opinion that these tests have been sent out to the public health laboratory by CDC. If it were up to me, I would like to see that these methodologies also be translated out to the sentinel laboratories as well who are serious about developing these networks.

Again, this is my personal opinion to think we have to be serious that we're all doing the same testing, the same quality of testing and we have the same testing parameters, because from my perspective in managing our network in Wisconsin, I could do it a lot better if we were all doing the same testing. I think public health labs are in a position to be able to do this. I don't in any way see any threat to the public health laboratory. I think there's going to be plenty of testing for everybody. In fact, our basic

mission is going to be a bit different, either the patient care or our surveillance mission, and I think those can coexist.

Rebecca Thank you.

D. Korzeniowski I'm sorry. That's all the time we have for questions. If your question was not answered, please e-mail your question to neoffice@nltn.org, and the speakers will be happy to reply by e-mail.

Again, I'd like to remind all of the participants listening in to our program to register and complete an evaluation form by January 9th. The directions are on your confirmation letter and general handout. The Web site for it is www.cdc.gov/phtnonline, and the verification code is FLU. When you have completed the process, you will be able to print out your CEU certificate.

That concludes our program. We hope that you can join us for our next teleconference, "What's New in the 2006 Standards for Antimicrobial Susceptibility Testing: New Recommendations from the Clinical and Laboratory Standards Institute" on January 25th and repeated again on

January 26th. Janet Hindler is the speaker. For further details, please go to our Web site at www.nltn.org/courses.

The cosponsors of today's program would like to thank our speakers, Carol Kirk and Pete Schultz, for a very informative program and also thank you for joining us. I hope that all of you will consider joining us for future programs and that you will make the National Laboratory Training Network your choice for laboratory training. From the State Lab Institute in Boston, Massachusetts, this is Denise Korzeniowski. Good day.

Coordinator That does conclude our conference call for today. Thank you all for participating, and have a great day.