

**THE CENTER FOR STRATEGIC AND  
INTERNATIONAL STUDIES  
AND THE HOWARD HUGHES MEDICAL  
INSTITUTE**

**“AVIAN INFLUENZA: BREAKING NEWS AND PUBLIC  
HEALTH AND SURVEILLANCE READINESS”**

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**MARCH 23, 2006**

*Transcript by:  
Federal News Service  
Washington, D.C.*

ANNE SOLOMON: All right, ladies and gentlemen. Thank you for your patience. I'm Anne Solomon of the Center for Strategic and International Studies, and on behalf of the Howard Hughes Medical Institute and CSIS, I'd like to welcome you to this session on "Avian Influenza: Breaking News and Public Health and Surveillance Readiness." This is the first of a series of sessions we're going to have on infectious diseases here on Capitol Hill, and I hope you all will come to all of them. We'll send you notices.

Our first speaker and our moderator is Dr. Robert Lamb. Robert Lamb is a Howard Hughes Investigator and Professor of Molecular and Cellular Biology at Northwestern University. Dr. Lamb will be our first speaker and the moderator for the entire session.

ROBERT LAMB: Thank you, Anne, and good morning. So I'm just going to give a very brief introduction about some influenza to put things in perspective, so you can understand the other talks that follow. In terms of the influenza virus impacting the United States, we see annual epidemics where 10 percent, 20 percent of the U.S. whole population could be infected. We see the highest illness rates in children and the highest complication rates in the elderly, and an average of about 36,000 deaths a year, most of those, in fact, among the elderly. Now, of course, occasionally, there are pandemics, such as, in fact, the 1918 Spanish influenza virus that in the United States is thought to have killed over half a million people. And over 100,000 people died in the pandemics that occurred in 1957 and 1968.

There are actually three different influenza viruses, of really which only two concern us here, one being influenza A virus, the one that everybody's worried about, the one that keeps changing and the one in fact there are multiple subtypes. Influenza B virus, on the other hand, is not ignored. The influenza B virus causes infections particularly in those in confined situations like schools, prisons, nursing homes, et cetera. And in fact, of course, the influenza B virus in the vaccine for influenza virus, it is a component of the vaccine. But influenza A virus is what we need to be talking about today, and there is also different sub-types, of different spike-like proteins on the surface, of which there are 16 different possible hemagglutinin spikes that can be obtained and nine different neuraminidase spikes that are in fact found on these viruses. And in humans, currently, the viruses are known as H1N1 – which is the hemagglutinin of type one, neuraminidase type one – H3N2, and H1N2. Can you push the next one? It's the arrow.

Now, the influenza virus subtypes, they all of them, sixteen hemagglutinins and nine neuraminidases, exist in aquatic birds. And this is known as the reservoir where influenza virus resides all the time. And these viruses can be isolated from these aquatic birds. As we said, for humans, we only see in fact the H1, H2, and H3 subtypes and the N-1, N-2. We find the viruses in other animals such as pigs and seals, and the viruses – some of these viruses – have been found in horses. But it's the aquatic birds, in fact, that

give us the greatest concern, because this is where all these viruses reside, and most of the time, these viruses, in fact, do not cause an apparent infection in these birds.

But once a distinct type exists as a virus, whatever subtype it is, we see antigenic changes in those viruses, and we what is known as antigenic drift that occurs in the hemagglutinin and neuraminidase, and these are in fact point mutations. And they are associated with seasonal epidemics, and the continued development of new strains in response to immune selection. And in fact, influenza viruses change more quickly than influenza B viruses, as it happens. But the other type of antigenic variation that we know exists is antigenic shift, and that is associated with pandemics, when you get the appearance of novel influenza viruses bearing a new hemagglutinin – or that should say or neuraminidase. For instance, in fact that's exactly what we see with H5N1 – what we're talking about today.

And so this gives us some idea of the generation of a pandemic influenza virus, going from in this case aquatic birds through these avian viruses. Because the genomes of these viruses are segmented, we can get reassortants forming. Some of the avian viruses can go into pigs. It's not clear, in fact, how important this route really is. And in fact, sometimes the viruses can go straight, in fact, from domestic poultry into humans, and then the human viruses can go back to pigs and we end up with a cycle, in fact, where you can end up leading to generation of a new pandemic virus.

So in terms of the timeline of the emergence of influenza virus is what we now happened, of course, was in 1918 was the emergence of the so-called Spanish influenza virus with its devastating consequences. And then, in fact, from there in 1957, we saw the arrival of the H2 hemagglutinin and then in 1968, the arrival of H3. We've had a reappearance, in fact, of the H1 hemagglutinin, it appears, in the so-called Russian influenza viruses. How that arose is still not completely clear. And these viruses have been co-circulating – the H3 and the H1 – up until the present time, going through antigenic drift, accumulating point mutations, the reason that you need to be revaccinated every single year because of those mutations that arise. And then, since 1997, we've seen various avian viruses appear, particularly the H5 virus, which we're concerned about because of its extremely high pathogenicity in birds, particularly domestic poultry, that hasn't been seen with most of the other avian viruses. But there's also – it should not be forgotten – H-9 viruses and H-7 viruses that came from avian species, which also in fact on occasion transfer over to humans.

So it's these viruses we're going to be focusing on today, but this puts it into perspective. And to really put this in perspective, Dr. Taubenberger is going to actually talk about the 1918 virus. And if I could have the next slide. In fact, these are newspaper headlines that in fact we've gained, because in fact this year – last year and this year – in fact, 1918 influenza virus has been reconstructed using sophisticated biotechnology, so that in fact this virus, in fact, we now have the virus. It's kept under high containment, so that in fact it can be studied so we can try and understand why this virus was so virulent, and why in fact it killed so many people in comparison to other influenza viruses. So with that I'd like to ask Dr. Taubenberger to come and tell us about his studies on 1918.

It was Dr. Taubenberger who is the person, in fact, who obtained all of the sequences of 1918 from various material that, in fact, enabled him to then the virus to be reconstructed from those nucleotide sequences.

DR. JEFFERY TAUBENBERGER: Thank you very much. I'm going to talk briefly about the 1918 virus, but make some comparisons between what we saw in 1918 and what we might be seeing now with H5 and what the future may portend. The next slide, please?

So as Dr. Lamb said, it's influenza A viruses that we're really concerned about, and it's an important pathogen every single year with the emergence of these drifted strains and having to make the vaccine every year to keep up with that. But what concerns everyone are the emergence of these pandemic strains, which are new influenza A subtypes that can spread rapidly in humans, and we know in the last 100 years, there have been three such pandemics. As was alluded, the 1918 virus was an H1N1 virus subtype, the 1957 H2N2, and 1968 H3N2. But actually, what we now know is that the 1918 virus actually is in a sense the direct ancestor of all subsequent human influenza viruses, even though that acquired some new genes from avian viruses in 1957 and '68. The core of that virus is still derived from 1918. So in a sense, 1918 is really the mother of all pandemics that we know about now.

I think if we take everything that we know about influenza biology now – let me rephrase that – this panel, if I take everything I know about influenza biology now and formulate a model of the next pandemic – next slide, please – it would be this. And I think let's break this model down. (Chuckles.) But other than this, I think we know a lot. I mean, this is really the frustrating problem is that you have quote-unquote “a very simple virus” and yet the biology of this system in its complex ecosystem is incredibly complicated, and we really don't understand a lot about influenza virus biology. That is, we know ultimately that aquatic birds and other birds are likely to be the natural reservoir, whether we know what the extent of that natural reservoir is. We don't know how they move around and adapt and evolve in their wild animal hosts. We don't know how they get into domestic animals like domestic poultry – chickens, turkeys, quail – or domestic mammals like pigs and horses and humans. We know that it happens, but we don't know how it happens. We can't predict how it's going to happen. And what we can say, if you saw the mortality from the last slide, is that pandemics are quite variable. 1918 was this horrible pandemic. Nineteen-sixty-eight was a relatively mild pandemic. And we don't understand the differences necessarily that led to that. We don't understand the genetic basis of why one virus is more virulent in one particular host than another. So there are a lot of things that we still don't know.

So ultimately – is there a pointer here? So we know that influenza viruses in wild birds tend to be GI viruses and they tend to be respiratory viruses in mammals, and so for me, really, the big question is how you go from here to here. And that's - so from the rear end of a duck to the nose of a human – and that's the question. So we know that it happens occasionally, but we don't exactly know how it happens. And that's the question. So the question is – next slide, please – can we work out in a sense some of the

common rules that would allow this to happen? We're using 1918 just as one additional model to try to understand this basis. Are there – even though pandemics are quite variable in their presentation and emergence – are there some commonalities that would allow us to understand some of the underlying ground rules of what would it take for an influenza virus adapted to life in a duck to become an influenza virus of a human?

We know that the 1957 and '68 viruses were reassortants, as Dr. Lamb said, in which a human-adapted virus acquired a couple genes – two or three genes – from a bird virus, and this mixed virus gave it everything it needed. It was human adapted, and yet it had a novel hemagglutinin and/or neuraminidase subtype that allowed it to spread in the population. So what about 1918? Let me just give you some brief history. The 1918 flu started spreading in the spring of 1918, expanded through the summer, especially in Europe, and then exploded into a major global pandemic in the autumn of 1918 in the northern hemisphere, in the spring, of course, in the southern hemisphere. We think that now the total mortality during the span of the pandemic was about 40 or 50 million people, that in the U.S. it was a little under 700,000 – or about 550,000 excess mortality. So to put that in perspective, a city like Philadelphia lost 16,000 people of which 11,000 died in the month of October. The U.S. military had an incredible casualty rate to flu. So of about 100,000 U.S. soldiers that died of all possible causes in World War I, over 40,000 of them died of flu. So these were young, healthy 18-25-year old men who dropped dead of this virus.

So the impact of 1918 is quite profound. If you look at life expectancy plotted from 1900 to 1960, we see a linear increase in life expectancy except in 1918 where you have about a ten- to twelve-year drop, all because of the flu. Next? And the reason for that is this unusual age-adjusted mortality in 1918, where influenza viruses before 1918 and subsequently, while they infect all ages of the population, tend to have lethal outcomes historically in infants and then importantly in the elderly. But in 1918, there was this new peak of mortality in quote-unquote “young, healthy adults.” And we do not understand the biological basis for this observation. It's clearly something that was unique about the 1918 virus or at least the interaction of the 1918 virus and people of this age group. And until we can understand the biology behind it, it's hard to know what the lessons that we should draw from this are. Was this something that was so unusual or so unique that it happened in 1918, but it won't ever happen again, or is this a characteristic of the virus that could be replicated in a future pandemic. And the answer is that we don't know. Next.

So the big questions are why was the 1918 so pathogenic and where did it come from? In this brief talk, I'm really going to touch briefly on the where did it come from, and then talk about one example of the future. So we now think, having sequenced the whole virus that it was unlikely or less likely to be a reassortant virus than the other two pandemics, and more likely to be a virus in which all of the gene segments were novel to humans before 1918. We think that in each case, it looks like an avian-like virus. We still don't know what the host was. We don't know if it went through an intermediate host before emerging in humans. We don't know how long this process took. We don't

understand all the genetic changes that had to occur to allow this to happen. But we know that it did happen. Next.

So if you look at the relationship of the 1918 virus to other influenza viruses, what you see is that the 1918 – this is sort of a family tree of influenza viruses, or at least one gene of them, and here are a bunch of bird viruses and here is the 1918 virus coming off as very close to the ancestor of classical swine H-1 viruses and subsequent human viruses to the present time.

So we think that the 1918 virus was derived from an avian-like source, but we don't know what that source was. We know that it got into humans at least by March of 1918, probably earlier. We don't know how much earlier. We don't know how long this process took. We don't know what the host was.

Next.

So using the information about 1918 and other pandemics that we have, can we model which genetic changes are necessary to allow a virus to jump hosts – go from a bird to a mammalian source? And I'm just going to talk about one specific example for the rest of the talk, which is changes in the receptor specificity of the hemagglutinin – the major surface protein on the surface of the virus that Dr. Lamb mentioned.

So the hemagglutinin bonds to sugar molecules on the target cells that it wants to infect in the form of the sugar that typical bird viruses bind on duck intestinal cells is subtly different from the sort of sugar that human viruses bind on the respiratory cells. And so it's thought that changes in this receptor-binding site are going to be important in this process of jumping between hosts.

Next.

So these are little sugars that are on the tips of glycoproteins that stick out from the membrane of the cell that the virus wants to infect. And as I said, the form of the sugar is subtly different between the, quote, unquote, "human" form and the, quote, unquote, "bird" form, although it's clearly emerging that it's much more complicated than this simple switch. But it's hypothesized that mutations in hemagglutinin at the receptor site are going to be critical in this process of adaptation.

Next.

So this is what a hemagglutinin protein looks like. This is actually the structural model of the 1918 hemagglutinin as crystallized in Wilson and colleagues at Scripps, and this is the part that sticks up away from the virus and this little pocket here is the receptor site, and this sort of head region is also the area that antibodies bind to when you recognize and fight off a flu infection, and this is where the predominant changes are that occur year to year in the mutation of the virus. But we're going to be thinking about the receptor-binding region right here.

Next.

And in a really wonderful technological development that my colleagues at Scripps, Jim Paulson and Ian Wilson's lab have developed is an array that places sugars of known structure on a glass slide, and you can bind the hemagglutinin proteins to them of different influenza viruses and see which kinds of sugars they bind to. Do they bind to the avian form or the human form, and particularly which kind?

And if you put a human adaptive virus on, it binds to sugars that end in a sialic acid linked to galactose with an alpha-6 bond. And it's not important to understand that. This is sort of the human form, and this is what a typical human binding pattern would look like. This turns out to be one of the 1918 viral hemagglutinins isolated from a person who died in South Carolina in September 1918. And this virus only binds to the, quote, unquote "human" form of the receptor.

Next slide.

Interestingly, and really curiously, a hemagglutinin sequence from a person who died of flu on the very same day, September of 1918 in New York, has a hemagglutinin structure that differs by a single amino acid in the receptor site, and that change, which has only one change from the avian form rather than two, actually doesn't bind the human form of the receptor very well at all – still binds the bird form better – but it has a blended specificity; it binds both the human form and the bird form. And since two of the five hemagglutinin sequences from 1918 that we know of have this structure, it suggests that this single amino acid change in this minimal binding to the human form was clearly enough to allow this virus to be transmitted efficiently human to human.

Next.

If you then mutate this to a form that was not seen in nature in which we changed that single amino acid back to the bird form, what you get is a classic binding of a typical bird virus that binds massively to the bird form of the receptor and not to the human form.

Next.

Now, if you go the other way around, if you take a typical low-pathogenic H1 subtype wild bird virus, hemagglutinin, and you put in just those two mutations in hemagglutinin, it converts itself completely to the human form. It only binds the human form and the receptor and not the bird form. So clearly for H1, those two mutations are all that's necessary.

Next.

So what about H5? The H5 structure turns out to be quite similar to H1. H5 and H-1 are more related to each other than they are, say, to the H3 subtype hemoglutin. And if you look at the binding of, in this case, one of the highly pathogenic human isolates from Vietnam from 2004, you can see that it binds predominantly to the bird form of the receptor and it binds to one sugar in the, quote, unquote, “human” category, but the sugar chemists tell me that this sugar is not known to be expressed in epithelial cells; it’s only present in milk, so it’s probably not a native receptor for the virus.

Next.

The structure would suggest, being so similar to the 1918 H1, that the same mutations that allowed H1 in 1918 to go from the bird to the human form would work for H5. Those mutations have not been found in any isolates that we know of, but we made this mutation – and here is the – to remind you, the H1 bird virus with those two mutations which no longer binds the bird receptor and only binds the human receptor. If you make those two changes on the this H5 virus, it actually no longer binds anything on the array, completely destroys the ability of the receptor to recognize sugars – next – which was a very curious finding.

Now, the H3 subtype hemoglutin that caused the pandemic in 1968 also had two amino acid mutations in a receptor from the typical bird form. So the next question was to look at if we acquired these so-called H5 mutations; that is, the two changes that would allow H3 to go from bird to human in H5. And if you make one of those changes, again, it destroys receptor binding. If you make another single change, it doesn’t decrease binding to the bird form, but it does increase binding for the human form for two peculiar sugars within the human form. And if you make both changes, as occurred in 1968, you get a virus shown here bigger with the hemoglutin specificity that it has reduced binding to the bird form, and now – a significant finding – to two particular sugars in the human class. Whether these sugars are actually expressed in reasonable amounts on different respiratory cells in the respiratory tree of humans is unknown, but this suggests at least a pathway, something like the New York forms of the 1918 virus in which you have a blended specificity to allow it at least a foothold into the human population.

Next.

So in summary, looking at a bunch of different experiments, if you just look at the Vietnam 1203 normal isolate here, the receptor site, it binds the bird form very well and not much to the human form.

Next. Okay, next.

Here is a natural variant of H5s that have had an amino acid change in the receptor site that has been seen in several reported H5 isolates of the last couple of years, which you have a single amino acid change in between those two amino acids I just described, 227, and it does not change its receptor pattern in this assay system, that it does not have enhanced binding to the human form.

Next.

But the one that has the two changes to 226, 228 decreases binding to the human form and increases binding to the human form – decreases bird binding and increases human binding.

Next.

So in summary, it looks like that it's not as simple to convert an H5 avian virus to the human form of the receptor as it was for H1, 2 and 3 subtypes. But there is a window, it looks like, at least experimentally, in which a virus that acquired the two mutations that H3 viruses had could bind to some, quote, unquote "human" forms of the sugars. Although the situation of course is much more complicated because this quote, unquote "bird" form of the receptor is also – the bird-form sugars are also present on cells lining the respiratory tree, and I think it's not just a plus-minus switch – bird form to human form; you have viruses that bind all the way in between, that mainly bind bird viruses and a little bit to the human form and vice versa. And we don't really understand the significance of where you are in that setting. And it's probably not clearly just changes in hemagglutinin that are important for this process of human adaptation and transmissibility, but this is probably just one of the important factors.

Next.

So my last slide is just that implications of the kind of work that's been done is that we think that the formation of the 1918 virus was different from the other pandemics that we know about – the '57 and '68. We think that it's more likely that being a human avian reassortment it was more likely an entirely novel virus derived from an avian-like source. And we think that this information can help us model the genetic basis of influenza virulence, which I haven't had a chance to talk about, and also model the genetic basis of human adaptation and so have some implications.

I think that's my last line. Yes, thanks.

DR. LAMB: Well, thank you, Jeffery. (Inaudible) – David Nabarro, a coordinator for the United Nations on avian and human influenza virus.

DR. DAVID NABARRO: Well, a really very good morning to everybody from me, and also from a colleague who I brought with me who also works in the U.N. – Peter Scott-Bowden, who is sitting just close to the camera there. We are both really pleased to be with you today. It's a very important gathering for us and also of course an important subject. In just checking, first of all, can you hear me clearly from wherever you are? Yes? And can you see this to some extent? I'm just checking font size and visibility, all that.

Right. I've got about 20 minutes on the timetable to just try to bring you up to date with where we stand in terms of dealing with the avian influenza epizootic and preparing for the next human pandemic from a global perspective. And I'm going to do it myself if that's all right by you, because you did a really good thing, which I was trying to send you a nonverbal message to do, which was to turn to the computer around, and you received my message.

So H5N1 in birds, revisionist, is an epizootic that's moving rapidly across the world and it has the potential – but I think, listening to Professor Taubenberger – potentially still a little bit undefined to itself become the cause of the next influenza pandemic. But if it's not H5N1, it could well be another influenza virus.

But the extraordinary thing about H5N1 is it's a very virulent and horrible virus. It has also moved into 20 countries during the last six weeks. And I just checked the reports this morning. Overnight we've got reports of it moving into the Gaza Strip and also being found in settlements in the West Bank. In fact, each day there is a new country or a new location. I would have, had we not had such an excellent start up, reminded you about the differences between seasonal influenza, avian influenza, and pandemic influenza, but instead what I want to do is to focus on the reason why this all matters, and first of all, let's just look at the avian influenza epizootic. It's not a trivial problem. A hundred and fifty million dead poultry from disease and control is probably an underestimate. The economic consequences may be at least \$10 billion for the poultry industry, but also remember that for poor people, a chicken is a really good short-term savings account. And all of us who've worked in poor communities know that poor people are using their chickens as a hedge against a rainy day, when a child is sick or whatever.

And there have been these sporadic human cases – obviously some are very well known; the large number of human cases and deaths in Vietnam – but we've been seeing extraordinary things in Egypt over the last few days, in Azerbaijan, and in Iraq. And there is mounting public concern about what this all means and then what might be the impact of the next human pandemic. It's a local phenomenon with global implications, whether it's a small, isolated cluster of human cases that's contained or a major pandemic. Just think of what SARS did – a well-controlled epidemic of a viral disease, less than 1,000 people died, five countries affected, but conservatively estimated at \$50 billion worth of economic costs. A pandemic will cause loss of life, but also short-term absenteeism.

An analysis by the International Monetary Fund that's just been released suggests that there will be disrupted supplies and also reduced demand, and probably threats to rule of law, security, and the continuity of governance in some locations – i.e., it's not just the health impact that concerns governments; it's the broader impact.

Now, let's just look at H5N1 – moving through June to December 2004, an Asian phenomenon; by December 2005, and then into March 2006, stretching out and moving into Eastern Europe and Africa. And this is out of date, as you can tell. It's gone further

than that, so that during the last eight months it really has shifted, and we keep a regular map that's produced for the U.N. by the World Food Program, who know how to do maps, and that looks awful on the screen. But if you go into the various websites that exist and stumble across this website, which is in the World Food Program's collection of pages, it's most the extraordinarily regularly updated chronicle of how this problem has extended across the world and is now a very profound issue for African countries.

I returned yesterday morning from Gabon where we had 40 countries come together and focus on what's going on. I spent time with the colleagues from the presidential office that's tracking issues in Nigeria, where it's moved into Ogun State and is now going to Lagos. It's in the commercial poultry sector but in some places – in a number, for example, moving into the backyard. Eleven states affected out of, I think, 36 in Nigeria but moving on to probably – it was 11 confirmed when I was in West Africa, and we suspect it will move to many more. So we've got Nigeria badly affected, Niger, Cameroon – Eritrea recently reporting H5, and other African countries declaring.

The Western European problem is well known. Indonesia – weekly reports of death and a very complex situation. India, we've still got new outbreaks being reported at intervals. Afghanistan – I was talking to our United Nations coordinator in Afghanistan; a major problem in that country. Azerbaijan and Armenia you know about. Southern Russia – huge bird die-offs recently. In fact, it's a kind of really continuously spreading phenomenon right across the world.

And you know as well as I do that we have to treat this as a potential candidate for pandemic influenza even if we don't have certainty. And I was very interested – Jeffery did point out – that there are so many unknowns. I think given the unknowns, the right solution for all of us is to be prepared rather than to be standing back and saying, well, we don't believe it but we may want to discuss that a bit during the session after I've finished. And for the WHO, the World Health Organization, we're in pandemic alert phase three: heavy infections with a new virus but no, or very infrequent, human-to-human spread. But that, says the World Health Organization, that's the time to get prepared because once you move into phase four or phase five or phase six, you can't prepare anymore; you've got to get going.

So how are countries preparing for a potential pandemic? First of all, they've got to have scenarios. What – (cell phone rings) – oh, sorry about this. This is a mistake by me. I've got a very nice ring tone – new ring tone. (Laughter.) I just tried it out. Shall I take the battery out because I don't know how to switch this phone off? Done.

So three pandemic scenarios. Scenario one is that things continue as they are, possibly for years with bird flu widespread in many countries in the world, sporadic human cases like we've got right now, and enormous impact on the livelihoods of poor people and others due to the killing of birds or loss of employment in the poultry industry.

The second model is looking more at the '50s and '60s case of a moderate and perhaps localized pandemic. We've managed to get good-quality containment capacity throughout the world. We've put on the fire blanket. We limit the pandemic. The third model is a more widespread, high-impact pandemic; the worst-case scenario perhaps more like 1918 or worse. And what we need to do, I believe, is to be encouraging colleagues to be able to deal with these variations on this scenario because they have different implications for how governments work. But whether we are talking big or small, a pandemic has an impact that goes beyond human health. Remember the impact that I've already described on livelihoods, and my colleagues in the Food and Agriculture Organization are telling me of significant increased vulnerabilities as a result of poultry losses.

I think we need to recognize that a pandemic does impact on rule of law and governance. We don't want to be sensationalist, but the truth is that even SARS had an impact on the position of governments, the credibility of governments, and certainly a pandemic in a country that's affected by instability will have considerable impact on the capacity of whatever law-maintaining authorities we have in place to do their job.

Pandemics will increase humanitarian needs and organizations like the World Food Program, United Nations Children's Fund, and nongovernmental groups like World Vision, represented in this room today by Dr. Anne Peterson, they will be playing a major role in trying to ensure that humanitarian response is adequate. And as I've already mentioned, economic systems need attention.

Briefly now into the response. There has been a strategic approach developed really since November last year, brought to the table very much by U.S. government institutions: your Department of Agriculture, your Centers for Disease Control, your Department of Health and Human Services, of which that is part, and others, bringing to the table to the international community the importance of a strategic approach that starts by working on the animal disease, stamping it out at the place where the infection occurs, and then at the same time seeks to prevent the emergence of a pandemic by limiting human exposure to H5N1 and other viruses, containing the pandemic when it starts, and mitigating its consequences.

These few words on this slide which I've just gone through are the result of considerable global thinking in which you collectively have had a major involvement and where I think we've got more understanding of what we've got to do in a relatively small number of weeks than we've had in many other infectious conditions.

Now, what we've also got is understanding of what needs to be done. I'm just giving you sort of headlines because I think you know most of this. At the center is an information campaign, a global information campaign, through which ordinary people – men, women and particularly children – know how to reduce the risks that they face. We've got still too many people getting sick with bird flu at the moment because they're playing with dying or dead birds or trying to even just to look after them and to recover them, but more often than not, they're just simply wandering around with them and

giving themselves huge infective doses of virus that makes them sick. And that should not be happening because we should be able to inform people about how to avoid it.

We need better warning of disease in birds and veterinary services, an area that's been neglected for the last 30 years, prompt detection, containment and management of human cases when they occur. Well, that makes sense but we've got to improve our capacity to do this. This bird flu is not going to go away in a hurry and we're going to get human cases for some months to come.

To move forward – it was clear from the earlier presentation – you can't understand what's going on without the viruses, and so we need international biomedical cooperation of a very high standard and nobody hiding viruses away in refrigerators or giving them to their own manufacturers of new diagnostics and other devices. They've got to be global public goods and transparency on what's going on in countries. We've seen an increase in transparency since we've started moving hard on this issue in October last year – again, as an initiative from your State Department and the International Partnership on Avian and Pandemic Influenza, but more is needed.

There are big issues around stocks of human antiviral medicines, particularly oseltamivir or Tamiflu, on consumables like masks and protective equipment, and on whether or not we will have vaccines available quickly, particularly for poor countries, and whether we will have the supply system to get them in place. The United Nations is working with governments to get that right, but it's still – these are not straightforward issues. There is a lot of strains in this work to what we've had on AIDS medicines, and we've got to get it right.

To get effective action at the local level, joined-up government that brings together health, agriculture, interior, trade, finance and ensures that all bits of government are working together is key, together with effective private sector partnerships, involvement of the nonprofit organizations with the media inside the tent working with us rather than outside the tent asking us what we're up to. That doesn't mean we shouldn't be subject to critiquing, but the media are part of the response, and an important part as well.

When pandemic does start, the crisis response capacity that's going to be required will be extraordinary, and it's where civil military cooperation will be key. We've got a lot of experience from the tsunami of completely new styles of civil-military working. That's been taken forward in the Pakistan response, but we will need to go back to learn lessons from tsunami work when we apply it pandemic, and that's already going on through the U.S. government taking the leadership role with specific command, working with the U.N., working with the non-governmental groups and others.

And I put it last, but it's almost the most important: The poultry sector is not yet right. It's not being run right. The health issues in the poultry sector need a lot of attention. Big consuming companies like Yum! Brands, who own Kentucky Fried Chicken, or McDonald's want to see better health inside the poultry sector, and making

sure that all commercial producers respect the World Organization for Animal Health Standards for good quality. They also want to see veterinary systems in all countries upgraded – so not just the poultry sector but all animal sectors where there is a juxtaposition of issues between the wild, the domestic and the commercial brought up to scratch. Because, as CDC have pointed out through work by Lonnie King and others, between 60 and 70 percent of emerging new infections are going to come from the animal kingdom, and we've got to be looking out for them.

So a range of interventions is necessary that involve animal health, human health, economics, governance and humanitarian action, joined up between government, private sector, military and civil society. It is starting to work, and perhaps we feel that we've been able to have something to do with that within the United Nations because we've been working together like we never have done before.

Now, there is financial and other support available. It's not straightforward; it's what I call multi-pathway financing. Governments came together in Beijing and pledged a lot of valuable technical and financial assistance, but unlocking that money and getting it to countries like Niger or Nigeria or Egypt or Azerbaijan, all of which actually need cash quite badly at the moment – linking the money sources and the consumers together is getting to be quite tricky. And that's simply because the sort of things we're trying to do in countries in terms of building up veterinary capacity or improving public health isn't easily done just with a check; it requires a lot of hand holding, support, technical assistance, and the countries themselves understand that.

I was talking with colleagues – the minister from the prime minister's office from Cameroon the day before yesterday, and they are well aware that it needs technical support, operational assistance of the kind that we've had to do on HIV, working with countries, and we've had to do inside our own countries. But we're having to do it a lot faster because, frankly, this issue is moving much, much more quickly than most other issues we've had to deal with in public health. And so my own group is currently focused on how to bridge the gap between need and supply when it comes to finance and technical assistance. And I pay enormous tribute here to the work of the CDC and the support that's been provided to countries by the U.S. Agency for International Development. It may not be a fashionable thing to say, but these two organizations working together and working separately have done an enormous amount to make a difference. My travels to Nigeria two weeks ago, working with the government, working with CDC, seeing how they've brought real-time PCR – polymerase chain reaction – assays into making sure that the tracking of human and animal avian influenza is of the standard that the Nigerians want. This has been superb technical cooperation. Let there be more.

But we also need to work with governments on their national plans on whether or not they've got ongoing processes in countries that are going to keep these problems under control, high-level inter-ministerial direction, committees, risk analysis going on in the country, and then good strategy and actions that bring together the best of communications, animal health, human health and pandemic health with community

engagement. For some countries that's been difficult, but in my conversations with the president of Ukraine less than a month ago – I was sitting in a country that perhaps in the past hasn't been known for this, and him describing how, with communities in Crimea, he himself, with his government, has been engaging with them in open dialogue. It's very difficult if you're a small-scale poultry farmer, having to kill all your chickens not knowing when you're going to restock to be able to simply expect that you're going to get a compensation at a dollar a bird and that's it. I mean, it's great if they've got the compensation, but the issues are absolutely awful for these small businesses who've often struggled from next to nothing. At the same time – again, as the president said – the importance is to be able to know when you're going into crisis mode and having the right way to do it.

Coordination is my job, my team's job, and we're making sure that the coordination is the best we can do at country level between our different agencies and globally. And perhaps just to tell you that this is not straightforward; it requires being sure that we've got the right international partnerships that work, building on what you've done from the United – (audio break, tape change) – like we discussed earlier this week in Gabon, so that we can get samples to where they're needed, or like the environment program which looks after the wetlands, or the U.N. World Tourism Organization to try to make sure that the travel and tourism industry reacts in the sensible way to the threats of influenza and doesn't suddenly close down and cause billions of dollars worth of damage.

I think I've probably given you as much as I can usefully do in this event except just to give you my six outstanding priorities that I'm worrying about and one or two other points that relate to them, depending on whether I'm going to be cut off by our moderator.

My six priorities are Africa – what are the risks going on in Africa for African nations as a result of the move of avian influenza into that continent a month ago? Well, actually it was several months ago but it was detected a month ago. What is the information that's reaching different audiences so that they don't do wrong things but they do right things so that poultry are not needlessly killed, so that the poultry industry is not destroyed, but at the same time so that everybody does know what they can do to reduce the risk? How are we going to maintain animal health in an environment where vet services have not frankly been the top of the national priority for investment in most of the world's countries in recent years? How to revitalize public health, which we all know – that's why we're here today – has often been neglected? How to ensure that when the pandemic comes along, economies, governance, society, our whole humanitarian environment works efficiently? And perhaps, importantly, given the way you're focusing this discussion, how to harmonize the production of vaccines and diagnostics so that the world's science, the world's production capacity, and the world's governments come together in the kind of thing that those antitrust legislators don't really like very much, in ways that get the goods produced quickly, in an economic way, and made available to the people who need them without driving down the cost so much that it destroys the markets and the productive capacity?

The communications issues are monster, but they're not impossible, and together with a number of commercial groups, UNICEF have been helping us to get a "birdwise" campaign going and active at country level. But we've also got to do a streetwise hygiene campaign that focuses on four key message in relation to hygiene. Just to stimulate some of the discussion – though I'm not sure it needs it – should we be scared? There was an article in the Christian Science Monitor this week that says perhaps it's all being overplayed; perhaps there are some of us who are trying to scare too much. Well, personally, I don't know whether to be scared, and I don't think anybody knows, because I don't know what the risks are; I just know they exist. And I think that the worst that we can do, those of us working in public health with an issue like this, is to withhold information. I mean, governments get into trouble. Azerbaijan had difficulties. They didn't know how to handle what was going on.

Also, if you don't engage communities, then they themselves can't make judgments. So what we're trying to do is to encourage responsible responses by governments, involve the media, and work for global action that harnesses the energies of multiple actors, and encouraging leadership that brings in different communities, creates coalitions to give a response. And in the process there will be fear, but there will also be the beginnings of confidence, and it's confidence that will be useful, not just for an influenza pandemic, but for other pandemics. We are very vulnerable, and so what should I as an individual do? Any of us? Work through the issues as best we can, discussing them. I think it's right that people all over this country, encouraged by Michael Leavitt and Julie Gerberding and others, are discussing these issues.

There is a program on National Public Television, or whatever – "The Charlie Rose Show" yesterday – and I was very interested in some of the ways in which Julie Gerberding and Michael Leavitt were talking through the issues, talking to the American public, knowing that there would be some fear, but at the same time trying to help them work through what this means.

Remember that frontline public health and security personnel are going to be those on whom we depend. Protect the Tamiflu and other gear for them. They matter. We've got to know where we are going to be during a pandemic. Are we going to be at home? Are we going to be moving to hospitals, are we going to be trying to find refugees? Most of us, I think, feel that it's best to be preparing to hunker down and sustaining our own capacity to respond, but there is no doubt now is the time to get ready.

Thank you very much, indeed.

DR. LAMB: Well, thank you very much. We're now going to actually take questions from the floor.

Q: Yes, I have one question for Dr. Nabarro and one for Dr. Taubenberger.

Dr. Nabarro, there has been a lot of talk for many, many, many months about the critical need for funding to pay appropriate compensation to the owners of sick birds so they'll be willing to report it and turn them in, and yet we've heard rumors that that money is not forthcoming, with people pointing at each other and saying, oh, it's the World Bank that should do this. Where do we stand with regard to the availability of money to pay the compensation to the farmers for their dead birds so they will report these outbreaks?

DR. NABARRO: I think the first step on compensation is the government itself, working with local communities, has to decide on the best way to compensate. In Nigeria, for example, government has some understanding of who owns poultry flocks with between 250 and a million birds in the flock, but they have no understanding at all of who owns the small poultry flocks. So it's extremely hard to run a compensation scheme when you don't have basic information about where the birds are that are either likely to have died or been killed. The possibility for fraud or for underpayment is very great.

Therefore, for the larger poultry flocks, a government-run compensation scheme is reasonable. For the smaller poultry flocks, it probably has to be done by community groups being given some resources and then themselves deciding how those resources should be distributed to the people. Such schemes are being developed in Nigeria and in other African countries as we speak. The resources for them initially must come from the national government. It's no good the government saying we can't do anything until the donor gives us money, but at the same time, once the government has started the scheme and has shown that it's got the mechanisms to ensure that there is not widespread fraud or misuse of the compensation monies, then there are resources available to borrow from the World Bank at very low interest, and there are also resources that are going to be available from the international community, probably a little slower to come onstream; we're probably waiting another month.

But I would not want people to say this is not working at all. I think much more difficult is getting the resources to build up laboratory capacity in some African nations, and also to do assistance with pandemic preparedness planning and the like, and that's simply difficult because it takes time to go through the necessary project appraisal procedures for these kinds of activities, and one of my – I did say it in my presentation but I'll give you more detail now – I'm working personally very intensively with the World Bank, with the major donors, to try to make sure that if there are shortcuts that we can put in place without endangering the security of taxpayers' money, we do just that.

But thank you for your concern, and if you have a professional involvement in this, could you please give me your visiting card before I leave so that we can keep in email contact?

Q: My question for Dr. Taubenberger touches on something you didn't have time to explore in your talk, which is the determinant of pathogenicity. My understanding is that the case fatality rate of the 1918 virus in humans was something like 3 percent, and

yet when you took the reconstituted virus and put it into mice it was like 100 percent lethal. And now we have this circulating in the world that's like 50 percent lethal in humans and 100 percent lethal in poultry, let's say, but not in all poultry, and some are just asymptomatic when they're affected. How will we go about understanding these differences so that we can have some idea of whether we're going to be facing a 3-percent problem or a 100-percent problem in terms of lethality?

DR. TAUBENBERGER: Thank you for the question and the opportunity to talk about things that I didn't have time to talk about in the talk. You bring up excellent points, and I think the best answer, unfortunately, is that we don't understand at all yet what all the determinants are that makes one particular virus behave in a way differently from another virus in a particular host.

So I think it's too simplistic to take models done in the experimental setting in a live animal like a mouse and say, here is a result that we can relate directly to what happened in humans in 1918. Clearly the basis of infection is different, the dose is different, the species is different. And as you say, even incredibly pathogenic viruses like the current H5 viruses that can kill 100 percent of certain species of birds, can cause asymptomatic infections in other species of birds. So there is nothing different in the virus. The virus is genetically identical. So clearly the entire difference is in the response of the host.

So disease really is absolutely a two-way street. It's the interaction of the particular pathogen and the host. And so what happened in 1918 is still unclear. As you said, the case fatality rate in the U.S. was around 2 ½ percent, so I'll point out that contrary to that – so that means that 97 ½ percent of the people who got ill in 1918 got better with no vaccines, no antivirals, no antibiotics, nothing – maybe some aspirin. And so clearly while this is, as far as we know, the worst pandemic on record, and 2 ½ percent case fatality is a terrible rate and horrible for flu, it still means that while the virus was probably identical, or close to identical from person to person, that the response was quite different.

So I think the big questions are to understand specifically why in 1918 did you get this big bump of mortality in young, healthy adults? Was it innate to the virus? Was it a theory that's been as old as the 1940s, that this was an over-robust immune response in the people who were in the prime of life to this virus, and that the over-robust immune response itself was a component of the pathogenicity? Was it, alternatively, that these people at that time in that age group had a very unusual immune response, perhaps based on prior exposure to viruses in the past – when they were children, for example – that led to this unusual response and we just can't distinguish those?

So right now, for example, the H5, as was alluded to by Dr. Nabarro, that there have – most of these cases have been in younger-age populations, and I've seen in the press a lot of links between that and 1918, that somehow there is a correlated pathogenicity there. But is it that that reflects the demographics of those populations? Is it that it reflects that children are interacting with these chickens and that it's not a

biological phenomenon but a behavioral one, in a sense? But we don't know. In both cases there is experimental evidence to say, with the H5 – some H5 viruses and with the 1918 viruses that you do have an extremely robust immune response in animal models and that that immune response probably does contribute to pathogenicity, but we still don't understand it.

So this long, convoluted answer to your question – the simple answer is that we just don't understand all the factors that control it, and a lot more work needs to be done.

DR. LAMB: Could you tell us who you are and your affiliation before you ask your question, please?

Q: Yes, I'm Peggy Eastman, Washington writer for Emergency Medicine News. Dr. Nabarro, you referred to – you said the poultry sector was not yet – (inaudible) – and you referred to the fact that we need radical reforms. What exactly does that refer to? Is it the way that the birds are kept in the cages? Is it the way they are processed? What did you mean by that?

DR. NABARRO: Thank you. I think I'm going for two for that question. It's a very tricky issue to answer. The poultry sector is in segments: the backyard chickens wandering around the village – we've all seen it, those of us who have traveled; the small commercial producer with perhaps a few hundred birds at a time; the medium-large commercial producer, who has perhaps got some thousands, and then the very, very large producers who between them have got millions, with some individual farms with a million. And they're very different. Obviously the big producers often have quite integrated plants. They produce their own embryonated eggs and then go right through to dealing with the production of the meat on the plant, and then immediate refrigeration and marketing up and straight into refrigerated vehicles and into airplanes and flying all over the world. The small producers are taking their chickens to markets where they're being sold, and often killed at the market point with quite interesting ritualized procedures for killing so that, for example, blood can be taken off and then drunk raw because of its properties.

Now, actually these very large producers often have the best biosecurity, the best veterinary support of all, and in a way, they're the ones that get most frustrated about the problems in the other segments of the sector. I think they've realized that it would be extremely damaging for them to be trying to affect too much what goes on in the backyard part of the sector. And so for backyard producers, it's very, very important for us to be working to ensure that there are chicken coops that can be produced at low cost being made available and also to be trying to encourage the better respect for a sick chicken in the village.

I think the problem areas are the in-between groups, the small commercial groups where perhaps biosecurity is poor and the risk of the birds when they're sick being sold quickly and causing the movement of disease in the local area, or even more widely, is

quite substantial. And it's just getting the right standards in the sector for biosecurity, both for poultry rearing and for poultry marketing that I think needs to be put in place.

I hope that's a reasonably clear answer on a very complicated issue. The Food and Agriculture Organization, particularly in Asia, has gone into this in great detail, and they have a technician, Dr. Watanee (sp), based in Bangkok, who gave one of the best presentations of the issues in the different parts of the poultry sector that I've ever heard, and that information is available; it's in the public domain. I'd be happy if you could get your email address to me to ensure that you're in contact with those people.

DR. LAMB: Dr. Choppin.

Q: Purnell Choppin, HHMI. I guess this is for Dr. Nabarro, who is a wonderful doctor. And I was happy to see the word "media" appear in his – but it seems to me to get the information out, it's a two-edged sword because the media also has the ability and almost the need to increase the panic when it occurs. For example, in all of the places you've read in the papers, how many times have you read that 97.5 percent of the people who are infected with the swine flu survived, because that's not news because news is – and so how are we going to go about letting the media get out the information that's helpful and without having it increase the level of panic? And as an example, the SARS, which was less than 1,000 deaths around the world – that's 1/30<sup>th</sup> of what occurs during a normal flu year in the United States alone – but that was news. That was panic. It was the deadly disease.

And so how do we – somehow or other the media has gotten involved in not only distributing the important good information but trying to deal with a system of panic, and that's a very, very – (inaudible).

DR. NANCY J. COX: It's a very good question, Dr. Choppin, and I think it's something we struggle with on a daily basis because we want to get our measured messages out there to the public. We want to educate the public. There is so much confusion about what a pandemic is versus regular seasonal flu, what the H and N subtypes mean, whether – we get all kinds of questions from the public about whether it's safe to eat turkey at Thanksgiving, and the questions go on and on and on. So it's really the responsibility of public health authorities and large organizations like the WHO and the U.N. to get out those responsible messages so that the media can transmit those to the public. And we can be accurately informed about where we are within the spectrum of very low-risk to a high-risk situation with regard to a pandemic.

We can put the appropriate public health measures and other measures into place. We have some time now. We can be prepared. And one of the very strong messages that I would like to get out is that as we prepare for a potential pandemic, we are preparing for any public health emergency, and what we learn through this experience will enrich our ability to respond to whatever the next threat is that comes down the pike.

Other comments?

DR. NABARRO: I'd just like to say I just agree totally, and I've just been writing down what Dr. Cox has just said. As we prepare for a pandemic, we prepare for any emergency. The unknown is fearful and therefore we need to be trying to help people to handle that fear. If, at the same time, we are somehow perceived to be exacerbating that fear by the way we speak, then I think we need to be called to account. And the more we can enter into partnership with media groups and journalists, the better the situation will be, and if from HHMI you have any research or other experience that you could make available to us to help us get that partnership right, I for one would be really pleased to hear about it. I think it's important.

Q: Dave Heyman from the Center for Strategic and International Studies. (Inaudible.) I'm interested in if we get to the point where there is a human-to-human transmission, there will probably at that point – depending upon when it comes – (inaudible) – what are the recommendations that you're putting together? To what extent, including non-pharmacological interventions – and I know I've been working with Marty Cetron at the CDC on this – to what extent is that going to be – there was a little bit of that in your presentation. I'm wondering if there should be more of that given that that would probably be the first course of action.

DR. NABARRO: Thank you very much. You know, I think you are right, and probably it should have been a stronger part of what was spoken by me, but I suspect it will come up a lot in the next presentation – I don't want to anticipate. When we focus on what ordinary people can and should be doing, we have to start with social distancing as a central activity and then move on from that to the use of various kinds of protective gear in order to reduce the likelihood that the virus will move.

I think there are still some questions about the potential utility of ordinary paper face masks and whether or not more sophisticated masks are going to be key. And that – again, there is useful guidance on that from the WHO and the CDC. But I think you are correct that as part of the process of helping citizens get ready, we do need to be helping them to understand that to avoid exposure is key, and there are techniques for doing that. They're well tried, but they need to be talked about and encouraged to put in place, or taken.

DR. LAMB: Thank you, David.

So we're now going to move on to Dr. Nancy Cox's presentation. Dr. Cox is chief of the influenza branch at CDC, and she's going to tell us about her work.

DR. COX: Thanks very much, Bob, and I'd like to really thank the organizers of the meeting for this wonderful opportunity to talk about what we're doing to prepare for a potential pandemic in the public health system.

One of the things that I really do want to emphasize is that – and I said it before – what we're doing now to prepare for a pandemic has a lot of additional benefits because

whatever we do will allow us to be better prepared during the regular seasonal influenza epidemics that we have. We'll have better availability of vaccines, antiviral drugs, perhaps even new antiviral drugs, and community health protection from other threats.

Now, I just wanted to update you on the number of H5N1 cases and deaths. Currently the case fatality rate is 56 percent. Very recently cases were reported in Azerbaijan, as Dr. Nabarro mentioned. And an increasing number of countries have reported human cases.

The severe cases are really quite severe. You can see the progression here in the chest x-rays from day 5 to day 10. Death is really not – death from this particular pathogen is not a pleasant death. And physicians have commented that it's very difficult to manage patients. In fact, some of the physicians in Vietnam have said that it's more difficult to handle – to manage, clinically, patients who are ill with H5N1 than those who are ill with SARS.

I just wanted to make – I know this slide is very busy and you won't be able to see from the back, and Dr. Nabarro talked about the march of avian influenza from Southeast Asia across through the Middle East and other parts of Asia into Western Europe now. And one of the things that I'd like to emphasize is that as part of the U.S. government response, we have put in place bilateral agreements with a number of the countries that you can see that have the hatch lines here. And what we are trying to do, by putting in place bilateral agreements and providing a source of funding is to encourage capacity building within these countries. And as Dr. Nabarro said, this is a very time-consuming process. We have to help increase their laboratory capacity, their capacity to investigate outbreaks, to stamp out the disease, to protect humans, and indeed, in many of these countries we are encouraging the countries to extend their influenza surveillance networks into the rural areas so that they can actually pick up the disease. And so we don't – and we're working very closely with our counterparts at USAID and FAO, and we certainly don't want humans to be sentinels for the poultry disease.

Now, in terms of surveillance objectives – public health surveillance objectives, we need to have sensitive systems so that we can detect the occurrence of pandemic influenza should it happen in the United States. We'll want to detect and investigate the initial H5N1 cases or disease associated with other subtypes. We can't forget that there are other avian influenza subtypes out there that could pose a pandemic threat. And of course we will want to identify and investigate the initial small clusters of human cases of high-path H5N1 should we have introductions into the United States. At the very first signs of human-to-human transmission, a rapid response is essential. And this is something that the U.N. and WHO is working extremely hard on, and we're working hand-in-hand in terms of preparing a rapid response curricula that can be rolled out, not only in the United States but abroad. We want to be able to determine and track the trends and the impact of disease in affected areas, and then we want of course to assess the effectiveness of our guidelines and then use the data to inform decision-making and determine if we need to change the guidelines.

In addition, we are determining currently, and will continue to monitor antigenic and genetic changes in circulating influenza viruses and we will be looking for the prevalence of antiviral resistance in case our antivirals might be found to be less effective than we hope.

So much has to be done at the county and local and state levels. And these are the folks who are going to be on the front lines. So what are we doing? We're providing standardized influenza reagents for influenza testing and research. A lot of that is being done through the WHO network. We're promoting development of point-of-care rapid diagnostic tests. There is actually quite a lot of U.S. government funding for industry and university efforts in this regard. It will be very important to have better point-of-care diagnostic tests developed. We're training epidemiologists, lab staff, and other health professionals in response and investigation efforts in the U.S. and abroad, and we're informing the healthcare providers and the public of the cases, the reporting requirements, and how to appropriately use the health services that are available.

So what will happen when the first U.S. case of H5N1 is diagnosed in the United States? So we know that physicians, hospitals and so on, other healthcare workers, are already alert about the need to be looking for H5N1 cases because of what's occurred abroad. Once an astute physician has determined the travel history of a severe case of respiratory disease, the preliminary diagnosis is likely to be done at a state health department lab or one of our laboratory response network labs, which have been provided H5 diagnostic reagents. The confirmation would likely occur at CDC for the first cases in the United States. We would then immediately have a health alert network report that would go out, along with a press briefing. There would be tracing of contacts of the individual treatment or prophylaxis with antivirals of the individual and potential contacts. We would enhance national surveillance. And we would be continuing to provide news briefs and education as we moved on.

Of course we would be continuing our routine surveillance for seasonal influenza, enhancing our surveillance for H5N1 cases, monitoring the health status of travelers from affected areas. We're already doing that to a certain extent. We'd be monitoring illness and infection among healthcare workers. We saw that this was extremely important in SARS. We would also monitor laboratory workers for occupational infections. And we would be looking at what is happening in the agricultural sector. And we will be – if a pandemic were to occur, we would be tracking hospitalizations and deaths, monitoring workplace safety and continuity of operations in the critical infrastructure, and assess the need for changes in disease containment and medical strategies, as we learned from the experiences.

So right now we are determining changes in the viruses, and we conduct epidemiologic studies that are linked with the laboratory data so that we can monitor whether the treatment guidelines that are in place are appropriate so that we can determine something about vaccine effectiveness, antiviral effectiveness and resistance,

changes in the receptor binding specificity, as you've heard so much about this morning, and changes in pathogenicity using animal models.

So here is a family tree of the H5 viruses, and we're concentrating on the hemagglutinin gene because this is the primary gene, and what we know is that the progenitor of all of the viruses that are circulating in all of the nations that you've seen colored in green in my previous map, a progenitor is the goose/Guandong '96 strain, which caused an outbreak in South China in domestic geese. All of the H5 viruses are related to this virus. This is the '96 virus; we're in 2006. The viruses have had a wonderful opportunity to continue to evolve, diversify, infect new species, and undergone many, many genetic changes.

What the WHO system has been doing is monitoring these changes and selecting – and I don't think you can see it very well from the back of the room, but we've selected quite strategically from this family tree of viruses, viruses which will be good candidates for vaccine – reference viruses that can be then used by industry, with funding from the government, to produce pilot lots which can be tested in volunteer populations. So once again, I just want to emphasize that seasonal influenza preparedness will be enhanced greatly by pandemic influenza preparedness.

I'll go through some of the next slides very quickly because we do have a complex system in place to monitor what is going on with respect to influenza during the regular seasonal flu. We look at pediatric hospitalizations, we look at pediatric deaths, we have state and territorial epidemiologists who are reporting on a weekly basis the level of influenza activity in their states. This is the only state-based system that we have in place. We have a system that looks at excess influenza and pneumonia deaths. We have a network of laboratories that provide information to CDC and a subset of viruses so that we can look for changes in the seasonal viruses. All of this information is brought together, disseminated on a weekly basis on the CDC website, provided to WHO so that it can be published in the WER, and it's also provided to a number of very, very important partners and audiences.

And I think I'll go through the rest of the slides fairly quickly. This just shows where we are this season with respect to the viruses that are circulating. The majority of the viruses are influenza A viruses, shown in red and yellow here. These are untyped. This is one of the things that we worry about because we're not subtyping all of the influenza A viruses that are detected in the laboratories. The proportion will go up as the season goes up. But we can see we're still having an increase in activity.

Just wanted to mention that with respect to public health diagnosis, we recognized a couple of years ago that it was extremely important to have our public health laboratories ready to diagnose the first cases of H5 should they enter through travelers or other ways, and so we developed a specialized test at CDC based on the sequence database that we had from our family trees of the viruses. We developed a real-time polymerase chain reaction assay. This is currently the only diagnostic test for H5 that's been approved by FDA. The reason it was approved by FDA is that it could potentially

be used for patient care. This assay has been distributed to state health departments and the laboratories that are in the laboratory response network.

CDC is now working with industry to commercialize these tests. We are not in the business of commercializing tests ourselves. We work with public health. And then we're also working with USDA and the Department of Defense and WHO to coordinate the diagnostic tests that are used. And so we can have a reasonable amount of confidence that if a patient is positive in one laboratory, that another laboratory testing the same specimen will come up with the same result.

We also have a system of – and I apologize you really can't see this graph very well – we have a system of sentinel providers, sentinel physicians who are out there reporting to us the amount of influenza-like illness that they see on a weekly basis. And we had a very severe season in 2003, 2004. We had a lot of early illness. The influenza season peaked at around Christmastime. You can see in red, this is where we are today. We've had really quite a moderate influenza season, but there is still quite a bit of activity going on. And then we have our statewide report so we can see the level of influenza activity by state.

I also mentioned the mortality system, and I'll spend just a minute talking about this because the United States is unique in having this particular mortality reporting system, which could be extremely useful during a pandemic to try to monitor what is going on with respect to mortality. In this system we capture about a quarter to a third of U.S. deaths and we look at the total number of death certificates that are filed in a given week and the number with pneumonia or influenza listed in any place in the death certificate.

Once again, you can't see this slide very well, but, again, that severe season that I mentioned, the 2003-2004 influenza season was one where we saw a very striking peak of excess deaths, and this exactly what we might expect to see during a pandemic if it were to be a severe one, only the peak would be higher because the attack rates undoubtedly would be higher.

So we're really assessing what we have in place with respect to influenza surveillance – where our gaps are, where the weaknesses are, how can we improve, how can we get more real-time data, how can we disseminate that data very quickly to everyone who is going to want to know, and especially the media will want to know on a daily basis where we are within a pandemic.

So the advantages are right now we can quickly assess excess death. We have mandatory reporting of pediatric influenza deaths. Many other countries don't have that. And we have ongoing, for many years, extremely good partnerships with our state health departments, local health departments, and with our global partners. But I have to say that this is a voluntary reporting system. We're not paying these folks to do what they do. And in a pandemic it might be impossible to sustain certain parts of our current surveillance system, and so we're looking for new ways to enhance surveillance. And the

detection of H5 cases, or any new strain of course will depend on astute clinicians recognizing the disease and knowing what to do. So we are, as I mentioned, working to expand our system.

Thank you very much for your attention.

DR. LAMB: Thank you, Dr. Cox, very much. Now, the next talk is going to be Dr. Farzad Mostashari, who is from the New York City Health Department.

DR. FARZAD MOSTASHARI: Thank you. Thank you for having me. I'm going to talk about biosurveillance in public health practice and its potential utility for flu surveillance, and I really could not have had a better introduction than the speakers that went before. I'm also going to add some cautions about some of this new technology.

So let me give you some background on biosurveillance, as some have called it, or syndromic surveillance – talk about some of the potential utility for influenza surveillance that this might offer with specifically talking about findings from New York City, and then talking about some implications for nationwide surveillance.

Public health surveillance is defined as the systematic, ongoing collection, collation, analysis and interpretation of health data essential to the planning, implementation and evaluation of public health practice. And some of the public health surveillance goals – and Dr. Cox described them very well in the pandemic arena – include detecting outbreaks. And she mentioned the initial cases of the H5N1, for example, or small clusters of human cases guiding monitor and control activities, detecting those individual cases, but also monitoring the distribution and spread, estimating burden and impact, prioritizing allocation of resources, understanding the natural history of the disease, and providing a basis for the epidemiologic research that will need to take place.

It's important to note that there are many kinds of public health surveillance – passive surveillance, the voluntary reporting that Dr. Cox mentioned. There are disease registries like death certificate reporting. There is active surveillance that can take place, usually for short periods of times; sentinel surveillance. This takes place with sentinel provider reporting. There can be behavioral surveillance where we get our information about flu vaccination across the country. Secondary data-source analysis like hospitalizations, tapping into those. And just to mention that what I'm talking about today is syndromic surveillance, or also known as biosurveillance, is really one of many. These systems really do need to all, I think, work together. There is not a replacement; it's an addition potentially.

So what is syndromic surveillance? I think if we take the same definition of surveillance – it is surveillance – and just add a few modifying phrases. So it's systematic, ongoing, collection and collation analysis interpretation in real time, and it's existing health data rather than kind of custom collected essential for the planning and implementation and evaluation of public health practice. And then there is an added kind

of focus, I would say, somewhat, of emergency response being a focus area. But the concept really is that there is a tremendous amount of information that is already available in electronic format in a timely way, and if we could access that information that was collected for another purpose and use it for public health surveillance, we would have the ability to have the data collected. If we develop new statistical methods we can have it analyzed in real time and then interpreted and acted on.

So this is some slides from the American Health Information Community, the presentation that we helped put together for Secretary Leavitt, and just to – in the environmental scan there are many, many state and local public health agencies that are investigating these new methods. State and local public health agencies do bear the primary responsibility for public health surveillance outbreak response, and have existing relationships with clinical providers and the public. They do possess a wide range of public health informatics capacity and desire to innovate, but many have begun to implement electronic clinical lab reporting, linkages to clinical information systems, information on regional health information organizations and other electronic surveillance methods.

There are over 100 programs across the country that are going to be similar to what I'm describing today. The Center for Disease Control coordinates nationwide health surveillance, provides resources and expert guidance to state and local health authorities, have established the Public Health Information Network, Outbreak Management Systems. And BioSense is a new program that supports the connection of clinical care to public health and supports what has been termed situational awareness at a national level. There are many systems that one could potentially tap into. I have here a table that you could probably read in the handouts or afterwards on the presentation. We monitor emergency department visits. There's about 10,000 of those every day that we get reported, and that's going to be kind of the focus of what I'm going to be talking about today. But we also monitor ambulances dispatched, pharmacies, worker absences. Outpatient clinic visits is something that we're starting to look into and school nurse visits.

So emergency departments we monitor – we get daily transmission – daily – from 77 percent or 50 of the 62 emergency departments in New York City, which is about 90 percent of all ED visits in the city. This is the kind of data you get. It's very simple data – age, sex, zip code, when they came in, what their chief complaint was, and in some cases a discharge diagnosis. So, you know, it's a very – it's not – this is what I'm saying, that this is existing data tapping into a hospital registration system. This is not a surveillance system specifically for influenza. We do daily statistical analyses, looking both for citywide temporal aberrations as well as spatial cluster detection. And we do signal follow up by reviewing line lists, checking with other systems, calling emergency departments to heighten their awareness, and rarely requesting that EDs augment testing. The investigation has been very difficult.

So just a quick summary of our experience over the past six years or so is that we really are able to see clear seasonal patterns in this kind of data. We do have 15 sharp

spikes associated with known events like the blackout, for example. And we've used the system actually in daily public health practice to reinforce public health messages around virulent GI illnesses, heat wave, blackout, asthma, and influenza. And it really, I think if we want to say, what's it been good for, it's really been a very flexible, multi-purpose tool to enable us to have our finger on the pulse of the health of the city in a way that we didn't have before. The shortcomings also have also become evident. Many localized outbreaks that are reported through traditional methods have not been detected through syndromic surveillance. And conversely, we have seen very many spatial clusters that have never been able – been able to connect to any actual disease outbreak, and these are very difficult to investigate.

So in terms of the evolving evidence for the usefulness of syndromic surveillance, I think if we had to guess, we would say influenza surveillance might actually be at the top of our list in terms of what it might be useful for, but also monitoring other citywide outbreaks, ad hoc analyses in response to local events, enhanced case finding possibly for reported disease outbreaks – outbreaks that have already been reported. But localized outbreak detection I would say we – we feel has lesser likelihood of usefulness. So let me give some examples of how syndromic surveillance could potentially improve or add to existing influenza surveillance for regions: early notification, severity and duration, age-specific patterns, and potentially monitoring the stockpiling of antivirals.

This doesn't come across too well unfortunately in this room, but I was giving a talk similar to this one November 19<sup>th</sup>, 2003. And I was saying, well, if you look at respiratory illness throughout the city over the past 12 months or so, 13 and over population, there's a sharp spike associated with the blackout. Febrile illness had gone up in the previous flu season down. And I said, listen, in the past few days, there has been an increase, a march upwards in febrile illness throughout the city, as well as respiratory illness. And I said, we don't know what this is, but it's probably not flu because it's too early. Well, sure enough, it was flu. It was the beginning of the very large peak that we saw in 2003. If we had been monitoring children – this was 13 and over – we would have seen it even earlier. It took us a couple of weeks to actually verify that this was indeed due to influenza. This was quite early, and at the time, our assessment of where the citywide activity for influenza was – was really very little, maybe sporadic.

So second is severity and duration. So this is a graph very similar to what was shown for PNI mortality with a cyclical model patterning. But instead of mortality across the country, this is emergency room visits for fever and respiratory illness in New York City alone. And it correlates very well with influenza isolates – A isolates in gray and B isolates in red here. So we go along here, we see this sharp spike associated with the 2001-2002 H3N2 and then a smaller one with the – with Influenza B isolates that increased. And this was the B/Victoria, and I'll be talking a little bit about that story. The following years in H1N1 predominance – very little increase in emergency room visits and indeed in mortality. This is the 2003 H3N2 Fujian strain that was quite early and caused a lot of morbidity, as well as mortality. And then this is the following year –

the H3. So let's focus in on here – we see kind of this rabbit ear here in terms of emergency room visits.

If we look at our existing flu surveillance systems – this is from the MMWR, the summary of the 2001-2002 influenza season – this is the systems that really Dr. Cox described. So percent visits for I-life (ph) from the sentinel physician system, goes up and comes down. Positive isolates goes up and comes down. Regional or widespread state EPI (ph) assessments goes up and comes down. And then PNI deaths lag behind, as you would expect deaths to. So there is no rabbit ear here in the national picture. And one of the kind of clues as to what was happening was the viral isolates, similar to what was shown earlier for this year, for that year, there was a small number of B isolates that were detected. But as Dr. Cox described a few months later, these – this flu B isolate really was a new or reappearance and global spread of an influenza B virus that had not been – that family had not been seen in the western hemisphere for some 14 years. So this was, in a sense, a test case of what happens when a virus that had not been seen for many years reappears.

And this is – there's no way you can see this. But this is breaking it down by age. And I think this is kind of interesting that, if you have 10,000 visits a day, you can start to break it down in a much more granular way in terms of what the age distribution is. So we can examine the effects of this, not only citywide, but also on different age groups. And I'm going to take you through. So 65 and older population – there was hardly any increase in emergency room visits during this period, either for the flu A period or for the flu B period. For the 18 to 39 year olds, you see the sharp increase with the flu A period, very little with flu B. This is similar to what was seen in the mortality data and the hospitalization data. But as you get into the younger age groups, the five to 12 year olds have a tremendous peak, not with the flu A, but with the flue B. These are children who had never seen this flu B before. And then again, as you go down, it tends to be – actually be less in the under four and the preschool population.

So what you can do is you can kind of take this model and turn it into a visual presentation of those excesses. So each of these is kind of a citywide, but then you can also break it down into by age group and stratify it going across. So this was the flu A period, and this is the following flu B period. And what we see is a sharp cliff as there is really essentially no increase in morbidity in response to the flu B outbreak that the population that was 18 and over had already seen, had already been exposed to. The other way to do it is just to turn it on its – look at a – the top down view of it, and then we can see color-coded the intensity of the increase by age group going across. This is this year's data up to last week about.

A few things are interesting to note on this. One is, as has been notice, children lead. So in the H – in the influenza A outbreaks, the H3N2s, we see children – either the under 5 group as in the first – as in the first year presented here – or really all school age children under 18 here present first. And then a week later it's the 18 to 39s. A week later is the 40 to 64s. A week later is the 65-plus. The other interesting thing to note is that this peak, this flu B peak, is really so sharp, so dramatic and really went virtually

undetected by us at the time even. We were not getting flooded by calls from the emergency rooms saying that we're seeing, you know, all these school age kids coming in. But yet if you do look at the data as a pattern, you're able to see the forest. Antiviral stockpiling we published at MMWR a couple weeks ago looking at prescriptions from pharmacy sales for Tamiflu and seeing that both through our pharmacy system, as well as through Medicaid prescribing, there was a sharp increase not correlated with viral isolates.

So what's next for us? In terms of public health and health IT, on October 24<sup>th</sup>, Mayor Mike Bloomberg announced a \$25 million plan to provide public health oriented electronic health records to community health centers in a New York City project that I'm leading. Our goals are to improve preventative or chronic disease care through this, to reduce disparities, but also to improve public health surveillance and response. We have some preliminary experience with a community health center, with electronic health records. And if you look at the emergency department chief complaint fever/flu that I just showed you – this is the 2003-2004 season – you see the viral isolates, you see that the ED visits go up pretty early on relative to the viral isolates. And this is data from the electronic health record if you look at measured temperature greater than 99.9 – proportion of all visits that had a measure temperature higher than 99.9. And if you combine that with data that is available in the electronic health record, measured temperature greater than 99.9 and a respiratory diagnosis, you see that the peak is higher relative to its baseline and potentially even earlier. So there's two electronic health record use cases. One is that the Department of Health might increase – detect an increase in respiratory illness among adults, and the second is that the electronic health record itself might signal a provider then to collect travel history, and a nasal wash for the Department of Health for pickup and viral ID. So that's kind of the dream in terms of what the future might bring.

I want to reiterate that in terms of the likely utility of these methods for pandemic flu, I don't think it's going to be very useful for detecting those very first cases of the outbreak. Individual cases – I think, our traditional systems, our communication with providers, our education are really what's going – what's going to really matter there. But in terms of monitoring the distribution and spread of the illness in real time, I think it is a timely way to do so, which provides a lot of information in terms of the age granularity. And when Dr. Cox mentioned that in the midst of a pandemic it might be impossible to sustain voluntary reporting, the advantage of these systems is that it depends on automated reporting from information systems. So it does not impose an additional burden on provider, estimating burden impact and prioritizing allocation of resources.

So what is needed? I think there has to be an engagement from the influenza experts who really understand this in these new methods. And I would think that a nationwide pilot potentially for more timely age-specific morbidity surveillance during our seasonal epidemics could help prepare us for the pandemic when it does happen. And, you know, I would say that there are over 100 systems like this that have already been built there. If CDC says this is the case definition whether through chief complaint

or discharge diagnosis, we could provide that information in a very – in a very timely way to CDC and clearly linkage of real time morbidity data to rapid diagnostics and genomics. The point has been made – Dr. Taubenberger made it today – that, even in the midst of a pandemic – the North Carolina and the New York case – the virus can shift, can change, can mutate, and can have changing pathogenicity. So having ongoing morbidity surveillance tightly linked to the laboratory findings are really critical, and I don't think we're there yet.

Cautions – so the first – and this is, I think, the most important part of this – whenever we're talking about new technologies and that can get caught up in the hype cycle, it's not about technology. It's about epidemiology is my first caution. We cannot let this become a technology driven informatics project to suck up all the data and stick it in some warehouse for data mining purposes. That's not going to succeed. It really has to be led by, shaped by, focused by the content experts and the epidemiologists.

I would also say don't disrupt local systems and relationships. Local public health has the mandate for public health investigation and response, and there are many, many systems that we have already established throughout the country, not just in New York City, but most of the other large cities, already tapping into this kind of data. And there is a – a seduction to saying, let's create a national system, won't we? Why don't we just get everyone to report from the hospitals, from the health centers directly to CDC? And then we'll have national surveillance. I think the risk you run there is that you disrupt those relationships that have already been established and need to be established with the local health agencies. When, in this country, raw surveillance data is pressed through the filter of local health departments, I don't think we want to have local public health out of the loop on surveillance activities. I don't think CDC wants that. I don't think anybody wants that. So the risk of setting in place an external parallel process to have centralized data collection, I think, is a risky one.

The other caution is it's very easy to drown in data. This data is incredibly complex, and the more data you get, you know – less is more sometimes. If you know what you want, if you know what the question is, you can analyze it; you can act on it. But if you're just getting bombarded with everything in the hospital information system, it's very hard to make heads or tails out of that. And finally, I think, beware the privacy backlash. Setting up a national warehouse even of anonymized or partially anonymized or maybe anonymized data will, I think, inevitably cause a privacy backlash that could really jeopardize all of our public health surveillance and response activities.

So those are – those are my slides, and I want to particularly thank my colleagues Rick Heffernan and Don Olson, who contributed much of the data for this, and as well as the entire Department of Health Surveillance Team. Thank you.

DR. LAMB: Well, thank you very much, Dr. Mostashari. We're going to take a very short break now, but please don't all disappear because we actually have one more talk and questions to come. And the one more talk, in fact, concerns really new

diagnostic methods. So we'll just take this very short break for 10 minutes and then come back.

(Break.)

DR. LAMB: So our last speaker is going to be Dr. Matthew Lorence, who is from Affymetrix, and he's going to talk about new diagnostic methods for influenza virus.

DR. MATTHEW LORENCE: Actually, I'm going to take a slightly different perspective and talk about the difficulties or challenges of translating new genomics tools into the diagnostics and public health testing markets. Essentially, the development and use of genomic tools in the research laboratory is accelerating our understanding of the etiological agents and the mechanisms by which they cause disease. These same tools must be applied to the surveillance and detection of emerging and reemerging diseases like pandemic influenza, which have the potential to cause high mortality and significant economic damage. And this translation must be faster. And although there are numerous underlying issues, they can be addressed and overcome.

So where are we with respect to the state of technology with respect to identification and detection of pathogens? Essentially there has been a big paradigm shift going on recently. The phenotypic methods which have been developed for decades and used for decades, which are typically traditional growth-based methods like carbon source utilizations, serotyping, substrate conversion – they have limitations. They tend to be very low in terms of types of discrimination. And then there's the whole issue of non-cultivable organisms among others. Just because you can't grow it doesn't mean it's not there. There has been a big shift in the technology to genotypic methods, that are based on either genetic signature or genetic sequence of the organism itself. And these methodologies include real time PCR, DNA sequencing, and hybridization assays. And while they provide much greater amounts of discrimination, they also have some limitations like the multiplex capability, being able to look at lots of pathogens or lots of signatures simultaneously. And sensitivity can be an issue when there's a low amount of pathogen in the sample or there are large numbers of multiple pathogens.

So the other shift that's going on, particularly in the research laboratory, are multiplex detection methods that are genotypic based like micro-arrays. And multiplex detection allows multiple signatures per pathogen to be detected, which means you have both detection and confirmation because now you're seeing multiple sequences or signatures that represent that pathogen. And also multiple pathogens can be detected (?) simultaneously. And what this does is it really shifts the question that's being asked by the epidemiologists, from is this specific pathogen present to what pathogens are present because now, instead of just defining your question to the things that you specifically want to detect, you can essentially see everything that's present.

So why hasn't this moved into the – to the diagnostic arena much faster? Well, and I think the real reason is that there are very differing characteristics and needs of the

diagnostic versus the research user. Essentially the diagnostic user – and I'll simplistically lump the public health testing into this as well – they perform routine testing. And they need reproducibility and consistency in their testing methods because they can't afford to have the results change. If you're in the basic research market and you do an experiment and it doesn't work, that's okay. You try to figure out what went wrong, but you go back the next day and do it again. When you're dealing with diagnostic testing and patients' lives and health are at risk, that kind of lack of consistency is difficult to deal with. And I think what's also important is that the people in the diagnostic testing markets are paid to do testing, not to do research. They have to obtain results. Research really belongs where it currently is – in the research testing and the research markets. And I think this and other factors lead to a sort of resistance to adopt new technology, not because there's not an interest to adopt the technology, but it's the implementation of this technology and all the surrounding needs of this specific sector that makes that technology adoption or translation from the basic research lab difficult. And it's really an issue of development, which is what happens in basic research, versus implementation, which is the use of that same technology in routine testing.

So what are some of the major issues? I said there are many, but some of the ones that I think are most important are – at least for the commercial sector, one is development costs because developing a new diagnostic is expensive and time consuming and it's difficult. In addition to the traditional costs of money and people, there's also time because the time that it takes to develop a diagnostic and go through the entire process is very long. And the market may change during that process. There are opportunity costs because the resources that a commercial entity will invest in developing a diagnostic could just as easily have been devoted to developing a new tool for the academic market, where the hurdle for getting into the marketplace is lower. And of course there's regulatory compliance, especially with a diagnostic, where that adds not only, again, time, but also a great deal of cost to the process.

Another factor is the market potential. What is the true size of the market? Obviously companies need to develop products that are going to be sold not just to one or two interested users, but to a large number. And specifically when you look at the academic or the research markets versus the diagnostics markets, there is this big difference between price and volume. The research market – it tends to be a lower volume, but the price charged per test or per sample can be quite high, whereas in the diagnostic market, the goal is to do a large volume of testing, and therefore it drives the price down to something lower. So there's that need to deal with that change in the way the marketing is performed. And then there's the window of opportunity. Essentially, by the time a product gets developed and it gets into the market, it may not – it may no longer fit the need for which it was originally developed, or other technologies or tests may have come along which will supercede that one.

There is also risk management issues. This was mentioned by others before. But product liability for commercial entities remains a barrier to entry. Not only the liability in terms of potential tort litigation, but there's also the cost of insurance that you would

have to have to do this. Now, the government has done some, but the government can do more to reduce these barriers to entry. We've all heard about the Bioshield laws, which apply primarily to the therapeutics and vaccines manufacturers. But the SAFETY Act was something that the government passed shortly after the anthrax letters in 2001 to encourage high-tech companies to move into the arena of surveillance and detection of novel or emerging threat agents. And although, for the government, the SAFETY Act was a huge change in the way things were done, for those in the commercial sector, it simply didn't go far enough. And although – I don't have the actual statistic, but I do know that, if you look at the number of companies that have gone through the rather long and laborious process of getting their products SAFETY Act certified so that they can be – they can have this reduction in liability that comes along with it, the number is still very small.

Now, not to be totally pessimistic, there have been some initial successes of very new genomics technologies transitioning into the diagnostics marketplace. This first one is the AmpliChip array developed by Roche Diagnostics, and it's the first FDA-cleared microarray device or multiplex genotypic device on the market. It really was designed to analyze cytochrome P450s in the liver so that physicians could make intelligent decisions about drug dosing. And the key thing is that, although this was launched at the end of 2004, the first commercial availability of this very same technology upon which this device is based was in early 1990. So it took about 15 years for this technology to finally transition to an FDA-cleared device. Unfortunately, that's not atypical.

One of the other things that I think is a critical factor are clinical benefits, meaning diagnostics must provide benefits to the patient because they, in fact, are the ultimate consumer of that. The other thing that's very important is to develop demand from the clinicians because the clinicians are going to order diagnostic tests that provide them information that they can use in making treatment decisions for the – for their patients. So the results must provide relevance the clinicians can actually act upon. And it's very interesting to me. I fortunately – although I only have one sibling, she is a primary care physician. So she makes house calls, at least when my kids are sick. And the benefit to me is, then, I can talk to her about the symptoms that I'm feeling and different disease states, and she even lets me suggest what treatments I might want to have.

But it's also discouraging to me because, as a relatively informed patient, I still see her treating my symptoms. It's typically get lots of rest; don't get dehydrated. If you get a sinus infection, take an antibiotic. But it still hasn't really progressed much from very long ago, when she first came out of medical school. And I think it's very important for us to also consider that results can increase patient confidence because the information that gets provided to the patient gives them some indication that the physician may have an idea of what's going on, not necessarily because it may change the treatment decision. If my sister had access to diagnostics that allowed her to say exactly what bacteria or what virus or strain of virus I was infected with, it would change the fact that she would tell me to rest, drink lots of fluids, and take antibiotics if I get a sinus infection. But it would certainly make me feel better about the fact that something

is happening. So I think the fact that there's little information also just increases anxiety in the patient because they feel that progress is not being made. So although not all information can be acted upon clinically, there is information that can make the patient, the ultimate consumer, feel better about the diagnostic tools that are being employed.

Now, there has been some early progress in trying to develop diagnostic tools for infectious disease detection and surveillance using these new genomics tools. There has been – there are some examples here, and I won't go into great detail. But profiling microbial communities is something that's been developed by Dr. Gary Andersen at the Lawrence Berkeley lab. This is important because it allows researchers to look at very complex mixed samples but be able to identify specific organisms that may be present in that mixed sample. We also now have the ability to detect large numbers of causative agents.

The respiratory pathogen microarray developed by Dr. Dave Stenger at the Naval Research laboratories actually allows his group to look and detect specific pathogens in a sample even though multiple pathogens may be present. In the specific publication that he put out recently, they detected group A strep and simultaneously detected antibiotic resistance. So you had not only identification of the causative agent, but you had actionable results for the clinician in terms of what antibiotics could be prescribed. The other interesting thing was that, in addition to group A strep, they were also able to identify multiple pathogens in those samples. So there was co-infection with adenovirus, with chlamydia pneumoniae, with strep pneumoniae, and other agents. So it shows that a comprehensive tool can be developed, where you can simply take a sample from a patient and be able to see exactly what happens to be in them and, at the same time, perhaps have clinical course of action as well. And there's other work specifically being done in influenza by Dr. Kathy Rowlen at Colorado University, where she has developed devices to look at multiple serotypes, currently the circulating serotypes H3N2 and H1N1 and also H5N1. And the critical part is that this can be done in less than 12 hours.

The last thing that I think is really important are partnerships to accelerate the successful translation of new technologies into the diagnostic markets. And we really need these partnerships to facilitate the transition, and additionally we need a process to facilitate those partnerships. And the reason is, I think, that if you look at the commercial sector and the diagnostics markets, they have different and sometimes competing goals. Companies are very concerned about the return on investment that they make in developing products, and companies, at least like mine, like doing cool science as well. Goals in the public health arena – the agencies are really there to protect the public from disease, and they use gold standard methods that are tried and true.

So when it comes to translating new technologies, the companies really understand their technology. They really get it. They develop the technology. They optimize it to the point where it's extremely robust, and in addition – not only knowing its strengths and its weaknesses – they know how to make it, they know to test it, they know how to package it up, and they know how to distribute it. What they don't always understand are, what are the true needs of the customer? If you look at the other side at

the public health laboratories, they really understand what their needs are. They know that they need better, faster, more sensitive, more accurate tests, however that translates into specific specifications. But they're the ones who can tell the companies how their technology can provide a solution that meets their needs. But they shouldn't necessarily be the technology developers. It really takes a partnership between the two to take that developed technology and implement it and translate it into the lab.

And there's really a need to compete – I'm sorry – to collaborate and not compete. And collaboration does happen. We are the – we are the fortunate beneficiary of a collaboration with Dr. Cox at the CDC to develop a tool to provide epidemiological surveillance of H5N1, looking at even single nucleotide changes as the virus mutates to provide more accurate tracking and perhaps even identification of increased virulence or antiviral resistance should it occur. But there have been examples where there has been competition between the commercial and the public health sectors, where the public health sectors have essentially put devices together and then distributed those devices to others within the market. And going back to what I said earlier, this is a real challenge for the commercial entities because they do develop that technology and they want to help the technology address the concerns in the public health sectors. But at the same time, they have to be concerned about protecting their IP and being able to make a return on their investments.

We also need more funding to really allocate into translating this technology to speed up the adoption. And I'm not talking about funding to buy products. That's obviously a critical step. But once those products are in the laboratory, they need to be used. And that really means that the technology users have to be able to evaluate the technologies out there and see how well they meet their specific needs, rather than just picking a particular technology because they happen to like the sales rep. There has to be verification testing of these new technologies with real world samples because just because they work in the laboratory with a – essentially an artificial sample that has a spiked-in target doesn't mean that it's going to perform the same way in a different matrix when that is a clinical sample from a patient. And there has to be training and certification of the users because once the technology is in place, you have to know that the same test is going to give the same results everyday with the same user or different user so that you can actually anticipate what that data is going to mean.

And then for commercial entities, there's the whole idea of doing business with the U.S. government. It can be very challenging. There's the Federal Acquisition Regulations – need I say more – and CRADAs. And CRADAs, although they may have a cooperative spirit in them, they require large investments by the commercial entities and sometimes onerous IP terms on the part of the government. That makes it very difficult for commercial entities to see the ultimate return on their investment.

So I'd like to end with making maybe a somewhat simplistic proposal, but we clearly need, in this instance, an influenza surveillance network. I think there is a model that was developed at the CDC by Dr. Bala Swaminathan in the food-borne disease group. And the real brilliance to me about his model was that, instead of all the samples

being transferred into the CDC and the CDC having to use its limited resources to try and process all those samples, he pushed data generation back onto the local public health labs so that he was multiplying his efforts through others by having the local labs part of his network actually do the data generation. And then the data was transferred to the CDC for analysis. The other thing that really made this work is that his group developed consistent methods and procedures and that they trained and certified the members of the network laboratories. So in order to be able to generate data that you would then send to the CDC and be added to the PulseNet database, you had to know exactly what methods were being used, you had to be trained, and they had to know that you used them properly, even so far as specifying specific products and reagents that should be used.

The end result is PulseNet has grown to not only all 50 states and some county laboratories, but it now has international members as well – the U.K., Japan, Canada. So it has been a great success. And not only did they – have they moved from what they started with originally, which was looking at E. coli 0157 and Salmonella food poisonings, they've added more organisms to their surveillance. The bad news is – is this took more than 10 years to develop. In the case of a pandemic influenza or some other emerging disease that has the potential to cause great devastation, 10 years is not going to cut it. We have to be able to do this much faster. So I propose that we really need a FluNet version of PulseNet and that this will – this is necessary because we need to generate the epidemiological data faster to see how the virus is changing and to see how it's moving. Again, I think there are too many samples that are being processed by precious resources at a very few centralized testing laboratories.

We also need rapid expert analysis. So having the data put into one place where the local – where the true influenza experts can look at that data and make intelligent assessments about it quickly is a critical need. We also then need to implement those public health solutions that they come up with after analyzing the data rapidly. And as mentioned by Dr. Taubenberger, there is a great need to monitor surveillance not just in animals, but in – not just in humans, but in the animals that are the reservoirs of these diseases as well because just because we know what's happening, that doesn't mean that we understand the whole picture, especially with a disease like avian influenza, which obviously transfers from an animal reservoir to humans. We also need adequate funding to make these types of surveillance networks a reality, and it has got to be a global program with international participation and coordination.

So as I said, new genomics tools are accelerating our understanding of the etiological agents and the mechanisms by which they cause disease. These same tools must be applied to the surveillance and detection of new pathogens, and the translation of these tools into this marketplace have to happen much faster. We have a lot of issues that we have that are underlying all this, but I think they can be easily overcome with the right amount of efforts. And money helps as well. And finally, I think we need to establish an influenza surveillance network, not just for influenza or H5N1, but a global network that can start with influenza and expand to include other naturally and sometimes intentionally caused epidemics so that we can protect public health in a much more effective manner. Thank you.

DR. LAMB: Well, thank you very much, Dr. Lorence. We're now going to take questions for any of the speakers, if the speakers would like to come and sit front. We're afraid Dr. Nabarro had to go. He had another meeting to go to so he's not to be in that. And before you ask your question, could you tell us who you are and your affiliation please?

Q: I'm Greg Shipp. I'm with a company called Nanosphere, and I'm vice president of medical affairs. Question to the last three speakers: Would there be a role for a – we've got PCR-based diagnostic moving forward, it looks like. Would there be a role for a direct genomic detection system that does not require PCR, could move out into the community hospital, into, you know, internationally, cost effective, and is as accurate as PCR? Also can be done in four hours. Not that I have one yet.

DR. COX: (Chuckles.) Is there a role for one? Most definitely. One of the things that we have been discussing very dynamically with a lot of different partners is the need for basically a point of care test that's inexpensive, easy to use, doesn't require a lot of training, and can be used to detect both human and animal infections. And so there is funding that will become available over the next months and years for development of point of care tests that wouldn't require such sophisticated labs. Now, actually developing a point of care test that is as sensitive as real time PCR is an incredible challenge.

Q: Yeah, Alan Glass with Senator Biden. I'd like to bring up an issue for Dr. Cox and Dr. Mostashari that's come up in a number of recent congressional hearings. And that is, are we making progress on who's in charge? So for example, let's say there's a small outbreak of avian influenza among humans in New York City, and it's people who work in New York. A couple of them live in Greenwich, and a couple of them live in Fort Lee, and at the same time, there's a whole bunch of chickens that have died in Pennsylvania. Who is going to be coordinating – and let's assume this is all H5N1 – who is going to be coordinating a uniform, specific response. You've got three different local jurisdictions involved. You've got three different states involved. You've got numerous federal agencies involved. Do we feel confident that we know who is going to be developing this, or is the response going to be a fragmented response based on New York City doing one thing, Greenwich Health Department doing another, Pennsylvania Department of Agriculture doing another thing?

DR. COX: I see someone is looking at me. What I would like to say at this point is that we haven't really got to that level of detail yet. There's a great deal of discussion that's going on. On the international front, the State Department has taken the lead and is coordinating efforts of HHS, USDA, USAID, of course, and Department of Defense. So we have it worked out in the international arena, but it does become quite complex when you have so many jurisdictions involved. And there are a lot of discussions about how – if there's a human case, what involvement would USDA have? If there's a – if the first importation is in birds – a migratory bird or a smuggled bird – then what role would the human health side have? We're working out those details. There's a lot of discussion.

There is a lot of joint planning going on. There are many exercises that are taking place. We're working very, very closely – that is to say HHS and USDA are working very, very closely together to get those plans worked out just between these two agencies. And I think I'll turn the microphone over to my colleague to talk about the New York City perspective.

DR. MOSTASHARI: I think that – Dr. Cox talked about the interagency collaboration, coordination. In New York City after the West Nile experience in 1999, I think there was a very good example of a couple of things – one, definitely the need for tighter collaboration between human health and veterinary and wildlife scientists and agencies. But it also, I think, point out – even though it was multi-jurisdictional – pointed out how it should work in terms on the human health side, where the local public health authorities have the mandate, have the responsibility for protection of health in their district. There's no question about that. But there's also – doesn't mean that it has to be uncoordinated just because the mandate is state and local. And in that context, we – we worked very closely with CDC, looking to CDC for guidance. And all the jurisdictions did that, and so there was, you know, one message. And everyone stood shoulder to shoulder. So that, to me, seems like the way you do it. You don't have to have – you can have coordination without command and control.

Q: Paul Dematric (ph)– (off mike) – CSIS. (Off mike) – basically saying that H5N1 – (off mike) – birds, the type they carry – (off mike). And that's the primary reason why there hasn't been interspecies transmission to humans so far. Perhaps Dr. Taubenberger could comment on, one, the validity of that observation, and two, how big is the impediment from where – (off mike) – are today relative to the strain and how they might mutate to actually infect us?

DR. TAUBENBERGER: Thank you. I think the comment that I would like to make – and then maybe Dr. Cox would like to comment as well – is that the situation becomes more and more complex as we look at it. I think that this sort of simplistic view that there is a quote, unquote, bird form and a human form of the receptor, I think, is breaking down. The studies, some of which I presented today, as well as some of the studies that you referred to – work of Dr. Kawaoka and his colleagues – shows that, within the human respiratory tract, there clearly are sugars that are quote, unquote, the human form and quote, unquote, the bird form and that they're mixed and different cells have different sugars. I think that when you look in even more detail at the kind of sugar array – the data that I presented in my talk that had been developed by my colleagues at Scripps – you find that there – there are sugars that are quite related, and yet human viruses bind to some subset of the quote, unquote, human receptor, and other human viruses bind to a completely different subset of quote, unquote, the human receptors.

And I think the way to think of it is that it's not an on-off switch. I think maybe the best analogy would be like the balance in a stereo, you know, that you can have the sound be halfway in between or all the way to the left, all the way to the right. And I think that the binding of hemagglutinin to receptors is something like that, that it's – there's a total continuum. And while adaptation to receptor modifications to allow the

virus to gain entry to certain is probably an important facet of how an influenza virus is going to adapt to a new host, I think it's undoubtedly just one of a number of mutations that have to occur. The temperature optimum in which the virus replicates is probably important, and that may also be a factor. The core temperature of birds tends to be a lot higher than of mammals, and influenza viruses are probably adapted to a higher temperature of replication. That may also favor the movement of these avian-like viruses deeper into the lung, not just receptor specificity. So that's just a really complex problem, and I think the more you look into this biology, you realize that there are no simple –

(Audio break, tape change.)

Q: – to the previous point, I think after terrorism, terrorist attacks, anthrax attacks, and – you know, a great deal of federal, state, and local planning occurred. But Hurricane Katrina showed us that we still really hadn't worked out these relationships in a seamless way. And I think it's urgent that we do this for pandemic preparedness. But my question really focuses on the strength of the scientific evidence when it comes to the natural history of this illness. What do we know in terms of studies about sub-clinical cases in various countries? And two, what is the scientific evidence that shows the ethnicity of Tamiflu currently in the cases that have been shown? And the third question relates to the vaccine. We're spending billions of dollars to develop a vaccine based on a strand of the virus from Vietnam. The Virus, as we know, is rapidly mutating. What do we know about the possible effectiveness if there is a pandemic flu, which will be a different virus than what – than the Vietnam virus?

DR. LAMB: Dr. Cox, I think that's all yours. (Chuckles.)

DR. COX: Okay, so I'll take the third part of your question first. What do we know about the vaccines that have been developed relative to their effectiveness if a pandemic were to occur tomorrow? We don't really know how effective the vaccines would be. What we can say is simply that we have tested convalescent serum, that is, serum from a patient who recovered from infection by a group one or clade one virus, the first family of viruses that caused human H5 infections and that the antibody developed by that individual or those individuals did not really neutralize or inhibit the growth very well. There was some inhibition, but it wasn't very effective in inhibiting – those antibodies weren't effective in inhibiting of viruses in the second family or clade two.

So what we realized is that we need to develop at this point of time a two-pronged strategy. First of all, we have to develop vaccine reference strains. And in the family tree I had in red, but I know it was very hard to see, the different viruses. Viruses spread throughout the family tree, which are developed into reference seed viruses that can be used in – to make pilot lots that can be used in trials in humans. And then we can look at the cross reactivity, and we can have this library of strains that's available, that cuts down on the time that's required for vaccine production. And so that's one strategy. Another strategy is to look very carefully at the hemagglutinin and to look to see if there are ways that we can modify the hemagglutinin so that we induce a more broadly cross reactive

response in an individual who is vaccinated. And that's a very high priority, a very important line of research that must be undertaken because of the diversity that we see.

Second part of your question had to do with whether or not we know if Tamiflu and zanamavir will be effective in treating and prophylaxing individuals and specifically with respect to treatment of individuals. And one of the big difficulties is that many of the patients who have had H5N1 were not originally suspected to have this disease. And so they went from clinic to clinic, from hospital to hospital until they were diagnosed. And so it was very late during the course of infection that they were given Tamiflu. And we know that Tamiflu is most effective when given in the first 48 hours of infection. There have been no controlled trials. It would be unethical to do so. And so what's being done now by the NIH is what I think is a very important program where they're setting up a clinical trials network of hospitals in the countries that have been affected. Now they won't be able to do – as I said, it would be ethically incorrect to withhold antivirals from patients who are diagnosed with H5, but they can actually look at outcomes, so in patients who were treated versus patients who weren't treated, the time course of treatment, and so on. So I think that we really don't know at this point how effective antivirals will be, but in the test tube, they are effective. In animal models, they are effective. So there is hope there.

Q: (Off mike) – family members of close contacts and distributions that were – (off mike.). But I guess what you're saying is that the timeframe has lapsed from when – (off mike) – and their close contacts are identified.

DR. COX: In some cases, family members have been given antivirals. In addition, in some cases where there were very large poultry outbreaks in certain countries, the government has decided to provide antiviral prophylaxis, but we really don't know how effective that was because this is a virus that is not very efficiently transmitted from – from the birds to people. So there are a lot of unknowns there. What we see in the test tube gives us a lot of hope, but we don't have good clinical, empiric data that tells us that these antivirals will actually be useful, whether or not we might have to use slightly higher doses or treat for longer periods of time than we do with normal seasonal flu. And so there are many questions that hopefully can be answered by the clinical trials network that's been set up by the NIH.

DR. LAMB: Then let's come actually to the first question, I think, that was asked and actually which I think is so important. And that is actually, what in fact are the antibody levels of other people who haven't got sick and gone to the hospital in the countries where H5 is endemic? And that is, are there studies on this now? And in fact have people been infected asymptotically or not?

DR. COX: There is not as much information as we would like. But if we – if we look back at the information that has been accumulated since 1997 when the first outbreak in Hong Kong, what we can safely say is that asymptomatic infections can occur, but they are relatively infrequent. There was a – there was some data presented by Cambodian colleagues at a recent meeting in Atlanta, and they had looked at contacts of

patients and had found that the majority of these contacts had absolutely no antibody to H5N1. So it is not – again, it's not highly transmissible. There are a few instances where poultry cullers have been infected. There are very few instances where healthcare workers have been infected. But basically, it's – you can look at it in two ways. Basically, the case fatality rate that you see on the slide is probably an overestimate, but it's probably not a gross overestimate based on the serologic surveys that have been done to date.

Q: (Off mike) – serologic, you know, epidemiologic study of the rate look at the natural history, look at serum prevalence in countries with systematic – (off mike) – methodology?

DR. COX: There is not, but we would like there to be. And so for example in Nigeria, where there has been a lot of exposure of humans to dead sick birds, there will be a sero-survey conducted. And we're helping to provide some of the financials and technical support for that sero-survey. We would very much like to see sero-surveys done on a much wider scale in countries like China, Vietnam, and Thailand, where there really ---here there has been circulation in the bird population for a much longer period of time. Hopefully some of those studies will be done in the coming years – months and years.

Q: (Off mike) – New England Science writer. There was a report recently in The New York Times just a couple days ago that information was being sent to the WHO confidentially by some countries only under the assumption that it would not be shared. I'd like to ask in a general sense, is there information from other countries that you do not have that would be useful to have at the CDC and what sort of information that might be and if there are any countries that are particularly unforthcoming?

DR. COX: I think that what we had seen early on during the H5N1 era was that countries were very, very reluctant, particularly on the agricultural side, to come forward because of the economic consequences of announcing that they had H5N1. And the economic consequences are really considerable, as Dr. Nabarro pointed out. We've moved on from that – from that point. Countries – many of the countries that have been recently affected by H5N1 have been very open about what's been going on. They have provided information about the clinical aspects, about the epidemiologic aspects. They provided viruses to reference labs. Some of the data from the sequence analysis has been uploaded immediately into the public databases. Other countries are still rather reluctant to share the information so widely because they want their own scientists to be able to publish. And so this is – this is an issue that we are working very closely with WHO on and hope to be able to provide some solution within the next months.

There have consistently been some barriers with respect to sharing information from between the agricultural sector and the human health sector, and I think you heard Dr. Nabarro's comments in his talk. And then he further elaborated on exactly what he meant with respect to things not being as transparent on the agricultural side as we would like. And I think that's where we would really like to have more information. And so

but there is a lot going on. There is a lot of sharing, and I see a lot of improvement, if I look at the situation two years ago compared to what's going on now.

DR. LAMB: In the back.

Q: Dr. Cox, you talked about the scenario of the first human case of H5N1 in the United States. How long would it take for a confirmation that the person had the virus?

DR. COX: You may or may not be surprised to know that travelers who have returned from spring festival or Tet celebrations in Asia and have come back to the United States with acute respiratory illness have gone to physicians. The physicians have taken the travel history. Specimens have been collected, tested by state health departments, and then sent on to us for confirmation or sent directly to us. It's happened several dozens of times over the past few years. It actually takes a relatively short period of time. Once we receive a – the specimen at CDC, we can turn around a result within four hours using the real time PCR assay. So unless the results are equivocal, we can give an answer back to the state health department, who can then in turn give the answer back to the clinician. And so this has – this has happened, as I said, several dozens of times over the past few years. And in all cases where influenza has been detected in these patients, it has been H3N2 – normal human influenza.

DR. LAMB: Are there any other questions? Yes, sir?

Q: Does anybody want to comment on how good the evidence is that this global spread is actually through migratory birds as opposed to movement of poultry or pets or things of that nature? And how important would knowing that answer be to figuring out where it's going to be next?

DR. COX: Perhaps I could make a couple of comments, and then Jeff could comment as well. What we have now is quite a bit of genetic data that has demonstrated very conclusively that the viruses that have moved across the Middle East into Eastern Europe and now into Western Europe are closely related to viruses that caused the migratory bird die-off in Chang Hai (ph) Lake, China. So at least from the point of view of the ancestry of the viruses, we can see that the viruses are related to a migratory bird die-off. In addition, what we can say is that in some of the countries in Europe, the first instances of detection of H5N1 have been in dead migratory fowl. So the conclusion, at least at this point, is that migratory fowl do play some role in the spread of the virus. There's no doubt that there are many other mechanisms for spread of the virus. But at this point, I think it's fairly clear that, you know, that they're certainly not a culprit, and we shouldn't be shooting wild birds out of the sky as has been suggested in some situations. But there is a clear role now.

Q: I was thinking more in Nigeria, where it has showed up first apparently in the domestic poultry industry without too much evidence of it being in wild birds.

DR. TAUBENBERGER: I don't have any direct information about what – what's happening in the strains in Africa right now. I think there's just a general – I agree with everything that Dr. Cox has said. It's clear just if we back up just for a minute. If we look at the history of the so-called high path avian viruses, remember when we've said that avian influenza viruses are present in a number of species of wild birds, and they generally cause no symptoms in these birds. These high path viruses are basically diseases of domestic poultry – and that they evolve independently in domestic poultry – not really diseases of wild birds. So what we're seeing now with the current H5 situation, in a sense, is historically unprecedented that you have a virus, in a sense, that might have developed in domestic poultry but now clearly has moved into various wild bird species. And so for example, the mute swans that are dying in Europe are probably in a sense the sentinels just like some different species of birds were sentinels for the movement of West Nile virus in the U.S. in the past.

But it's unclear what this really means in the sense that, are these viruses being brought in by domestic poultry and then spilling over into local wild bird populations? And some bird species might be susceptible and die, and some bird species may be completely resistant to infection or show disease of the virus. And how much is actually being carried by migrating wild birds? I think most people would agree that the birds that become immediately ill with this rapid course and death are unlikely to be migrating long distances. So it's probable that we're seeing the effect of the disease in birds that are susceptible and then die locally, and that there certainly might be wild bird species that are spreading the virus perhaps asymptotically long distances. But we're not actually doing surveillance in them because we don't – we don't recognize them because it's easy to recognize a bird that's dead. And so and this is really a difficult problem, and I think that it's clearly mixed. And so, I mean, there were examples of H5 infected birds being attempted to be smuggled into Europe, you know, these eagles that were infected that showed up. And so clearly it's mixed.

And I think then, if the big question is, will H5 appear in the Americas? I guess the answer is nobody yet knows, and if it does, it could be via a number of routes. It certainly is theoretically possible that it could be brought into the United States by an unknown species of migrating birds from an unknown flyway. There are flyways in which you go from Asia and Siberia up into the subarctic and then can cross into Alaska or Canada. I think that there are some known flyways that go between the poles even across the East Coast of the United States, for example. So you could imagine a virus coming in from Europe and Siberia through Greenland down into the east coast of the Americas and even to South America. But it could, of course, be brought in through, as has been said, the legal or illegal importation of birds, exotic birds, poultry, and so on. It could come theoretically in the form of a person infected. And so I think all of those options are available, and I think, like everything else, all of those things probably all happening at the same time. And we just don't – I think it's too simplistic to blame wild birds, which I suspect is kind of a NIMBY phenomenon thing that nobody is responsible for wild birds so therefore to blame them makes it easy.

DR. LAMB: Okay, well, thank you very much. I would like to thank all my other speakers, and I think Anne Simon (sic) wants to have the final word – Solomon, sorry.

DR. SOLOMON: Yes. On behalf of the Howard Hughes Medical Institute and the Center for Strategic and International Studies, I would like to thank Dr. Lamb and all of our panel members and thank you for coming. As I said at the outset, this is the first of a series that Howard Hughes and CSIS are sponsoring this spring. The second will be on April, the 6<sup>th</sup>, and will be on countermeasures – vaccines, diagnostics, therapeutics for avian flu and other infectious diseases. Please be sure and sign at the sign in sheet, and we will send you an announcement of all these sessions. And thank you all for coming.

(Applause.)

(END)