

**CLINICIAN OUTREACH AND COMMUNICATION ACTIVITY  
CONFERENCE CALL  
AVIAN INFLUENZA UPDATE  
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**STATUS OF AVIAN INFLUENZA OUTBREAK IN ASIA**

The following summarizes what CDC and the World Health Organization have learned about the current influenza H5N1 outbreak.

- There have been outbreaks of H5N1 avian influenza in Vietnam since December and human cases since January.
- The most difficult aspect of an international outbreak is to get accurate information on which to base public health decisions, and information about what was going on with the outbreak was very sketchy.
- CDC now has a team on the ground in Vietnam, with people working in Hanoi and in Ho Chi Minh City to try to get more information.
- We also have placed people in Bangkok more or less permanently, so they have been working closely to get information from Thailand.
- There are CDC people in China who are also trying to help get information from that country.
- There have been a number of countries affected by poultry outbreaks in Asia, and so far only two countries have reported confirmed H5 influenza cases in humans, and those are Vietnam and Thailand.
- Human cases: Currently there have been, officially, five laboratory-confirmed cases in Thailand, and all five of the victims have died. In Vietnam there have been 15 laboratory-confirmed cases and 11 of these have died.
- We suspect that these reported cases are really the tip of the iceberg, because surveillance and other issues, reporting, etc., are not great in many of these countries. It would not be at all surprising if there were quite a few more cases than what have been officially confirmed by the governments to WHO.

**UNCONFIRMED HUMAN-TO-HUMAN TRANSMISSION**

- As reported in the recent Health Alert Network report, there has been mention of a cluster of human cases in Vietnam involving possible human-to-human transmission of H5N1. However, this has not been confirmed. Information has been difficult to get, because CDC people have not been allowed to interview family members.

- Information on this cluster is coming from the Vietnam government's Ministry of Health, so we have been sort of one step removed from many of the primary information sources.
- The possibility of this cluster involving human-to-human transmission has implications for our country and for infection-control practices and treatment and prevention here.
- We do actually expect to see cases of human-to-human transmission, but what we are really afraid would happen would be that we would see efficient human-to-human transmission that would be sustained. That has not been documented anywhere yet.
- We saw human-to-human transmission in 1997 in Hong Kong, but that outbreak did not take off and there was no pandemic associated with it. So we are not at all surprised to hear about limited human-to-human transmission. However, what we are really trying to be very vigilant about is something that ends up being efficient transmission that is sustained within the community, and that, again, has not been documented so far in this outbreak.

## **CLINICAL PRESENTATION OF CASES**

- CDC has not received much information on clinical presentation in the confirmed human avian flu cases, again, because our people have not been allowed to go to the hospitals. This situation is improving, and we are slowly getting permission from the Vietnamese and Thailand governments to do so. As you can imagine, the politics of these international outbreaks are always very sticky.
- Many of the cases that we know about have occurred in children, not in adults. Almost all of the infected individuals had had contact with sick or dead poultry.
- All persons with confirmed cases of avian flu have all been admitted to hospitals with pneumonia and sometimes ARDS-like presentations. Many of them have ventilated and, again, the majority have died, so this virus is quite pathogenic, as far as we know, in humans.
- We do not have good denominator information. Work is ongoing to try to set up studies to examine the situation, to see if there are, in fact, persons who have been infected but who have no symptoms or fewer symptoms doing sero-studies, etc.. Those studies have not gotten off the ground yet, again, because of a lot of political considerations. So the cases that we know about have been severely ill, and most of them have actually died.

## **PREVENTION: VACCINE AND ANTIVIRALS**

### **Vaccine**

- In regard to actually preventing and treating influenza H5N1, prevention, as with garden-variety influenza, would best be served with a vaccine, and there are a lot of efforts ongoing right now to develop a vaccine based on the viruses that are circulating currently.
- Unfortunately, we could not use viruses from last year's H5 mini-outbreak in Hong Kong. There had already been a good deal of work going forward in making a vaccine

from those viruses, but the current viruses are genetically distinct enough that it was thought that progress would have to be made with a new vaccine based on these viruses. So that work has been ongoing at CDC and a couple of other labs.

- The best-case scenario for having a virus available for a vaccine for the human population is several months from now. This means that if, for instance, an explosion of human cases were to occur tomorrow, that vaccine would not be an option.
- What we have seen in prior pandemics in the last century is that the second wave of disease, which usually occurred a few months after the first wave, tended to be the worst wave. So even if a vaccine for influenza H5N1 is not available for several months, it could actually be quite useful considering that we would expect the second wave potentially, again, to be worse than the first wave. At that point, we would have a vaccine and would be able to use it in the human population.

## Antivirals

The absence of a vaccine for the earlier stage of the H5N1 outbreak leaves us with options of isolation, quarantine, and antiviral use. Cliff McDonald will talk about isolation and quarantine in just a moment. I'll talk briefly about antivirals.

- The genetic profile of the avian viruses that we have looked at so far at CDC and elsewhere have indicated that the viruses isolated from humans will probably exhibit resistance to amantadine and rimantadine, the adamantane drugs.
- This hasn't been born out in susceptibility testing yet. That testing is ongoing and takes a good while, but there have been classic mutations in these viruses such that we have every expectation that they would exhibit resistance to both of those drugs, amantadine and rimantadine.
- The H5N1 viruses are, however, exhibiting a pattern that is consistent with susceptibility to the neuraminidase inhibitors, so oseltamivir and zanamivir would be expected to be effective in prophylaxis and in treatment for these viruses. However, obviously there have been no clinical studies that would indicate that that is the case. We would, though, expect that they would be effective in prophylaxis especially, and possibly in treatment.
- We know that these drugs are not great for treatment of even garden-variety influenza. One needs to start treatment within 48 hours of symptoms. The main outcome that is of benefit is that the length of symptoms is reduced by between one and two days when you start within 48 hours of symptom onset.
- There is really scant-to-no evidence that antiviral drugs for influenza prevent death or other serious complications in patients who are infected. They are really drugs that have much more utility in the realm of prophylaxis, although we certainly recommend that they are used for treatment, especially in cases where a severe disease is being exhibited, even though we don't have good evidence that they work for that.
- Regarding supply, it seems that since these drugs, especially the neuraminidase inhibitors, first became available in the late 90s, they did not catch on in the clinical community until more recent years.

- At the present time, there is not a huge supply of these drugs nationwide or even worldwide. The supply is very similar to what was seen with the flu vaccine domestically this year and in previous years.

### **Supplies of Antivirals**

- Pharmaceutical companies have an obligation to manufacture a certain amount of a drug or vaccine; however, they will not exceed what they perceive to be the demand. In the past there has not been as much demand for these influenza antiviral agents as one might expect, so there is a limited supply now available.
- That was probably noted by clinicians even in this past season when various communities were reporting that they were running out of drugs, etc., and especially the suspension form of the drug for use in pediatric populations.
- CDC has worked to acquire these antiviral drugs for the national pharmaceutical stockpile, and that is an ongoing effort that actually has been in process since before this current avian influenza outbreak began and as a part of the ongoing development of the national pandemic plan.
- That leaves us at this time with some of our most effective means for control early in an outbreak likely being antivirals, but also isolation and quarantine measures.
- The philosophy of how antivirals, quarantine, and isolation would be used would likely change in the course of the outbreak depending on whether there was efficient and sustained transmission from person to person.
- Influenza is a different bug than SARS, and it is almost certain that if there were efficient and sustained transmission of an avian influenza virus, one would have to use different measures to contain it than what were used with SARS. In fact, containment would really be sort of a relative term, because influenza just behaves differently than SARS behaved, as far as what we know of SARS based on our limited experience with it.
- Efforts early in a potential pandemic would be very aggressive to limit spread within the hospital community and limit spread within communities themselves, with the understanding that influenza is a different kind of virus. Once it gets out, it really does spread efficiently from person to person. A lot of measures would be implemented early to try to slow it down in hopes that a vaccine would be out within a few months and could be used, especially in anticipation of a second wave, which would possibly be worse than the first wave of the disease.
- The CDC Web site also provides information on some specific control and diagnostic testing measures, which are more laboratory focused.
- I would encourage everyone who has not already done so to look at the CDC health advisory that came out on the Health Alert Network two days ago. That is available on the CDC Web site, and it gives more information on the history of this particular outbreak. <http://www.cdc.gov/flu/han020302.htm>

**L. Clifford McDonald, M.D.**

**Medical Officer**

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**Clinical and Infection Control and Occupational Health Emergency Response Teams for Avian Influenza**

- I have been in a leadership role along with Scott Harper and Lisa Delaney on the Clinical and Infection Control and Occupational Health Emergency Response Teams, leading the response to avian influenza, or influenza H5N1.
- One of our charges has been to develop guidance for isolation or for infection control, trying to prevent transmission of H5N1 in healthcare settings.
- We know that there has been limited human-to-human transmission even back in 1997 when there was H5N1 in Hong Kong, but that was very limited and actually only demonstrated by serologic studies that could be interpreted in different ways. That is partly, also, because if you have been to Asia, you realize that there are many opportunities to have exposures to domestic poultry.
- The other major concern is that H5N1 has a high pathogenicity, and not just for domestic poultry. Even if we look back to the total pool of serologically positive persons, back in 1997, the mortality rate with apparent infection does appear quite high, even when you account for some persons possibly being infected below the current limit of clinical detection.
- The mortality rates that Scott mentioned to you are, of course, in excess of 80%. That is for known clinically apparent disease in Vietnam and Thailand right now. Then, of course, there is the question of person-to-person transmission in Vietnam and also the concern of the possible recombination of the avian virus with human influenza genes that could occur in other hosts, including humans.
- Because of these concerns, we held two calls with the Healthcare Infection Control Practices Advisory Committee (HICPAC) over the last several weeks, and we have also had calls with other flu experts. From these meetings, we have come up with these isolation recommendations.

## **INFECTION CONTROL**

- As many of you know, the current recommendations for infection control of human flu consist predominantly of droplet precautions. Droplet transmission of human flu would be predominantly via large respiratory droplets that do not transmit through the air well and fall on surfaces within, usually, three feet. This is thought to be the predominant mode of transmission of human flu.
- There is some literature to suggest airborne transmission of human flu, but none of the epidemiologic data is sufficiently forceful to show that airborne transmission plays an important role in transmission of influenza in humans.
- So droplet precautions are recommended and droplet transmission is thought to be predominant, but what is true with human flu may not necessarily be true with avian flu.

- As Scott mentioned very correctly, H5N1 is not SARS, but we don't know exactly how it will act either, whether it will act just like human flu from the beginning or not. So we don't know exactly how it would be transmitted from person to person and how it is transmitted may, in fact, evolve very quickly over time.
- Finally, our sense is that the best time to contain an outbreak is early on. Because of these concerns and considerations, we have recommended isolation in our interim guidelines for infection control for H5N1, very similar to how we isolated SARS. This includes:
  - Contact precautions or the use of gloves and gowns whenever coming in direct contact with the patients,
  - Eye protection in the form of goggles or eye glasses whenever coming within three feet of the patient, and
  - Airborne precautions, which entail, whenever possible, the use of an airborne isolation room. Such rooms have negative pressure to the outside environment. They also have special air-handling characteristics, such that the air in the room is changed 6 to 12 times every hour. Recommendations include the use of a fit-tested NIOSH-approved N95 or higher respirator for respiratory protection for the healthcare workers who enter that room.

### **Identifying Persons to Isolate**

- The bigger issue in our current situation is who should we suspect of having an H5N1 infection so that we can institute such precautions. Again, we are working under the assumption here that there will be a period of time when spread may be contained through infection-control precautions. Otherwise we would not be recommending any special form of infection control. Of course, we are operating under the assumption that there is perhaps some window of opportunity when isolation and infection control could play a critical role.
- At this time we recommend isolating and testing in a public health fashion persons with severe disease, who have had a recent travel history to any of the countries where there is current documented outbreak, either in domestic poultry or in humans or both, of H5N1. The listing of these countries is on the CDC Web site that we refer to in this guidance document.
- Persons who have a travel history and have severe respiratory disease, which is defined as radiographically confirmed pneumonia, acute respiratory distress syndrome, or other severe respiratory illness requiring hospitalization should be isolated. Those persons who have such radiologically confirmed pneumonia or severe disease and are hospitalized would be isolated in this fashion described above and would undergo testing.
- Public health laboratories would be involved in this testing, because of the nature of the testing.
- The other group that could be considered on a case-by-case basis after consultation with state and local health departments is the person who has less severe disease but provides

a history of actual contact with domestic poultry or a known suspected human case of H5N1 in an infected country within ten days of their symptom onset.

- In the near future we will be recommending that only healthcare workers who have been vaccinated with the influenza vaccine that is currently offered for this year's strain should care for a suspected or documented H5N1 patient. The idea is to reduce the opportunities for persons to be infected with both H5N1 and the prevailing strain if H3N2 or other influenza A at the same time.
- Other guidance that we will be considering in the future is prophylaxis recommendations. We do not have those right now, but because there is that opportunity to practice prophylaxis with antivirals, we will certainly be addressing that in the future.

## **QUESTIONS AND ANSWERS**

**Frank Pollin**

**Minnesota:**

I was a few minutes late to the call and I hope you didn't already answer this. Is there any definitive evidence yet that there was or was not any human-to-human transmission?

**Scott Harper**

There has not been definitive evidence that that occurred. There has been difficulty in getting primary information, despite having CDC personnel on the ground in Hanoi. They have not been able to go and actually interview the family where that occurred. What happened was actually three out four family members died in relation to a wedding party that occurred. It looks like all four people were probably infected, although the first person who died did not have testing done. For two of the four, it's unclear that they had poultry contact. The other two definitely had poultry contact. That is the only cluster that is of concern at the moment. Again, according to the Vietnamese government with whom our team has contact on the ground there, no other family members or attendees at that wedding were ill. So it does not appear that there is any sort of efficient or sustained human-to-human transmission at the moment, and those two particular cases it is still up in the air.

**Lori Lane**

**California**

Could you please explain again why healthcare workers need to be vaccinated against the current flu? Let's say we had a case here in California. They need to be vaccinated again, I'm assuming. Could you explain that again?

**Cliff McDonald**

I'm sorry. Just to clarify that, we are not saying they have to be vaccinated again. Of course, the goal in healthcare facilities, as you know, is to vaccinate healthcare workers. We achieve that with variable success in different healthcare facilities, but if there is certainly an opportunity to select those who have been vaccinated or go on and vaccinate others who were not vaccinated

last fall, then preferentially we recommend that the healthcare workers caring for the H5N1-infected patient have received the human influenza vaccine for this season.

The idea behind this is that vaccination would provide them some protection, at least, against the prevailing strains in the community of human influenza and reduce the possibility that they would be co-infected with H5N1, while at the same time incubating the human influenza strain from the community.

This has been something that has been recommended in those persons who are responsible for culling birds in Asia by the WHO and it has been put forth as an idea also from HICPAC, that we should include this in the future, and we feel like that seems very reasonable.

**Martha Cooke**  
**Illinois**

I wanted to ask a bit more about what you talked about with the history of the second wave in a pandemic. I think it sounds very different from what normally happens during the flu season, in terms of the second strain predominating. I just wanted to hear more about how and why that happens.

**Scott Harper**

Thanks for your question. I'm not sure that, really, people know why it happens, but it was documented especially well in the 1918 pandemic. Pandemic influenza is also a little strange in that it doesn't necessarily follow seasonal patterns as we see with garden-variety influenza. If one looks back at what happened with the 1918 pandemic, activity was starting to be seen in the spring of one year and then peaked out. It was actually then the second wave, which started up later on in that year.

It is really unclear about why that would happen that way, but it does lead to some rationale, from a public health decision-making process, to say that it's very worthwhile to go as fast as we can to generate a vaccine so that it possibly would be available before the first wave is over, and certainly before the second wave began.

I'm sorry. I don't have a lot of satisfying information on why that actually occurs, other than that you have a huge population in the world that has not seen this particular strain of influenza before as opposed to what we see year in and year out when many people do have some underlying immunity to what is circulating. That may have something to do with it, but the population immunity and dynamics are quite different with a pandemic strain of influenza than they would be with an H3N2 strain or an H1N1 or a B.

**LJ Tan**  
**Illinois**

This is LJ from the AMA. A quick question about when you talked about the vaccine. The last I heard was that this H5N1 is lethal in eggs. Can you tell me a little more about the details about the vaccine production and if it's still going on in eggs or is this the recombinant DNA process?

**Scott Harper**

Hello, LJ. I don't really know a lot about the vaccine process, so let me preface my answer with that. Part of the goal when using reverse genetics to come up with a vaccine strain is to keep it from being pathogenic in eggs so that, in fact, we can grow large amounts of the vaccine virus, as you would with a usual season.

I don't have background in molecular genetics or in any of these procedures. I can get you in touch with Nancy Cox and these folks over in the lab who are doing that sort of thing in conjunction with folks in London and Rob Webster's group at Saint Jude's in Memphis. Those are the three main labs currently working on this right now. But your point is well made, that it is highly pathogenic. The goal through these reverse genetic techniques is to develop a strain that is not, and also that is not pathogenic for purposes of testing it out in animals.

**LJ. Tan**

Can I quickly follow up on that? The question then is, obviously, are we close to a vaccine?

**Scott Harper**

No, LJ. It will be several months before something like that is available, because we had to actually kind of retool and start over completely with this particular outbreak. We had been hoping that we could use what had been developed for the mini H5 outbreak that occurred in Hong Kong about this time last year. A lot of progress had been made on that particular vaccine-strain for that virus. When we finally received some viruses from the current outbreak in the lab here, it looked like it was different enough, that if you tried to make a vaccine based on last year's virus, it would not likely be effective against what is circulating right now. So we are looking at several months before something like that would be available in the marketplace. That's why some of these other measures are really being focused on right now, while folks in the various labs are working overtime to try to generate that.

**Marguerite Neill**  
**Rhode Island.**

I would like to go back to Dr. Pollin's question about the human-to-human transmission and this unfortunate cluster. Do we at least know whether the individuals who are affected were symptomatic at the time of this wedding reception, because what I'm getting at is whether we really are looking at the right population denominator to assess whether transmission occurred?

**Scott Harper**

Part of that is known and part of it is not known. Ideally, what would happen would be that folks could go in with some pretty detailed questionnaires and also have the ability to do epidemiologic work on these folks and get some information from that. Again, the biggest problem has been that there has been sort of a buffer and we haven't been able to get primary data. It has all been data that has been relayed to us pretty much secondarily, so we have had similar questions to this.

One thing that we are really interested in is there was a man who was first ill, the groom, and he died. His two sisters and new wife were all infected. There are viruses available from the two sisters, although we don't have them here. It would be really important, also, to look at those viruses genetically and see whether or not they have acquired human influenza viral genes. Those viruses are in Hong Kong right now.

The fourth person, the wife, who survived, would potentially be a real gold mine for information, but again, it has just been politically incredibly difficult. Part of that is understandable, because what happens is you show up at a house, whether it's for doing this kind of surveillance work or data acquisition, or if you are doing it gathering from pigs and chickens or whatever. People put on all of their protective equipment. The police and tons of reporters show up apparently. So the family is understandably grieving and going through these processes and they get quite agitated about having such attention being paid to them. Then the government, also understandably, says, "Look, you are causing too much hubbub and you just can't get more information right now. We'll get all the information that needs to be gotten." So one can really see how these information gaps develop, but that is really all we know for the time being.

**Marguerite Neill**

Do we have any qualitative information from any cases, not just this cluster, on shedding?

**Scott Harper**

No. Apparently, though, there is a lab in Ho Chi Minh City associated with the Oxford group. They are really set up to do a lot of nice studies with not only viral shedding, but looking at cytokine responses and some other potentially interesting clinical and lab information. Again, there have been some problems there with the government, because the government would like to be able to certify the Oxford lab and be able to say, "Yes, you can grow these viruses in BSL3+ conditions." So they, in fact, have not been allowed to actually grow viruses there and look for viral shedding.

Testing has just been a real big issue. We have had a couple of laboratory people on the ground, trying to increase and improve laboratory capacity in Vietnam, but I don't know if you have worked on international outbreaks before. There are just a lot of sensitivities within countries and also with WHO. Things just don't occur at the same pace that they would in this country because of that and for other reasons. So we are very much hoping that, especially down in the

south, that laboratory can get up and running pretty soon so that we can get more of that kind of information.

**Marguerite Neill**

Thanks very much. Your points are all well taken. I think the message that we are getting loud and clear from all of you is that we are not making any assumptions necessarily that the behavior of this avian flu, even in the humans, will be like it has been in the past or like the regular flu.

**Scott Harper**

That's right. Also, I think that it could change throughout the outbreak. So if there is at some point a recombination event or recombination events that might make it more likely to have a virus that was efficiently transmitted, things could really change in a very short period of time. So we are also trying to be flexible in that regard, in terms of getting information out and making recommendations.

**Herbert Young**

**Kansas**

Herbert Young with the American Academy of Family Physicians, following up on LJ's question a bit, on the vaccine. Several months away—then what? Testing of some sort? Then when would a decision be made as to how much vaccine to make and how it would be distributed and so forth?

**Scott Harper**

Actually, talks about that issue have been ongoing for a long time. There have been different scenarios proposed about things, especially about who buys it and who distributes it. The industry would prefer to have the current channels of distribution and manufacture, etc., in place and used, whereas what we have seen in the public health community is more of a preference for having the federal government and state and local governments take many of those roles.

That has been an ongoing discussion for a long time, for years actually. As always, I think that in public health we tend to be frequently more reactive than proactive, so when our hands get forced, decisions get made pretty quickly. Those discussions are ongoing, especially over through the National Immunization Program and some in conjunction with us here in the National Center for Infectious Diseases.

Another group in Health and Human Services is the National Vaccine Program Office headed up by Bruce Gellin. His group has actually been the main one responsible in the recent past for working on the pandemic plan. Those are discussions and decisions that will be made at pretty high levels within the department of Health and Human Services, and those discussions are ongoing. To answer your specific question, I don't know when answers will be forthcoming, but there is a lot of talk about that ongoing right now.

**Martha Cooke**

**Illinois**

Thanks for taking a second call from the American Academy of Pediatrics. I wanted to inquire as to what is known about the numbers of cases in children, and also the outcomes of those cases.

**Scott Harper**

I don't have a breakdown of those in front of me, and part of that is because we don't necessarily have that information for all of the cases, but we do have demographic information for a lot of them. The vast majority of the cases have been in children. The problem with relaying that kind of information is that it's all numerator data.

It could potentially be very similar to what was seen in this last influenza season, where as soon as the media reports, especially, started coming out of Colorado, about the pediatric deaths, despite their having occurred in previous seasons and having already occurred in Texas with this season, that was really the impetus to start looking for them.

So it's still unclear to us if what we are seeing is due to the fact that this is more pathogenic in kids or is it just being seen more in kids? We have no good grip at all on how surveillance - well, surveillance is not being done, mostly, and where it is being done, and when cases are being picked up, we also don't have a clear idea of what their case definitions are. Our folks there have been really trying to give suggestions on what kind of case definitions should be used, how surveillance should be put into place, etc.

We do know that in Thailand the CDC has an emerging infections program and they have, over the last year or two, set up respiratory disease surveillance in a couple of provinces. Early on, in talking to people there right now, the suggestion is that there could potentially be quite a bit more activity ongoing, not just in kids, but in adults as well. Again, it's just so early in the process that we don't have more information on that.

**Martha Cooke**

Do you know if any of the laboratory-confirmed cases in children have survived?

**Scott Harper**

Yes, there have been survivals in the kids.

**Marguerite Neill**

Can I go where angels fear to tread and ask you about the change in the laboratory testing recommendations in the guidance document?

**Scott Harper**

Do you want me to go over that or did you have a specific question?

**Marguerite Neill**

As I am recalling this, there was not previously direction to undertake any and all respiratory specimen testing only in a BSL3 facility, whereas that recent advisory directs that.

**Scott Harper**

Do you mean in the prior H5 scares?

**Marguerite Neill**

Right.

**Scott Harper**

Part of that is happening in the context of ongoing, albeit apparently not heavy, SARS activity. We wrestled a lot with different issues, because a patient returning, for instance, from southern China, who had a febrile respiratory illness with X-ray findings, could be either SARS or H5 or something else.

So the decision was made by people, in conjunction with folks in the APHL and CSTE and with ongoing discussions over a period of about two weeks, to recommend that isolation procedures would only occur in a BSL3+ facility and that the diagnostic algorithm should start in a specified case, as the case definition, if you have seen the document, on who should be definitely tested and who should be considered for testing with PCR for the agents. Some states have that capacity and others don't yet, but are working on it. For those who don't yet have that capacity, the recommendation is to have the original clinical sample sent to Atlanta, where the PCR can be done.

It's not a perfect system, and we also are continuing to solicit input on that from people who are on the ground in the states seeing patients and working in the labs who run into difficulties with the algorithm. We really do want to hear about it so that we can improve it. But for the time being, this is what we have.

I don't know, also, maybe addressing part of your question, highly pathogenic H5N1, as far as I know, has always been a BSL3+ agent, or has been for quite a while, so that should not be cultured unless those facilities are available.

**Joseph Dalovisio**

**Louisiana**

I was wondering if you have any data based on past experience, epidemiologically, about whether there is any seasonality to expect with H5N1 like you see with other human influenza strains?

**Scott Harper**

I think it would have to be, at this point, seasonality in a poultry or bird population that was looked at, which probably would not be relevant to the human condition. There have just not been outbreaks of H5N1 at the kind of level that you would need to see among human beings to measure whether or not there is a seasonal component to it.

That being said, in prior pandemics, when a new virus has been introduced into the population, typically it's knocked out the old virus. Although now we have two A viruses in circulation, in the past it was usually one would get knocked out and the new one would take that niche, and then that one would become seasonal in the population after underlying immunity in the population had been built up to that virus, etc.

So, ostensibly, once this was a virus, if it developed into being one that is currently like H3N2 or H1N1 that is sufficiently transmissible and is not highly pathogenic where it wouldn't burn itself out, etc., if it were more like a garden-variety influenza virus, it would probably be seasonal. But I don't think with H5 viruses in human population there could have been any data collected yet to suggest that.

**Joseph Dalovisio**

What I was getting at was that since it has been an avian disease primarily with occasional spillover to humans, whether, if it was seasonal, we could sort of get to a point where the disease was dying down in birds and we would have to worry less about spillover in humans, assuming there hadn't been any recombinant events occurring.

**Scott Harper**

There is no published data to suggest that, and the countries that likely really have the problem with H5 viruses in birds have never produced data. Some of the countries that likely have these problems may have had the problems for a while, and it's only now coming out because of the widespread problems regionally. That's actually a really interesting question that could be looked at, at some point, but I don't think it has been and it certainly hasn't been published.