

Exercise 1

Surveillance for Avian Influenza in Animals and Humans

Objectives:

Group members will be able to find National Animal Health Laboratory Network (NAHLN) laboratories, describe when to report a potential case of avian influenza among poultry or humans, know techniques to enhance influenza surveillance, and apply avian influenza case definitions to human cases.

Instructions:

For this exercise, you and your group will discuss human and animal surveillance components of an outbreak of avian influenza in poultry. You will be presented with information followed by a series of questions. Your facilitator or one person in your group should read the information aloud to group members, and the questions should be discussed as a group. You may want to reference the National Animal Health Laboratory Network (NAHLN) handout during this exercise. This scenario was based on a Canadian outbreak presented at the 2004 Canadian Poultry Service Industry Workshop.*

Time allotted: 1.5 hours

Background: Day 1

The owner of a broiler breeder farm in Page County, Virginia, noticed that his flock of 12,000 broiler breeder chickens (Flock A) took double the normal time to consume the allotted amount of feed, and noted a slight increase in mortality. The adjacent flock of 9,000 (Flock B) was clinically normal. The farm owner suspected an issue with a recently delivered load of new feed and contacted his company veterinarian.

Day 2

The veterinarian visited the next day. A sample of eight dead Flock A birds was submitted to Harrisonburg Regional Animal Health Laboratory of the Virginia Department of Agriculture for further investigation. The suspect load of feed was removed and immediately replaced with fresh feed.

Question 1 – Does it matter which laboratory the samples were sent to? Hint, see NAHLN handout.

***Suggested Answer** – Testing for AI should be done at a USDA-approved laboratory with the capability of running the AI test. The handout indicates that the Harrisonburg laboratory is approved to conduct avian influenza (AI) and Exotic Newcastle Disease (END) tests.*

Question 2 – Should this problem be reported (i.e. to the state or national Department of Agriculture)?

***Suggested Answer** – At this point, it is probably too early to report the apparent outbreak, as it could be due to a number of illnesses, some of which might not be reportable, and the mortality is low. There are mandatory reporting requirements in place for LPAI and HPAI, but in this instance more clinical or laboratory evidence is needed before a report can be issued.*

The USDA National HPAI Response Plan

http://www.iowadnr.com/avianflu/files/Draft_NationalAI_ResponsePlan.pdf specifies clinical case definitions for highly pathogenic avian influenza in poultry. A flock with one or more of the following clinical signs would be considered clinically suspect for HPAI:

- *reduction in normal vocalization; listlessness; conjunctivitis; drops in egg production sometimes with pale, misshapen or thin-shelled eggs*
- *Respiratory signs such as rales, snicking, and dyspnea*
- *Neurological signs such as incoordination or torticollis*
- *A drop in feed and/or water consumption*
- *Swollen or necrotic combs and wattles*
- *Swollen head and legs*
- *Subcutaneous hemorrhage of legs*
- *Lungs filled with fluid and blood*
- *Tracheitis and airsacculitis*
- *Petechial hemorrhages on internal organs*

With or without the clinical signs listed above, an unusual spike in mortality would also be classified as clinically suspect for HPAI. Unusual mortality is defined as:

- *Commercial broilers: exceeding 4 per 1,000 for 2 consecutive days*
- *Commercial layers: 4x normal daily mortality for 2 consecutive days OR 5% drop in egg production over 3 days*
- *Commercial turkeys: exceeding 2 per 1,000 per day*
- *Backyard flocks: any sudden or significant mortality or drop in egg production*

In this case, we do not have the exact mortality among Flock A.

Question 3 – What surveillance activities for seasonal and avian influenza in humans should the local and State health departments be conducting on a ‘normal day’?

***Suggested Answer** – In the absence of HPAI in the US, surveillance activities will focus on human influenza. The CDC seasonal influenza surveillance website can be found at <http://www.cdc.gov/flu/weekly/fluactivity.htm>. At the local level, in addition to surveillance for seasonal influenza, efforts should include education of health care providers and public health professionals on the epidemiologic and clinical criteria for testing persons with respiratory illness for the presence influenza A (H5N1) virus (see CDC case definition at the end of this document). Local health departments should also be investigating any epidemiologically unusual cases or cluster of severe respiratory illness, such as investigating severe influenza in healthy adults and travelers, and clusters among health care workers.*

At the state level, the health department should be compiling and evaluating seasonal influenza surveillance data from local departments, and providing local health departments with a strong pandemic response plan. Again, cases of severe acute respiratory illness are the primary surveillance target, but these won't be of particular concern if there is no reason to suspect avian influenza so epidemiologic investigation is paramount.

At both the local and state level, surveillance for both respiratory morbidity and mortality should occur, this can expand in innovative ways such as by analyzing the number of influenza quicktests and percent positive over time. Linkages should also be strengthened between the human and veterinary health communities, perhaps through a HAN-type system.

Discussion Question – What specific surveillance activities has your state or local health department initiated in preparation for potential pandemic influenza?

***Facilitator** – Encourage participants to share the activities from their own jurisdictions.*

Day 4

Preliminary results by real-time reverse-transcriptase PCR on the Flock A birds indicate the presence of an H5 influenza virus. The farm owner and referring veterinarian immediately implement “self-quarantine” and ensure that all biosecurity measures are in place.

Question 4 – Now should this problem be reported to the state or national Department of Agriculture?

Suggested Answer – Yes. The Harrisonburg laboratory is required to report any positive H5 or H7 test results to the state veterinarian because these are the two influenza A subtypes that cause HPAI in poultry; the state veterinarian will report to the USDA via the area veterinarian in charge (AVIC).

Question 5 – What agencies, other than the USDA, or individuals should be informed of the preliminary lab results?

Suggested Answer – Some agencies/individuals include:

- The organized poultry industry in the state
- State / federal Wildlife
- State and local health departments and the CDC
- The governor's office of emergency management
- Other area poultry farmers
- The general population – to prepare them for potentially important updates

Note: If this event occurred in a large industry they would likely implement their own surveillance, antiviral distribution and depopulation plan.

Question 6 – If the final diagnosis turns out to be a low-pathogenic strain of avian influenza, would it still be important to report this outbreak?

Suggested Answer – Yes. LPAI H5 is an internationally notifiable disease and should be reported immediately. The State Department of Agriculture will want to assure that the virus does not spread any further, regardless of the strain, and may initiate culling of the flock. Low-pathogenic (LPAI) strains may still cause some agricultural losses, and they have the potential to mutate into a more virulent strain. From a public health perspective, there is minimal risk to human health posed by LPAI. It is also important to learn if this is Asian or North American lineage H5.

Discussion Question:

What do you think are criteria that should be met or trigger points for veterinary health to report poultry outbreaks to human health authorities?

Suggested Answer – Request input from the group; there are no standard answers for this question, but the necessity of communication between veterinary and human health should be noted.

Day 5

USDA was notified of the H5 diagnosis by the state veterinarian, and the Harrisonburg lab forwarded the samples to the national reference laboratory, the NVSL (National Veterinary Services Laboratory). Mortality in flock A increased to 1.3 % and egg production dropped approximately 20% over a period of 7 days. On Day 5, the NVSL reported that the submitted poultry samples tested positive for the low pathogenic avian influenza (LPAI) subtype H5N2, although confirmatory viral isolation was still ongoing.

Area wide surveillance among poultry, starting with adjacent flocks and those with epidemiologic links to Flock A, was initiated.

Question 7 – What action, if any, should Agriculture take upon confirming low-pathogenic avian influenza on a poultry farm?

***Suggested Answer** – The State animal health authority will need to take steps to depopulate, clean, and disinfect, (or less likely, vaccinate depending on the type of operation present) the affected premises. This may be a good time to reinforce training for procedures to handle HPAI.*

Question 8 – What action should public health take upon hearing a report of low-pathogenic avian influenza on a poultry farm? Consider that LPAI has the potential to mutate to HPAI.

***Suggested Answer** – Although there is minimal threat to human health from LPAI, public health should be prepared to deal with a worried public. Coordination between animal and public health agencies is required. This would be assisted by the presence of a regular vet-epi newsletter. Communication will be the most important action to take, including educating farm workers and the public about the low human health risk due to this outbreak. This is also a 'teachable moment' for educating farm workers and those who may handle poultry in their occupation or for cooking, about influenza prevention techniques through hygiene, and about appropriate personal protective equipment. Ensure that farm workers and others who are exposed to poultry infected with avian influenza receive the seasonal influenza vaccine. It is also a good time for public health workers to review their routine and special surveillance activities and data, as well as their avian influenza response plan. However significant damage can be done by overreacting. The economic damage to the poultry industry from a widespread panic would be considerable and could result in international bans on U.S. poultry products. Given only the confirmation of LPAI at this point, the economic damage could outweigh the public health benefit of an overzealous response.*

Day 6

Flock A was depopulated and the barn thoroughly disinfected. On Day 6 the younger Flock B in the adjacent barn experienced a very sudden increase in mortality. In this flock of 12,000 birds the mortality increased from 4 birds per day to 96, then 930 and then the owner reported that mortality was too numerous to count. On the first day of increased mortality samples of dead birds from Flock B were submitted for further investigation to the NVSL. Based on the gross pathology, the sudden extreme increase in mortality and the previous confirmation of AI virus in Flock A, highly pathogenic AI (HPAI) is suspected in Flock B (see USDA case definitions). NVSL begins genetic sequencing to determine pathogenicity of the virus late in the day, with results expected the next morning.

Question 9 – What new surveillance activities should the agencies involved undertake? How can public health enhance surveillance for avian influenza in light of the confirmation of the virus in poultry?

Suggested Answer – The level of response will be informed by laboratory data indicating that this H5 virus is related to other H5 viruses that have caused severe human illnesses. H5 influenza isolates can be divided into North American and Asian lineages, with the Asian lineage viruses producing the severe human health effects that have been observed across the world. Assuming this virus was related to others known to produce severe human disease then the following actions might be considered...

- *Active case finding among occupationally exposed. It is important to approach the local poultry workers (who may speak another language) in a culturally appropriate way. However they should be followed quickly in case they disperse. Consider working through the local workers representative who normally handles the concerns of workers.*
- *Sensitization of community to report unusual cases or clusters of respiratory illness, or persons meeting the CDC suspected case definition to health facilities.*
- *Consider need to add local non-public practices delivering healthcare to reporting network including private practices*
- *Expand respiratory illness surveillance and epidemiologic screening of persons presenting with pneumonia or ILI surveillance to more local hospitals and occupational groups*
- *Train all in the reporting network on procedures (forms, time for reporting, where, etc.)*

- *Door-to-door community surveillance inquiring about ill people and chickens*
- *“Creative” integration into local communication networks*
- *Telephone reporting hotlines*
- *Make sure laboratories forward all Influenza A unsubtypeable specimens from humans to appropriate State or CDC laboratory for Influenza A (H5N1) testing.*

In health departments, exposed persons – i.e. those who were in contact with the poultry and poultry products – should be monitored for 10 days for possible influenza symptoms. Healthcare workers, the occupationally exposed, and those who have traveled to the Page Farm should be actively monitored for symptoms.

Health departments should activate plans to conduct active surveillance for cases of severe viral respiratory illness. Surveillance should be enhanced in local hospitals and outpatient clinics.

Enhancing surveillance: In this case, when there have been no human cases, close monitoring of cases of severe respiratory illness and possibly testing severely ill persons with pneumonia, or ill persons with exposure to sick or dead birds for Influenza A (H5N1) will be important. Primary concern would be those who may have had poultry exposure. If poultry farms have occupational health doctors that care for workers, include these physicians in your surveillance network.

Active surveillance conducted by contacting and/or conducting periodic audits of hospitals, emergency and outpatient facilities, diagnostic laboratories, and physician’s offices is one way to enhance surveillance in the case of HPAI known to cause human illness or if evidence of human illness is detected. Surveillance data should be reported in daily, to allow for rapid response for treatment and containment. If the number of people exposed to the virus remains small, those at high risk could be screened for H5N1.

If human-to-human transmission is a concern, non-traditional sources of data such as school nurses, pharmacies, 911-calls, etc, might be used. However, these would be more useful for detecting a population-level increase of influenza (mostly likely seasonal), and would not be as useful for detecting individual cases of a novel influenza strain.

On the animal side, surveillance should have been initiated among poultry at neighboring farms within a specified radius of Flocks A and B. With HPAI suspected, enhanced surveillance would be initiated and zone surveillance established in accordance with the National HPAI Response Plan (3 km and 10 km zones around the infected premises). Active surveillance of the local wild birds should be undertaken.

Discussion Question – What networks are in place in your jurisdiction to bring together health, agriculture, vet, and wildlife in order to make decisions quickly on what surveillance activities should be undertaken and how? How will it be determined when public health should go on the farm? Biosecurity is an important concern—when does public health really need to go on the farm?

Facilitator – Decisions to expand surveillance to neighboring farms, etc, need to be made quickly and to involve all the stakeholders. Navigating these decisions will be easier if the plan and infrastructure is already in place. Encourage participants to share what they know about joint decision making in their jurisdictions.

Question 10 – Human surveillance based on clinical criteria will yield a large number of false positives. What epidemiologic context and/or clinical criteria should be employed as a red flag or trigger for raising the suspicion of potential human cases of avian influenza to a higher level and for collection of respiratory specimens from people for testing? At which point should a pandemic response plan be enacted?

Suggested Answer – The CDC Case Definition should initially be used as a measure of potential cases (shown at the end of this document along with WHO case definition that is used for international reporting). However, these were developed for the current US situation, in which there has been no identification of HPAI H5N1 virus on US soil. This is also intended to be used for reporting “Persons under Investigation”, “Suspect Cases” and “Confirmed Cases” to State Health Departments to CDC. Its not necessarily intended to be used as a trigger criteria to determine who would have laboratory specimens collected and tested for Influenza A (H5N1), those criteria are discussed further below.

The Influenza Division has drafted the following “trigger” criteria (see Health Alert Network update announcing the release of these criteria at end of this document as well). In the case of an outbreak of HPAI H5N1 among poultry in the US, criteria such as these may reflect cases with a link to AI or possible pandemic influenza. Participants should be allowed to discuss what they think might be appropriate criteria. Record consensus answers, and share this list after discussion is complete (or use this list to prompt discussion).

Testing for avian influenza A (H5N1) virus infection is recommended for:

A patient who has an illness that:

- requires hospitalization or is fatal; AND
- has or had a documented temperature of $\geq 38^{\circ}\text{C}$ ($\geq 100.4^{\circ}\text{F}$); AND
- has radiographically confirmed pneumonia, acute respiratory distress syndrome (ARDS), or other severe respiratory illness for which an alternate diagnosis has not been established; AND

- *has at least one of the following potential exposures within 10 days of symptom onset:*

A) History of travel to a country with influenza H5N1 documented in poultry, wild birds, and/or humans, AND had at least one of the following potential exposure during travel:

- *direct contact with (e.g., touching) sick or dead domestic poultry;*
- *direct contact with surfaces contaminated with poultry feces;*
- *consumption of raw or incompletely cooked poultry or poultry products;*
- *direct contact with sick or dead wild birds suspected or confirmed to have influenza H5N1;*
- *close contact (approach within 1 meter [approx. 3 feet]) of a person who was hospitalized or died due to a severe unexplained respiratory illness;*

B) Close contact (approach within 1 meter [approx. 3 feet]) of an ill patient who was confirmed or suspected to have H5N1;

C) Worked with live influenza H5N1 virus in a laboratory.

Testing for avian influenza A (H5N1) virus infection can be considered on a case-by-case basis, in consultation with local and state health departments, for:

- *A patient with mild or atypical disease (hospitalized or ambulatory) who has one of the exposures listed above (criteria A, B, or C); OR*
- *A patient with severe or fatal respiratory disease whose epidemiological information is uncertain, unavailable, or otherwise suspicious but does not meet the criteria above (examples include: a returned traveler from an influenza H5N1-affected country whose exposures are unclear or suspicious, a person who had contact with sick or well-appearing poultry, etc.)*

Pandemic response plans should probably contain criteria for when to enact them; however identification of avian influenza viruses related to those that cause significant illness in humans in this country, persons meeting criteria such as those listed in the potential triggers above, or any novel influenza virus infection in humans is probably enough reason to enact the response plan.

Discussion Question – Enhanced surveillance will increase the workload for hospitals and labs as well as the investigating agencies. This may overwhelm hospitals and present a barrier to effectively enhancing surveillance. How can efficient surveillance and testing be accomplished diplomatically, especially in the absence of human cases to give urgency to the situation?

Facilitator – Encourage group members to share their words of wisdom about tactfully accomplishing this goal.

Question 11 –What problems do you foresee in conducting surveillance for potential human cases of avian influenza?

Suggested Answer – *Some potential problems or barriers may be:*

- *The need for high quality epidemiologic criteria*
- *Before established human-to-human transmission, there will be many cases of respiratory illness detected that do not turn out to be illness caused by a novel influenza virus (false positives)*
- *Public awareness of AI surveillance activity may increase anxiety, leading to a high need for public communication and correspondence*
- *Running out of supplies due to conducting many influenza (seasonal or avian) tests on the worried well*
- *Potential language barriers between public health workers and poultry farm workers (can be overcome with planning). Poultry workers may easily be lost to follow-up.*
- *Identified cases of respiratory illness will need to be triaged for investigation based on the index of suspicion. Exposures such as the trigger points listed in Question 10 will receive higher priority*
- *Public health may not have a good enough understanding of how the poultry industry works to identify those at highest risk of having (had) exposure*
- *People may not report symptoms due to fear of job related implications or fear of being ostracized from the community*

Question 12 – See the WHO and CDC case definitions at the end of this document. Which set would you use as guidance, and why? Develop case definitions for potential human cases surrounding this outbreak.

Suggested Answer – *The WHO case definitions are designed to use for reporting purposes and to create standardization of data across different countries and regions. The CDC case definitions are similar, but are designed to be used to trigger laboratory specimen collection from human cases. The CDC set would be appropriate to use as a starting point in this investigation. The case definition should be modified to include details of the current outbreak. An example is below.*

A suspect case is a person who:

- *Has had a documented temperature of $\geq 38^{\circ}\text{C}$ ($\geq 100.4^{\circ}\text{F}$) and at least one following symptoms - cough, sore throat, and/or respiratory distress.*

and

- *Has had one of the following exposures within 10 days of the first symptom:*
 - *direct contact with (e.g., touching) sick or dead poultry on the Page County Farm*

- *direct contact with surfaces contaminated with poultry feces at the Page County farm*
- *consumption of raw or incompletely cooked poultry or poultry products, including blood, from the farm*
- *close contact (within 3 feet) of a symptomatic person who was confirmed or suspected to have H5N1 influenza*

and

- *Has a laboratory test for H5N1 that is pending, inadequate, or unavailable.*

A confirmed case is a person who:

Note: in an outbreak situation the laboratory and testing method may be specified.

- *Meets the clinical and exposure criteria for a Suspect Case (see above)*

and

- *Has a positive test for H5N1 influenza by one or more of the following methods:*
 - *isolation of an H5N1 influenza virus by viral culture*
 - *positive reverse transcriptase–polymerase chain reaction (RT-PCR) for H5N1*
 - *positive immunofluorescence antibody test for H5 antigen, using H5N1 monoclonal antibodies*
 - *4-fold rise in H5N1-specific antibody titer detected by microneutralization assay in paired serum samples*

Day 7: Conclusion

On Day 7, the NVSL reported that Flock B samples yielded highly pathogenic avian influenza (HPAI) that was a mutated form of the LPAI from the first barn. Flock A depopulation activities were completed and Flock B depopulation was underway. Zone surveillance yielded no additional infected flocks., No human cases were ever detected.

WHO case definitions for human infections with influenza A(H5N1) virus[†]

29 August 2006

Background

Prompt and accurate reporting of H5N1 influenza cases to WHO is the cornerstone for monitoring both the global evolution of this disease and the corresponding risk that a pandemic virus might emerge. In collaboration with several partners, WHO has developed standardized case definitions to facilitate:

1. Reporting and classification of human cases of H5N1 infection by national and international health authorities.
 2. Standardization of language for communication purposes.
 3. Comparability of data across time and geographical areas.
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Application of the H5N1 case definitions

1. The case definitions apply to the current phase of pandemic alert (phase 3) and may change as new information about the disease or its epidemiology becomes available.
2. National authorities should formally notify only probable and confirmed H5N1 cases to WHO. The case definitions for persons under investigation and suspected cases have been developed to help national authorities in classifying and tracking cases.
3. The case definitions are not intended to provide complete descriptions of disease in patients but rather to standardize reporting of cases.
4. In clinical situations requiring decisions concerning treatment, care or triage of persons who may have H5N1 infection, those decisions should be based on clinical judgment and epidemiological reasoning, and not on adherence to the case definitions. While most

[†] *Case definitions and investigation guidelines are undergoing revision by WHO and CDC. Please check for updated recommendations and definitions at the organization websites.

patients with H5N1 infection have presented with fever and lower respiratory complaints, the clinical spectrum is broad.

Case definitions

Person under investigation

A person whom public health authorities have decided to investigate for possible H5N1 infection.

Suspected H5N1 case

A person presenting with unexplained acute lower respiratory illness with fever ($>38^{\circ}\text{C}$) and cough, shortness of breath or difficulty breathing.

AND

One or more of the following exposures in the 7 days prior to symptom onset:

- a. Close contact (within 1 metre) with a person (e.g. caring for, speaking with, or touching) who is a suspected, probable, or confirmed H5N1 case;
- b. Exposure (e.g. handling, slaughtering, defeathering, butchering, preparation for consumption) to poultry or wild birds or their remains or to environments contaminated by their faeces in an area where H5N1 infections in animals or humans have been suspected or confirmed in the last month;
- c. Consumption of raw or undercooked poultry products in an area where H5N1 infections in animals or humans have been suspected or confirmed in the last month;
- d. Close contact with a confirmed H5N1 infected animal other than poultry or wild birds (e.g. cat or pig);
- e. Handling samples (animal or human) suspected of containing H5N1 virus in a laboratory or other setting.

Probable H5N1 case (notify WHO)

Probable definition 1:

A person meeting the criteria for a suspected case

AND

One of the following additional criteria:

a. infiltrates or evidence of an acute pneumonia on chest radiograph plus evidence of respiratory failure (hypoxemia, severe tachypnea)

OR

b. positive laboratory confirmation of an influenza A infection but insufficient laboratory evidence for H5N1 infection.

Probable definition 2:

A person dying of an unexplained acute respiratory illness who is considered to be epidemiologically linked by time, place, and exposure to a probable or confirmed H5N1 case.

Confirmed H5N1 case (notify WHO)

A person meeting the criteria for a suspected or probable case

AND

One of the following positive results conducted in a national, regional or international influenza laboratory whose H5N1 test results are [accepted by WHO as confirmatory](#):

a. Isolation of an H5N1 virus;

b. Positive H5 PCR results from tests using two different PCR targets, e.g. primers specific for influenza A and H5 HA;

c. A fourfold or greater rise in neutralization antibody titer for H5N1 based on testing of an acute serum specimen (collected 7 days or less after symptom onset) and a convalescent serum specimen. The convalescent neutralizing antibody titer must also be 1:80 or higher;

d. A microneutralization antibody titer for H5N1 of 1:80 or greater in a single serum specimen collected at day 14 or later after symptom onset and a positive result using a different serological assay, for example, a horse red blood cell haemagglutination inhibition titer of 1:160 or greater or an H5-specific western blot positive result.



Interim Case Classification Guidelines

The case classifications outlined below have been developed as preliminary guidance for use in the event of an avian influenza A (H5N1) outbreak in U.S. domestic poultry and should be adapted, as necessary, for the specific outbreak conditions. This guidance is based on the current state of knowledge regarding human infection with influenza A (H5N1) viruses; however, it may be modified for use during poultry outbreaks caused by other notifiable avian influenza viruses. As of this writing, influenza H5N1 has not been identified among animals or humans in the United States. In addition, no sustained human-to-human transmission of influenza H5N1 has been documented anywhere in the world, consistent with WHO Pandemic Phase 3 (Pandemic Alert Period)*. This guidance will be updated as our knowledge of the epidemiology of influenza H5N1 changes.

Proposed Interim Influenza Division/CDC Case Definitions of Influenza A (H5N1) in Humans

Report under investigation

Additional information needed on clinical and exposure information

Suspect case

Documented temperature ≥ 38 C (≥ 100.4 F) and one of the following: cough, sore throat, and/or respiratory distress AND

One of the following exposures within 10 days of onset

- a. Direct exposure to sick or dead domestic poultry
- b. Direct exposure to surfaces contaminated with poultry feces
- c. Consumption of raw or partially cooked poultry or poultry products
- d. Close contact (within 3 feet) of an ill patient with confirmed or suspected avian influenza A (H5N1) virus infection
- e. Works with live HPAI (H5N1) virus in a laboratory
- f. Laboratory test for avian influenza A (H5N1) is pending, inadequate or unavailable

Confirmed H5N1 case

Positive for avian influenza A (H5N1) virus by one of the following methods

- a. Isolation of H5N1 from viral culture
- b. Positive RT-PCR for H5N1
- c. 4 fold rise in H5N1 specific antibody titer by microneutralization assay in paired sera
- d. Positive IFA for H5 antigen using H5N1 monoclonal antibodies

Not a case

Negative avian influenza A (H5N1) virus testing result from a sensitive laboratory testing method using adequate and appropriately timed clinical specimens

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Updated Interim Guidance for Laboratory Testing of Persons with Suspected Infection with Avian Influenza A (H5N1) Virus in the United States

This update provides revised interim guidance for testing of suspected human cases of avian influenza A (H5N1) in the United States and is based on the current state of knowledge regarding human infection with H5N1 viruses. The epidemiology of H5N1 human infections has not changed significantly since February 2004. Therefore, CDC recommends that H5N1 surveillance in the United States remain at the enhanced level first established at that time. However, this revised interim guidance provides an updated case definition of a suspected H5N1 human case for the purpose of determining when testing should be undertaken and also provides more detailed information on laboratory testing. Effective surveillance will continue to rely on health care providers obtaining information regarding international travel and other exposure risks from persons with specified respiratory symptoms as detailed in the recommendations below. This guidance will be updated as the epidemiology of H5N1 changes. Note: CDC is revising its interim guidance for infection control precautions for avian influenza A (H5N1). These will be issued as soon as they are available.

Current Situation:

The avian influenza A (H5N1) epizootic (animal outbreak) in Asia has expanded to wild birds and/or poultry in parts of Europe, the Near East and Africa. Sporadic human infections with H5N1 continue to be reported and have most recently occurred in China, Egypt, Indonesia, Azerbaijan, Cambodia, and Djibouti. In addition, rare instances of probable human-to-human transmission associated with H5N1 viruses have occurred, most recently in a family cluster in Indonesia. So far, however, the spread of H5N1 virus from person to person has been rare, inefficient, and unsustainable. The total number of confirmed human cases of H5N1 reported as of June 7, 2006 has reached 225. The case fatality rate for these reported cases continues to be approximately 50 percent. As of this date, H5N1 has not been identified among animals or humans in the United States.

The epizootic in Asia and parts of Europe, the Near East and Africa is not expected to diminish significantly in the short term and it is likely that H5N1 infection among birds has become enzootic in certain areas. It is expected that human infections resulting from direct contact with infected poultry will continue to occur in affected countries. Since no sustained human-to-human transmission of influenza H5N1 has been documented anywhere in the world, the current phase of alert, based on the World Health Organization (WHO) global influenza preparedness plan, remains at Phase 3 (Pandemic Alert).^{*} In addition, no evidence for genetic reassortment between human and avian influenza A virus genes has been found. Nevertheless, this expanding epizootic continues to pose an important and growing public health threat. CDC is in communication with WHO and other national and international agencies and continues to monitor the situation closely.

Reporting and Testing Guidelines:

CDC recommends maintaining the enhanced surveillance efforts practiced currently by state and local health departments, hospitals, and clinicians to identify patients at increased risk for avian influenza A (H5N1). Guidance for enhanced surveillance was first described in a HAN update issued on February 3, 2004 and most recently updated on February 4, 2005.

Testing for avian influenza A (H5N1) virus infection is recommended for:

A patient who has an illness that:

- requires hospitalization or is fatal; AND
- has or had a documented temperature of $\geq 38^{\circ}\text{C}$ ($\geq 100.4^{\circ}\text{F}$); AND
- has radiographically confirmed pneumonia, acute respiratory distress syndrome (ARDS), or other severe respiratory illness for which an alternate diagnosis has not been established; AND
- has at least one of the following potential exposures within 10 days of symptom onset:

A) History of travel to a country with influenza H5N1 documented in poultry, wild birds, and/or humans,† AND had at least one of the following potential exposures during travel:

- direct contact with (e.g., touching) sick or dead domestic poultry;
- direct contact with surfaces contaminated with poultry feces;
- consumption of raw or incompletely cooked poultry or poultry products;
- direct contact with sick or dead wild birds suspected or confirmed to have influenza H5N1;
- close contact (approach within 1 meter [approx. 3 feet]) of a person who was hospitalized or died due to a severe unexplained respiratory illness;

B) Close contact (approach within 1 meter [approx. 3 feet]) of an ill patient who was confirmed or suspected to have H5N1;

C) Worked with live influenza H5N1 virus in a laboratory.

Testing for avian influenza A (H5N1) virus infection can be considered on a case-by-case basis, in consultation with local and state health departments, for:

- A patient with mild or atypical disease‡ (hospitalized or ambulatory) who has one of the exposures listed above (criteria A, B, or C); OR
- A patient with severe or fatal respiratory disease whose epidemiological information is uncertain, unavailable, or otherwise suspicious but does not meet the criteria above (examples include: a returned traveler from an influenza H5N1-affected country whose exposures are unclear or suspicious, a person who had contact with sick or well-appearing poultry, etc.)

Clinicians should contact their local or state health department as soon as possible to report any suspected human case of influenza H5N1 in the United States.

Specimen Collection and Testing Guidelines:

- Oropharyngeal swab specimens and lower respiratory tract specimens (e.g., bronchoalveolar lavage or tracheal aspirates) are preferred because they appear to contain the highest quantity of virus for influenza H5N1 detection, as determined on the basis of available data. Nasal or nasopharyngeal swab specimens are acceptable, but may contain less virus and therefore not be optimal specimens for virus detection.
- Detection of influenza H5N1 is more likely from specimens collected within the first 3 days of illness onset. If possible, serial specimens should be obtained over several days from the same patient.

- Bronchoalveolar lavage is considered to be a high-risk aerosol-generating procedure. Therefore, infection control precautions should include the use of gloves, gown, goggles or face shield, and a fit-tested respirator with an N-95 or higher rated filter. A loose-fitting powered air-purifying respirator (PAPR) may be used if fit-testing is not possible (for example, if the person has a beard). Detailed guidance on infection control precautions for health care workers caring for suspected influenza H5N1 patients is available.||
- Swabs used for specimen collection should have a Dacron tip and an aluminum or plastic shaft. Swabs with calcium alginate or cotton tips and wooden shafts are not recommended.§ Specimens should be placed at 4°C immediately after collection.
- For reverse-transcriptase polymerase chain reaction (RT-PCR) analysis, nucleic acid extraction lysis buffer can be added to specimens (for virus inactivation and RNA stabilization), after which specimens can be stored and shipped at 4°C. Otherwise, specimens should be frozen at or below -70°C and shipped on dry ice. For viral isolation, specimens can be stored and shipped at 4°C. If specimens are not expected to be inoculated into culture within 2 days, they should be frozen at or below -70°C and shipped on dry ice. Avoid repeated freeze/thaw cycles.
- Influenza H5N1-specific RT-PCR testing conducted under Biosafety Level 2 conditions is the preferred method for diagnosis. All state public health laboratories, several local public health laboratories, and CDC are able to perform influenza H5N1 RT-PCR testing, and are the recommended sites for initial diagnosis.
- Viral culture should NOT be attempted on specimens from patients suspected to have influenza H5N1, unless conducted under Biosafety Level 3 conditions with enhancements.
- Commercial rapid influenza antigen testing in the evaluation of suspected influenza H5N1 cases should be interpreted with caution. Clinicians should be aware that these tests have relatively low sensitivities, and a negative result would not exclude a diagnosis of influenza H5N1. In addition, a positive result does not distinguish between seasonal and avian influenza A viruses.
- Serologic testing for influenza H5N1-specific antibody, using appropriately timed specimens, can be considered if other influenza H5N1 diagnostic testing methods are unsuccessful (for example, due to delays in respiratory specimen collection). Paired serum specimens from the same patient are required for influenza H5N1 diagnosis: one sample should be tested within the first week of illness, and a second sample should be tested 2-4 weeks later. A demonstrated rise in the H5N1-specific antibody level is required for a diagnosis of H5N1 infection. Currently, the microneutralization assay, which requires live virus, is the recommended test for measuring H5N1-specific antibody. Any work with live wild-type highly pathogenic influenza H5N1 viruses must be conducted in a USDA-approved Biosafety Level 3 enhanced containment facility. Visit <http://www.cdc.gov/flu/h2n2bsl3.htm> for more information about procedures and facilities recommended for manipulating highly pathogenic avian influenza viruses.

Laboratory testing results positive for influenza A (H5N1) in the United States should be confirmed at CDC, which has been designated as a WHO H5 Reference Laboratory. Before sending specimens, state and local health departments should contact CDC's on-call epidemiologist at (404) 639-3747 or (404) 639-3591 (Monday – Friday, 8:30 AM - 5:00 PM) or (770) 488-7100 (all other times).

Travel Health Notice:

CDC has not recommended that the general public avoid travel to any of the countries affected by H5N1. However, CDC does recommend that travelers to these countries avoid poultry farms and

bird markets or other places where live poultry are raised or kept. For details about other ways to reduce the risk of infection, see http://www.cdc.gov/travel/other/avian_influenza_se_asia_2005.htm.

More Information:

Department of Health and Human Services at www.pandemicflu.gov
World Health Organization at
World Organization for Animal Health (OIE) at http://www.oie.int/eng/en_index.htm

*For the current WHO Pandemic Phase, see
http://www.who.int/csr/disease/avian_influenza/phase/en/index.html.

† For a listing of influenza H5N1-affected countries, visit the CDC website at <http://www.cdc.gov/flu/avian/outbreaks/current.htm>; the OIE website at http://www.oie.int/eng/en_index.htm; and the WHO website at http://www.who.int/csr/disease/avian_influenza/en/.

‡ For example, a patient with respiratory illness and fever who does not require hospitalization, or a patient with significant neurologic or gastrointestinal symptoms in the absence of respiratory disease.

|| Interim recommendations for infection control in health-care facilities caring for patients with known or suspected avian influenza are available at <http://www.cdc.gov/flu/avian/professional/infect-control.htm>.

§ Specimens can be transported in viral transport media, Hanks balanced salt solution, cell culture medium, tryptose-phosphate broth, veal infusion broth, or sucrose-phosphate buffer. Transport media should be supplemented with protein, such as bovine serum albumin or gelatin, to a concentration of 0.5% to 1%.

Information regarding Laboratory Biosafety Level Criteria can be found at <http://www.cdc.gov/od/ohs/biosfty/bmbl4/bmbl4s3.htm>.

##This Message was distributed to State and Local Health Officers, Public Information Officers, Epidemiologists, State Laboratory Directors, Weapons of Mass Destruction Coordinators and HAN Coordinators, as well as Public Health Associations and Clinician organizations##