

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.

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

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’?

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

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?

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

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?

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?

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?

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.

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 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?

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?

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? At which point should a pandemic response plan be enacted?

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?

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

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.

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>.

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