Guidance Document

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

November 7, 2008

This document provides revised interim guidance for testing of suspected human cases of highly pathogenic avian influenza A (H5N1) virus infection in the United States and is based on current knowledge regarding human infection with H5N1 viruses. This guidance has been revised from a HAN issued on June 7, 2006.

The epidemiology of human infections with H5N1 virus has not changed significantly since June 2006. Therefore CDC continues to recommend that surveillance for suspected human cases of H5N1 in the United States remain at the enhanced level. However, this revised guidance provides updated criteria for H5N1 testing and more detailed information on laboratory specimen collection than provided in previously issued CDC guidance.

CDC recommends that health care providers consider H5N1 testing for persons that have both a clinical syndrome consistent with H5N1 disease *and relevant exposure to H5N1 virus*. To date, there have been no reports of highly pathogenic avian influenza A (H5N1) virus infections among animals or humans in the United States. Therefore, successful identification of cases will depend upon health care providers obtaining information from patients who present with respiratory illness about their recent travel outside of the U.S. and their activities while traveling.

This guidance is being issued in conjunction with "Interim Guidance for Follow-up of Contacts of Persons with Suspected Infection with Highly Pathogenic Avian Influenza A (H5N1) Virus in the United States," available at http://www.cdc.gov/flu/avian/professional/#guidance.

This guidance will be updated as the epidemiology of human H5N1 influenza virus infection changes.

Current Situation:

The current epizootic (animal outbreak) of highly pathogenic avian influenza A (H5N1) among poultry and wild birds since 2003 has caused unprecedented widespread disease in wild birds and poultry in Asia, the Near East, Africa, and Europe. Despite extensive disease in birds and ongoing widespread human exposure to infected birds, human infections with H5N1 viruses continue to be rare. Since 2003, sporadic human H5N1 virus infections have been reported in Azerbaijan, Bangladesh, Cambodia, China, Djibouti, Egypt, Indonesia, Iraq, Laos, Myanmar, Nigeria, Pakistan, Thailand, Turkey and Vietnam. Although in the majority of these cases, avian-to-human transmission of H5N1 virus is believed to be the predominant mode of transmission, rare instances of probable limited non-sustained human-to-human transmission of H5N1 viruses have been reported. In some cases, the exposure source was unclear, possibly implicating an environmental source of transmission. The total number of confirmed human H5N1 cases reported to the World Health Organization (WHO) from November 1, 2003 through November 7, 2008 was 387, with a 63% case-fatality proportion (last case reported September 10, 2008). Current information regarding

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morbidity and mortality of human H5N1 cases can be obtained at:
http://www.who.int/csr/disease/avian_influenza/country/cases_table_2008_09_10/en/print.html

Outbreaks of highly pathogenic avian influenza A (H5N1) virus infection among birds have continued since 2003 and H5N1 viruses are considered to be endemic among backyard poultry in some parts of Asia, Africa, and the Near East. While transmission from infected birds to humans is still occurring, there has been no sustained human-to-human transmission of H5N1 viruses and the current phase of alert, based on the WHO Global Influenza Preparedness Plan, remains at Phase 3 (Pandemic Alert Period).* As this expanding epizootic continues to pose an important and persistent 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 highly pathogenic avian influenza A (H5N1) virus infection. Clinicians should notify their State Health Department immediately when they decide to test a patient for H5N1 virus infection so that appropriate testing and follow-up of contacts is initiated (See HAN Update: *Interim Guidance for Follow-up of Contacts of Persons with Suspected Infection with Highly Pathogenic Avian Influenza A (H5N1) Virus in the United States*.) CDC should be notified immediately in the event that any clinical specimens from suspected cases test positive for H5N1 virus. Human infection with a novel influenza A virus is a nationally notifiable condition.

Testing for H5N1 virus infection is recommended for a patient who has an illness that:

1. Requires hospitalization or is fatal;

AND

2. Has or had a documented temperature of ≥38°C (≥100.4° F) in the past 24 hours OR has a history of feverishness in the past 24 hours;

AND

3. Has radiographically confirmed pneumonia, acute respiratory distress syndrome (ARDS), or other severe respiratory illness;

AND

4. Has at least one of the following potential exposures within 7 days of symptom onset:
    a. History of travel to a country where highly pathogenic avian influenza H5N1 has been documented in poultry, wild birds, and/or humans,† AND had at least one of the following potential exposures during travel:
        i. Direct contact with (e.g. handling, slaughtering, defeathering, butchering, preparation for consumption) well-appearing, sick or dead poultry or wild birds;
        ii. Direct contact with surfaces contaminated with poultry feces or poultry parts (carcasses, internal organs, etc.) that might contain H5N1 virus);

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iii. Consumption of raw or incompletely cooked poultry or poultry products;
iv. Close contact (approach within about 6 feet) with a confirmed H5N1-infected animal other than poultry or wild birds (e.g. cat or dog);
v. Close contact (approach within about 6 feet) with a person who was hospitalized or died due to a severe unexplained respiratory illness;
vi. Visiting a market where live poultry are sold or slaughtered;
vii. Handling samples (animal or human) suspected of containing H5N1 virus in a laboratory or other setting.

b. Close contact (approach within about 6 feet) with an ill person with confirmed H5N1 virus infection;
c. Close contact (approach within about 6 feet) with an ill person who was under investigation for possible H5N1 virus infection;
d. Working with live highly pathogenic avian influenza A (H5N1) virus in a laboratory.

In addition, testing for H5N1 virus infection can be considered on a case by case basis, in consultation with local and state health departments, for:

1. A patient with mild or atypical disease‡ (hospitalized or ambulatory) who has one of the exposures listed above (criteria 4.a, b, c or d); OR
2. A patient with severe or fatal respiratory disease whose epidemiological information is uncertain, unavailable, or otherwise suspicious but does not meet the criteria above. An example would include an ill returned traveler that visited a country where highly pathogenic avian influenza A (H5N1) virus has been documented or is highly suspected in birds.

Clinicians should notify their state health department immediately when they wish to test a patient for suspected influenza A (H5N1) virus infection. Influenza H5N1-specific reverse-transcription polymerase chain reaction (RT-PCR) testing conducted under Biosafety Level 2 (BSL2) conditions is the preferred method for diagnosis. All state public health laboratories and several local public health laboratories are able to perform influenza H5N1 RT-PCR testing, and are the recommended sites for initial diagnosis. Emphasis should be placed upon proper infection control precautions and use of personal protective equipment for contact with suspected cases, collection of the proper respiratory specimens, and testing for influenza A, H1, H3, H5, and B by RT-PCR. Infection control precautions and PPE recommendations for direct care of such patients, including intubation can be found at: http://www.cdc.gov/flu/avian/professional/pdf/infectcontrol.pdf.

Specimen Collection and Testing Guidelines for Clinicians:

1. Respiratory Specimen Collection and Testing

a. Appropriate personal protective equipment (PPE) is recommended for any direct and close contact with a suspected or confirmed H5N1 patient or when entering a room where aerosol-generating procedures in such patients are being performed. In general, PPE should include respiratory protection (a particulate respirator that fits well and has undergone a fit check), at least as protective as a National Institute of Occupational Safety and Health (NIOSH)-approved N-95 filtering face piece, goggles, a face shield, non-sterile latex gloves, a gown and a head covering. If a particulate respirator is not available, other NIOSH-certified N-, R-, or P-class respirators should be used. Powered air purifying respirators (PAPRs) may be considered for certain workers and tasks (e.g., high-risk activities);

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however, aerosol-generating procedures should only be performed if using a particulate respirator. http://www.pandemicflu.gov/plan/healthcare/maskguidancehc.html#masks

i. 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).

b. Oropharyngeal (throat) swab specimens and, if available, lower respiratory tract specimens (e.g., bronchoalveolar lavage or endo-tracheal aspirate) are preferred because they have a higher yield for detecting H5N1 virus compared to nasopharyngeal and nasal specimens. Nasal or nasopharyngeal swab specimens may contain less H5N1 virus but are useful for detection of human influenza A and B viruses. Therefore, nasal or nasopharyngeal and throat swab specimens, as well as lower respiratory specimens (if available) should all be collected.
c. If possible, in order to increase the potential for H5N1 virus detection, multiple respiratory specimens should be obtained from the same patient on consecutive days.
d. 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 immediately into sterile viral transport medium and stored at 4°C until testing.
e. Use of commercially available rapid influenza diagnostic tests for the purpose of detecting H5N1 virus infection is not recommended. Clinicians should be aware that these tests have very low sensitivities to detect H5N1 virus compared to other methods, and a negative result does not exclude a diagnosis of H5N1 virus infection. In addition, a positive result does not distinguish between infection with human and animal influenza A viruses.
f. Clinicians should always consider diagnostic testing for other pathogens that can cause acute febrile respiratory illness since H5N1 virus infection of humans is very rare.

Testing Guidelines for Laboratory Staff:

Real-time RT-PCR is the preferred assay for H5N1 testing under BSL2 conditions. CDC has made H5-specific primers and probes available to state health department laboratories. In addition, the U.S. Food and Drug Administration (FDA) cleared a real-time RT-PCR device developed by CDC that can detect H5 (http://www.hhs.gov/news/press/2008pres/09/20080930a.html). CDC should be notified immediately in the event that any clinical specimens from suspected cases test positive for H5N1 virus, and clinical specimens should be shipped to CDC for confirmatory testing. Human infection with a novel influenza A virus is a nationally notifiable condition and should be reported and confirmed at CDC. Viral culture should NOT be attempted on specimens from patients suspected to have H5N1 virus infection, and generally should not done except at CDC, unless conducted under Biosafety Level 3 (BSL3) enhanced conditions.

1. H5-specific reverse-transcription polymerase chain reaction (RT-PCR)

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. Avoid repeated freeze/thaw cycles.

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2. Viral culture

   Isolation of H5N1 virus should not be performed except at the Influenza Division, CDC, unless enhanced BSL3 conditions are available. For viral culture, nucleic acid extraction lysis buffer should not be added to specimens. Clinical specimens from H5 positive patients should be shipped to CDC for confirmatory testing. 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.

Collection and Testing of Other Clinical Specimens:

Serologic testing for H5N1-specific antibody, using appropriately timed specimens, can be considered if other H5N1 diagnostic testing methods are unavailable (for example, due to delays in respiratory specimen collection). Serologic testing should only be performed at CDC.

1. Serological Testing

   a. Paired serum specimens from the same patient should be collected for H5N1 serology if possible: the first sample should be collected within the first week of illness, and a second sample should be collected 2-4 weeks later. Serological testing of deceased patients with only a single serum specimen may be possible upon consultation with CDC. A demonstrated rise in the H5N1-specific antibody level is required for a diagnosis of H5N1 virus infection. Currently, the microneutralization assay, which requires live H5N1 virus, is the recommended test for measuring H5N1-specific antibody.

      i. Any work with live wild-type highly pathogenic avian influenza A (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 results for human clinical specimens that test positive for H5N1 by RT-PCR at a laboratory in the United States should be confirmed at the Influenza Division, National Center for Immunization and Respiratory Diseases, CDC, which has been designated as a WHO H5 Reference Laboratory. Before sending specimens, state and local health departments should contact CDC Influenza Division Epidemiology and Prevention Branch at (404) 639-3747 (Monday – Friday, 8:30 AM - 5:00 PM or the on-call epidemiologist at (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 (for list see http://www.cdc.gov/flu/avian/outbreaks/current.htm). However, CDC does recommend that travelers to these countries avoid poultry farms and bird markets or other places where live poultry are raised, kept, or sold. For details about other ways to reduce the risk of infection, see http://wwwn.cdc.gov/travel/contentAvianFluAsia.aspx

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More Information:

Department of Health and Human Services: www.pandemicflu.gov

World Health Organization on Avian Influenza: http://www.who.int/csr/disease/avian_influenza/en

World Organization for Animal Health (OIE): http://www.oie.int/eng/en_index.htm

HHS Infection Control Guidelines:
http://www.pandemicflu.gov/plan/healthcare/maskguidancehc.html#masks

CDC Infection Control Guidelines: http://www.cdc.gov/flu/avian/professional/pdf/infectcontrol.pdf

World Health Organization Infection Control Guidelines:
http://www.who.int/csr/disease/avian_influenza/guidelines/aidememoireinfcont/en/index.html

World Health Organization Clinical Management of Human Infections with Avian Influenza A (H5N1) Virus:
http://www.who.int/csr/disease/avian_influenza/guidelines/clinicalmanage07/en/index.html

World Health Organization Guidelines for Pharmacologic Management of Human Infections with Avian Influenza A (H5N1) Virus:
http://www.who.int/csr/disease/avian_influenza/guidelines/pharmamanagement/en/index.html

Collecting, Preserving and Shipping Specimens For the Diagnosis of Avian Influenza A(H5N1) Virus Infection: http://www.who.int/csr/resources/publications/surveillance/CDS_EPR_ARO_2006_1.pdf

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

Writing Committee of the Second World Health Organization Consultation on Clinical Aspects of Human Infection with Avian Influenza A (H5N1) Virus. Update on avian influenza A (H5N1) virus infection in humans. N Engl J Med. 2008 Jan 17;358(3):261-73.

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*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.

§ 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%