# Utah Influenza Pandemic Response Plan

## Laboratory Role:

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Influenza Pandemic Response Plan
January 2008 version 2.1
I.  Rationale

The goals of diagnostic and surveillance laboratory testing during a pandemic are to:

- Identify the earliest U.S. cases of pandemic influenza (whether the pandemic begins in the United States or elsewhere).
- Support disease surveillance to monitor the pandemic's geographic spread and impact of interventions.
- Facilitate clinical treatment by distinguishing patients with influenza from those with other respiratory illnesses.
- Monitor circulating viruses for vaccine and antiviral efficacy

During the earliest stages of a pandemic, public health, hospital, and clinical laboratories might receive a large and potentially overwhelming volume of clinical specimens. Pre-pandemic planning is essential to assure timeliness of diagnostic testing and the availability of supplies and reagents, address staffing issues, and disseminate protocols for safe handling and shipping of specimens. Once a pandemic is underway, the need for laboratory confirmation of clinical diagnoses may decrease as the virus becomes widespread. Diagnostic testing for pandemic influenza virus may involve a range of laboratory assays (see Table 1. and Appendix 1.)

II.  Overview

The public health laboratory is a critical component of the overall public health response to pandemic influenza. The capability of differentiating common influenza from pandemic influenza depends upon the rapid detection and characterization that is available at the Utah Public Health Laboratories (UPHL) and the Centers for Disease Control and Prevention (CDC).

- UPHL contributes to national laboratory-based surveillance efforts on a year-round basis.
- Only through laboratory testing can the signs and symptoms of influenza-like illness (ILI) be attributed to a definitive pathogen.
- By identifying the pathogen best practices for appropriate treatment and control measures can be taken to limit/prevent the spread of disease.
- Standardized Laboratory Response Network (LRN) protocols assist CDC in understanding the significance of test results across the nation.

UPHL plays a key role in laboratory preparedness and response efforts. Federal funding has been used by UPHL to enhance technological capacity and capability for responding to public health emergencies in an all hazards approach, which includes pandemic influenza. Specifically UPHL:

- Provides accurate and rapid state-of-the-art testing for detection and identification of influenza subtypes such as H5N1.
- Coordinates year-round laboratory-based surveillance efforts within the state and contributes to the World Health Organization (WHO) data thru CDC.

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• Provides viral sample to CDC for ongoing characterization of viruses to select for upcoming vaccines and antiviral susceptibility testing.

UPHL works closely with state and local epidemiology, partner laboratories and other health care entities to support and assist in coordinating the diagnostic testing response for influenza by:

• Providing education, training, and guidance on safe use and interpretation of rapid influenza tests or other point-of-care testing technologies.
• Maintaining a close working relationship with veterinary diagnostic labs to monitor influenza activity within animal populations that may impact humans and human activity that may impact animals.
• Participate in the preparedness planning for the state's Pandemic Influenza Plan

III. The Interpandemic and Pandemic Alert Periods

Global and US Surveillance
The WHO has a worldwide network of surveillance laboratories providing information on influenza. In the United States they work in cooperation with CDC. UPHL is a participant in this WHO surveillance network (see Table 2).

Routine Surveillance Activities
• Information about year round influenza testing at UPHL is sent on a routine basis to CDC. Virus subtypes, patient ages and geographical information are reported on the “WHO Surveillance Form” and sent via fax. UPHL is currently building a new Laboratory Information Management System (LIMS) that is moving to be PHIN (Public Health Information Network) compliant and data will be shared electronically with public health partners and CDC.
• A random sample of influenza isolates are selected by UPHL and submitted to CDC three times during the influenza season. The samples are chosen to reflect early, middle, and late season isolates. Other samples of interest, outside the regular influenza season are also sent to CDC for surveillance purposes to monitor what is circulating in the population. All specimens that CDC requests for monitoring sporadic outbreaks and clusters of influenza in the state of Utah are sent by UPHL to CDC.

A. Roles and Responsibilities

Clinical and Hospital Laboratories
• Work within hospital system and parent corporations to address laboratory surge capacity issues. It will be the responsibility of hospital and clinical laboratories to maintain capacity for testing to support preliminary diagnosis of patients as being infected with Influenza A.
  * Make sure laboratory has plans to keep sufficient reagents, kits and supplies on hand for surge testing.
  * Ensure a means of tracking reagents and supplies
* Have plans for work coverage as some employees will be sick.
- Train personnel in the safe handling and management of respiratory specimens during an influenza pandemic.
- Do influenza A testing under appropriate biosafety level if a novel strain is not suspected and the patient has no travel history to an area with known novel influenza strain.
- Refer specimens from patients with suspected novel influenza to UPHL.
- Institute surveillance for influenza-like-illness among laboratory personnel working with influenza virus.
- Maintain contact lists and participate with information communication channels
- Report positive test results to state or local epidemiology as appropriate.

**Utah Public Health Laboratories**
- Perform LRN (Laboratory Response Network) & public health testing to support pathogen identification and subtype characterization as it pertains to surveillance and basic functions of public health illness tracking. It is not intended that the public health laboratory do basic diagnostic testing or act as surge capacity for hospital and clinical laboratories. UPHL may participate in surge capacity testing to support hospital and clinical laboratories if resources permit and public health needs allow the shift in resources. This decision will be made by UPHL and consultation with state Epidemiology.
- Support public health surveillance activities by participation in the WHO network and submitting samples to CDC for further characterization.
- Participate in pandemic influenza planning and exercises
- Institute surveillance for ILI among UPHL personnel.
- Develop and assist in reviewing response plans, brochures, checklists and other educational materials that aid healthcare personnel to work safely with viral specimens.
- Take the lead in maintaining communication channels to all participatory laboratories.
- UPHL facilities and staff may be used as surge capacity for Utah Veterinary Diagnostic Laboratory (UVDL) if human testing needs have been met or as animal testing provides critical public health surveillance information.
- Assist in educating laboratory scientists and other healthcare workers in the safe handling, packing, and shipping of respiratory specimens for testing (see Appendices 3 and 4).

**Utah Veterinary Diagnostic Laboratory**
- Perform diagnostic testing for influenza virus in animal populations as appropriate.
- Help in pandemic planning.
- Maintain contact lists and participate with information communication channels.
- May act as surge capacity facility for UPHL should need arise.

**Indian Health Clinics and Military Associated Laboratories**
- Participate in pandemic influenza planning and exercises.
• Train personnel in the safe handling and management of respiratory specimens during an influenza pandemic.
• Maintain contact lists and participate with information communication channels
• Assist in training staff for safe handling, packaging and shipping of respiratory specimens for diagnostic testing to UPHL or reference laboratory.
• If rapid testing methods are used for diagnostic work, ensure that healthcare personnel and lab testing staff have adequate PPE and work using proper biosafety measures.

B. Laboratory Testing

Clinical Laboratories (to include Military and Tribal entities that test)
• Test clinical samples for influenza or influenza A when the patient is not suspected of a novel strain of influenza and does not have a travel history or exposure to a novel strain.
• Forward specimens to UPHL for virus characterization or if a novel strain of influenza virus is suspected for identification.

Utah Veterinary Diagnostic Laboratory (UVDL)
• Test animal samples as is appropriate to their role in supporting surveillance in the animal population and/or diagnostic work as they define.

Utah Public Health Laboratories (UPHL)
• UPHL will provide influenza testing on a year-round basis to support public health surveillance, viral characterization for vaccine development, and supporting WHO and CDC collecting of viral agents for further characterization and archiving.

• PREFERRED SPECIMENS for UPHL Testing
  • For seasonal influenza: 2 nasopharyngeal swabs collected on a Rayon or Dacron swab with plastic or aluminum shaft. (cotton or calcium alginate swabs and wood shafts interfere with the PCR testing methodology and should NOT be used).
  • For Avian Influenza H5N1: 1 oropharyngeal swab and one nasopharyngeal swab collected on a Rayon or Dacron swab with a plastic or aluminum shaft.
  • Transport the swabs in viral transport medium (preferred) or in sterile saline.
  • If shipping of specimen is delayed, keep the specimens refrigerated.
  • Keep the specimens cool during shipping by using a cool pack. (wet ice may be used but be sure to keep paperwork and tubes separate from the ice).

• Routine specimens for influenza testing will first be screened by DFA. Positive specimens and all negative specimens will be
inoculated to cell culture for virus isolation.

- **Suspected novel strains** will first be tested using RT-PCR
  - The LRN protocol for H5N1 Asian strain will be done on a stat basis after a patient screening done by state office of epidemiology (assisted by local health personnel).
  - Subsequent characterization may be done using the APHL protocol for influenza A and subtypes-H1, H3, H5, H7 and influenza B.
  - Negative respiratory samples by these RT-PCR methods may be submitted to further testing by DFA & cell culture to determine the pathogen when a dangerous novel strain has **not** been detected by PCR.
  - Hemagglutination Inhibition (HI) testing is done from cell culture to determine H1 or H3 subtype of influenza A.
  - **Positive samples**, meeting CDC requirements for a novel strain, are sent to CDC. It is not recommended that novel strains be taken to viral culture unless the lab is BSL3+ and the scientists are experienced in working with highly pathogenic influenza virus. UPHL currently does not have this capacity and will ship specimens to CDC as they direct.

C. Laboratory Safety - Biocontainment

During the Pandemic Alert Period, specimens from suspected cases of human infection with novel influenza strains should be sent to UPHL for testing. The following guidelines should be used for handling and testing of samples suspected of containing a novel influenza virus:

- Commercial antigen detection testing - conduct all specimen manipulation and assays in a biosafety cabinet under BSL-II conditions.
- RT-PCR - conduct specimen manipulation and assay using a biosafety cabinet and BSL-II conditions (BSL-III is desirable if a novel strain is suspected).
- Virus Isolation/Culture - it is not recommended that virus culture be attempted if a novel influenza strain is suspected. These should be sent to CDC. If a lab has BSL - III enhanced lab space and is experienced in working with highly pathogenic influenza culture may be feasible. (see Appendix 4 for additional laboratory biosafety guidelines).

D. Collection, Handling, Packing & Shipping of Viral Specimens

1. Key Messages
   - Appropriate specimens for influenza testing vary by type of test.
   - Please call UPHL if assistance is needed for any phase of specimen collection, handling and/or shipping- contact website administrator for number if needed.
• Contact website administrator for UPHL address for shipping.

2. Respiratory Specimens

- Eight types of respiratory specimens may be collected for viral and/or bacterial diagnostics: 1) nasopharyngeal wash/aspirates, 2) nasopharyngeal swabs, 3) oropharyngeal swabs, 4) broncheoalveolar lavage, 5) tracheal aspirate, 6) pleural fluid tap, 7) sputum, and 8) autopsy specimens.
- Nasopharyngeal wash/aspirates or swabs are the specimen of choice for seasonal influenza testing.
- Oropharyngeal swabs are the specimen of choice for the currently circulating strain of Avian Influenza H5.
- Respiratory specimens for detection of most respiratory pathogens, and influenza in particular, are optimally collected within the first 3 days of the onset of illness.
- Before collecting specimens, review the infection control precautions for your institution.

a. Collecting specimens from the upper respiratory tract

1). Nasopharyngeal wash/aspirate
- Have the patient sit with head tilted slightly backward.
- Instill 1 ml–1.5 ml of nonbacteriostatic saline (pH 7.0) into one nostril. Flush a plastic catheter or tubing with 2 ml–3 ml of saline. Insert the tubing into the nostril parallel to the palate. Aspirate nasopharyngeal secretions. Repeat this procedure for the other nostril.
- Collect the specimens in sterile vials. Label each specimen container with the patient’s ID number and the date collected.
- If shipping domestically, use cold packs to keep the sample at 4°C. If shipping internationally, pack in dry ice (see shipping instructions below).

2). Nasopharyngeal or oropharyngeal swabs
- Use only sterile Dacron or rayon swabs with plastic shafts. Do not use calcium alginate swabs or swabs with wooden sticks, as they may contain substances that inactivate some viruses and inhibit PCR testing.
- To obtain a nasopharyngeal swab, insert a swab into the nostril parallel to the palate. Leave the swab in place for a few seconds to absorb secretions. Swab both nostrils.
- To obtain an oropharyngeal swab, swab the posterior pharynx and tonsillar areas, avoiding the tongue.
- Place the swabs immediately into sterile vials containing 2 ml of viral transport media. Break the applicator sticks off.
near the tip to permit tightening of the cap. Label each specimen container with the patient’s ID number and the date the sample was collected.

- If shipping domestically, use cold packs to keep the sample at 4°C. If shipping internationally, pack in dry ice (see shipping instructions below).

All types of respiratory specimens may be used in RT-PCR tests. Fresh-frozen unfixed tissue specimens may also be submitted for RT-PCR.

b). Collecting specimens from the lower respiratory tract

1. Bronchoalveolar lavage, tracheal aspirate, or pleural fluid tap
   - During bronchoalveolar lavage or tracheal aspirate, use a double-tube system to maximize shielding from oropharyngeal secretions.
   - Centrifuge half of the specimen, and fix the cell pellet in formalin. Place the remaining unspun fluid in sterile vials with external caps and internal O-ring seals. If there is no internal O-ring seal, then seal tightly with the available cap and secure with Parafilm®. Label each specimen container with the patient’s ID number and the date the sample was collected.
   - If shipping domestically, use cold packs to keep the sample at 4°C. If shipping internationally, ship fixed cells at room temperature and unfixed cells frozen (see shipping instructions below).

2. Sputum
   - Educate the patient about the difference between sputum and oral secretions.
   - Have the patient rinse the mouth with water and then expectorate deep cough sputum directly into a sterile screw-cap sputum collection cup or sterile dry container.
   - If shipping domestically, use cold packs to keep the sample at 4°C. If shipping internationally, pack in dry ice (see shipping instructions below).

c). Blood Components

- Both acute and convalescent serum specimens should be collected for antibody testing. Collect convalescent serum specimens 2–4 weeks after the onset of illness. To collect serum for antibody testing:
  - Collect 5 ml–10 ml of whole blood in a serum separator tube. Allow the blood to clot, centrifuge briefly, and collect all resulting sera in vials with external caps and internal O-
ring seals. If there is no internal O-ring seal, then seal tightly with the available cap and secure with Parafilm®.

• The minimum amount of serum preferred for each test is 200 microliters, which can easily be obtained from 5 ml of whole blood. A minimum of 1 cc of whole blood is needed for testing of pediatric patients. If possible, collect 1 cc in an EDTA tube and in a clotting tube. If only 1 cc can be obtained, use a clotting tube.

• Label each specimen container with the patient’s ID number and the date the specimen was collected.

• If unfrozen and transported domestically, ship with cold packs to keep the sample at 4°C. If frozen or transported internationally, ship on dry ice.

3. Shipping of Specimens

- All IATA and UDOT regulations for shipping of clinical specimens should be followed.

**Summary of Pertinent Shipping Requirements:**

The packaging should consist of three components:

(i) a leak-proof primary receptacle(s);
(ii) a leak-proof secondary packaging; and
(iii) an outer packaging of adequate strength for its capacity, mass and intended use, and with at least one surface having minimum dimensions of 100 mm × 100 mm;

For liquids, absorbent material in sufficient quantity to absorb the entire contents should be placed between the primary receptacle(s) and the secondary packaging so that, during transport, any release or leak of a liquid substance will not reach the outer packaging and will not compromise the integrity of the cushioning material;

When multiple fragile primary receptacles are placed in a single secondary packaging, they should be either individually wrapped or separated to prevent contact between them.

E. Communication & Reporting

1. UPHL currently reports results by phone, fax and/or email per the client's request. Electronic line reports go out to the Office of Epidemiology on a daily basis. New or novel strains of influenza and/or Avian Influenza would be reported by a positive phone contact.
2. UPHL is building a Laboratory Information Management System and will move toward PHIN compliance for electronic reporting as the system is ready. UPHL is working with the vendor LabWare, Inc. to implement PHLIP. In the interim, Electronic data exchange reporting is currently done via email & fax and via the PHIN compliant LRN Messenger.

3. UPHL lab results for H5N1 are currently reported to CDC via LRN Messenger which is an electronic data exchange system. CDC would be notified by the Office of Epidemiology by positive phone contact and UPHL would also notify their contacts in the LRN at CDC by positive phone contact.

4. More extensive communication information is located in Appendix 8, which addresses communication within the public health and laboratory communities.

5. UPHL Communication Algorithm

F. Surge Capacity Planning

1. UPHL Testing Capacity and Testing Cut-Off Triggers
   • UPHL has the priority for confirmation testing during a pandemic event and must reserve lab capacity to ensure
public health surveillance needs are met. Priority for testing will emphasize hospitalized patients.

- UPHL will work closely with the Office of Epidemiology since needs may shift during an actual pandemic. The following are guidelines to decide when testing is sufficient and specimens no longer need to be sent to UPHL for confirmation testing and also are guidelines for triage of specimens:
  - Specimens sent to UPHL for confirmation testing should already be screened for influenza A and determined to be positive.
  - Testing based on clinical symptoms of a patient may be done at UPHL if an influenza screen is negative after a case screening is done by the office of epidemiology.
  - UPHL will test appropriate submissions until 80% of for reagents have been used. Twenty percent of reagents will be held in reserve for special circumstances, preparation for a second wave, and case by case evaluation where it is determined testing should be done.
  - Each Utah health district will be able to send in 10 specimens (screened positive for influenza A) for every 100,000 people in their district, reserving at least one test per county in their district. More testing may be allotted after consultation with UPHL and based on case screenings by the Office of Epidemiology.
  - In addition, each hospital in the state will be able to send in 5 specimens/100 beds in their total bed capacity. The Veteran's Hospital in Salt Lake City will be counted with the other hospitals.
  - Each Military or Indian Tribal Clinic will be allowed to send 2 samples.
  - The hospital, military and Indian samples will not count against the health district’s quota of samples.
  - UPHL will work with the Office of Epidemiology to see where other testing is appropriate for public health surveillance purposes.

2. Staffing and Training
   - Cross-train personnel in the use of testing protocols and reporting of results using the existing surveillance systems for public health.
   - Establish back up plans for hiring temporary laboratory staff
   - Consider credentialing and licensing issues for workers in lab

3. Supplies and Equipment
   - Establish inventory system to determine current level of diagnostic supplies, including personal protective equipment.
• Determine mechanism to monitor consumption of supplies during the pandemic.
• Assess anticipated equipment and supply needs.

4. Alternate Testing Sites
• For surge capacity or if UPHL facilities should become unusable for some reason, alternate test sites, with BSL3 capability are available for use at the Veterinary Lab in Logan, the research labs of National Center for the Design of Molecular Function at Utah State University and Brigham Young University Microbiology.
• The Utah National Guard 85th Civil Support Unit has a mobile BSL3 capable laboratory space that they can make available to UPHL.

G. Partnerships

UPHL will build partnerships with clinical and hospital laboratories and keep them apprised of updated information. UPHL will also keep communication channels with CDC, local health districts, state office of epidemiology, the Utah Veterinary Diagnostic Laboratory, and the public information officer for UDOH. Indian tribe medical entities and military associated laboratories will also be included in the communication loop.

IV. The Pandemic Period

A. Roles and Responsibilities

Public health, hospital and clinical laboratories, and physician sentinel sites will continue to support surveillance for pandemic influenza through the same mechanisms that support laboratory-based surveillance for seasonal influenza.

It should be understood that resources, both material and personnel, will be stressed during the pandemic period.

1. Clinical Laboratories
• Perform diagnostic testing for influenza as technology and safety levels permit.
• Scale up to manage increased numbers of requests for influenza testing.
• Support surveillance activities- refer selected specimens from possible pandemic influenza patients to UPHL.
• Maintain other diagnostic services.
• If feasible, assist other laboratories in the state, which may need surge capacity help.
• Maintain communication with UPHL so laboratory services may
be coordinated.
- Report results of positive tests as mandated by the Communicable Disease Rule to state or local epidemiology.

2. Utah Public Health Laboratories (UPHL)
- Maintain surveillance activities.
- Scale up to manage increased number of requests for influenza testing.
- Work with federal partners to supply healthcare providers and clinical laboratories with guidelines on all aspects of specimen management and diagnostic testing.
- Work with federal partners to monitor the pandemic virus and conduct special studies with CDC related to vaccine development or other aspects of the emergency response.
- Maintain reference testing capability for influenza.
- Continue education of clinicians, healthcare workers & laboratorians.
- Share data/information in "real time".
- Maintain other diagnostic services or establish priorities of what may be put on hold.

3. Utah Veterinary Diagnostic Laboratory
- Maintain surveillance activity for the animal population
- Scale up to manage increased numbers of requests for influenza testing in the animal population.
- Share information with the lab groups
- Maintain regular services or establish priorities of what may be put on hold.

4. Indian Health Clinics and Military Associated Laboratories
- Maintain reporting activities to public health as stipulated in the Communicable Disease Rule
- Assure staff is trained in how to collect, package, & ship specimens for testing to reference labs or UPHL.
- Share information with the lab groups.
- Maintain regular services or establish priorities of what may be put on hold.

B. Laboratory Support For Healthcare Providers
- All laboratory groups should establish communication channels with their respective healthcare provider population to answer questions when needed, advise on specimen collection and shipping, and appropriate testing algorithms.

C. Laboratory Safety Biocontainment
- Commercial antigen detection testing - conduct all assays in a Biosafety Cabinet (BSC) under BSL-II conditions.
- RT-PCR - conduct all assays in a BSC under BSL-II conditions.
• Virus Isolation - all assays should be conducted under BSL-III with enhancements. (See Appendix 4).

D. Occupational Health Issues for Laboratory Workers
To protect the health of laboratory workers during a pandemic, laboratories should maintain the safety practices used during the Interpandemic and Pandemic Alert Periods.
• Conduct laboratory procedures under appropriate biocontainment conditions.
• Encourage routine vaccination of laboratory employees exposed to specimens with respiratory infections. (See Appendix 7).
• Maintain a fever watch protocol for all laboratory workers that manipulate or test from respiratory specimens in the lab.

E. Use of Diagnostic Assays During an Influenza Pandemic
All testing of respiratory specimens should be done using appropriate biosafety measures and with staff using proper personal protective equipment.

1. Rapid Diagnostic Tests
Rapid diagnostic tests based on antigen detection are commercially available for influenza. Laboratories in outpatient settings and hospitals can use these tests to detect viruses in 30 minutes. Some tests can detect Influenza A viruses, including avian strains. Testing, as it currently exists, is not capable of distinguishing between the subtypes of influenza. Rapid tests may not have the sensitivity and specificity of higher genre testing. Test results must be interpreted in light of known epidemiological information such as current status of influenza circulating in the community, travel history, known contact with another influenza patient. (see Appendix 6).

2. RT-PCR Subtyping
Influenza specimens may be typed and subtyped using RT-PCR. This method does not require the growth or isolation of virus.

3. Virus Isolation
This method requires growth of virus in culture. Identification of the virus is usually confirmed through the use of IFA (indirect fluorescent antibody) staining or hemagglutination inhibition (HAI) or RT-PCR to monitor circulating seasonal strains. If clinical or epidemiological data suggests that the human case of influenza might be due to infection with avian influenza (or other highly pathogenic strains), the virus should not
be cultured except under BSL-3 conditions with enhancements. Laboratories that lack BSL-3 conditions with enhancements should immediately contact UPHL, who will coordinate the shipping of the specimen to CDC for isolation and characterization.

4. Immunofluorescent Antibody Staining

Some laboratories may use IFA staining following virus isolation to identify influenza types (A & B) and some influenza subtypes using a panel of specific antisera.

5. Serologic Tests

Tests based on the detection of antibodies in the patient's sera can be used retrospectively to confirm influenza. Acute and convalescent (paired) sera are used to detect rising antibody titers in patient's sera. This type of cannot differentiate Influenza A subtypes. This method is of limited value in the monitoring of an ongoing influenza pandemic. Its greatest use is to provide historical population data for epidemiological analysis of prevalence of infection during the pandemic.

V. Appendices

Reference Testing Guidelines

UPHL and other local certified laboratories may conduct initial testing on patient specimens for Influenza A or potential highly pathogenic strains, if laboratory capacity is available and proper biosafety protocols are addressed. Due to the spread of avian influenza A (H5N1) in poultry in Asia and other countries, laboratories should be alert for avian and human H5 viruses or any other new and potentially highly pathogenic strain of influenza viruses. Procedures for diagnosis of human cases of Influenza A (H5N1) are provided in Appendix 2. Influenza A viruses other than currently circulating H1 and H3 subtypes should be considered as potentially pandemic if detected in humans (see Appendix 3).

TABLE 1: Use of diagnostic assays during an influenza pandemic

Public health, veterinary and clinical laboratories will use different types of diagnostic tests for influenza at different states of a pandemic. Each of the tests discussed below is described in detail in Appendix 1.

Virus Isolation

Virus isolation, growing the viral strain in culture, is the "gold standard" for influenza diagnostics because it confirms the virus is infectious. During a pandemic, virus isolation, followed by antigenic and genetic (sequencing) analysis will be used to characterize the earliest pandemic isolates, as well as
monitor their evolution during the pandemic. Laboratories that participate in the WHO Global Influenza Surveillance Network, such as UPHL, typically use virus isolation followed by hemagglutination inhibition (HAI), IFA staining, or RT-PCR to monitor circulating seasonal strains of influenza virus. If clinical and epidemiological data suggest that a human case of influenza might be due to infection with avian influenza A (H5N1) or another highly pathogenic avian influenza strain (see Table 3), the virus should not be cultured except under BSL3 conditions with enhancements. Laboratories that lack BSL3 enhanced facilities may either perform RT-PCR subtyping using BSL2 containment procedures or coordinate with UPHL to send the specimen to CDC for isolation and characterization.

Immunofluorescent Antibody Staining

IFA staining following virus isolation can be used to identify influenza types (A & B) and influenza A HA subtypes using a panel of specific antisera. In some cases, IFA can be used for direct testing of cells pelleted from original clinical samples. CDC's Influenza Branch produces and distributes a reagent kit to WHO collaborating laboratories that includes monoclonal antibodies for typing and subtyping currently circulating influenza viruses by IFA. Many laboratories use commercially available reagents to type influenza viruses by direct immunofluorescence tests (DFA).

RT-PCR

Influenza specimens may also be typed and subtyped using RT-PCR, which does not require in vitro growth or isolation of the virus. UPHL scientists are capable of using RT-PCR to identify human and avian HA (hemagglutinin) subtypes of public health concern. Association of Public Health Laboratories (APHL) members may access protocols and sequences of primers and probes used for influenza subtyping from the APHL website. UPHL is the Utah member to the national Laboratory Response Network (LRN) and has access to CDC's influenza RT-PCR subtyping protocols from the secured LRN website. Other RT-PCR protocols for avian influenza subtypes are available from the Utah Veterinary Diagnostic Laboratory in Logan.

Serologic Tests

Tests base on detection of antibodies in patient sera- e.g. enzyme-linked immunosorbent assays (ELISA), HAI, and microneutralization assay- can be used to retrospectively confirm influenza infection. Although microneutralization assay is the most comprehensive test for detection in humans of antibodies to avian influenza viruses, it is currently not available at UPHL.

Rapid Diagnostic Tests

Utah Public Health Laboratories
Influenza Pandemic Response Plan
January 2008 version 2.1
Several rapid diagnostic test kits based on antigen detection are commercially available for influenza. Laboratories in outpatient settings and hospitals can use these tests to detect influenza sometimes within 30 minutes. Some test kits can detect Influenza A viruses (including avian strains); others can detect Influenza A & B without distinguishing between them; and some can distinguish between A & B viruses but not the avian subtypes. The type of specimen used for any particular rapid test kit (e.g. nasopharyngeal wash/aspirate, nasopharyngeal swab, or throat swab) must be followed as per the kit vendor's instructions for testing to be valid. Substituting another specimen type may produce less than desirable results to even erroneous results. Rapid diagnostic tests do not require the in vitro growth or isolation of the virus. During a pandemic rapid test kits will be widely used to distinguish Influenza A from other respiratory illnesses (See Appendix 6 for additional information).

**TABLE 2: Laboratory support for seasonal influenza surveillance**

**U.S. Collaborating Laboratories of the WHO Global Influenza Surveillance Network.**

All state public health laboratories, including UPHL, as well as some tertiary-care hospital and academic center laboratories, participate in providing through CDC to the network specimen testing and laboratory data about currently circulating influenza strains. These data are used to develop recommendations for the formulation of each year's influenza vaccines, as well as to detect new human influenza viruses that might have pandemic potential. CDC's Influenza Branch Laboratory serves as the WHO Collaborating Center for Surveillance, Epidemiology, and Control of Influenza, along with the WHO Collaborating Centers for Reference and Research on Influenza in Australia, Japan, and the United Kingdom. The U.S.-based center provides CDC with weekly reports of laboratory-confirmed cases of Influenza A & B viruses by age group. These laboratories typically use virus isolation followed by antigenic testing with IFA or HAI staining or RT-PCR, to identify known subtypes of human influenza virus. If unusual subtypes are detected, or if the specimens cannot be subtyped using available techniques, the specimens are sent to CDC for further testing. UPHL sends several Influenza A & B specimens to CDC on a year round basis to assist in monitoring the circulating virus. UDOH Epidemiology and Local Health Districts also assist in setting up sentinel clinic sights, where participants from representative areas throughout the state collect specimens from patients with influenza-like illness to be sent to UPHL for influenza testing.

**TABLE 3: Avian influenza strains with high and low pathogenicity**

The U.S. Department of Agriculture (USDA) classifies avian influenza viruses as low pathogenic avian influenza (LPAI) viruses or highly pathogenic avian influenza (HPAI) viruses, based on characteristics of a virus' hemagglutinin cleavage site or its virulence to birds, as determined by laboratory testing. LPAI
strains are endemic in wild birds worldwide and are responsible for most avian influenza outbreaks in poultry. LPAI strains with H5 and H7 subtypes sometimes evolve into highly pathogenic forms. HPAI strains are extremely contagious and cause severe illness and high mortality rates in poultry.

**LPAI strains include:**
- H5N2, the cause of poultry outbreaks in New York, Maine, and California in 2002.
- H7N2, the cause of poultry outbreaks in Delaware, Maryland, and New Jersey in 2004.

**HPAI strains include:**
- H5N1, the cause of major poultry outbreaks in Southeast Asia and elsewhere.
- H7N7, the cause of a 2003 outbreak in the Netherlands
- H7N3, the cause of a 2004 outbreak in British Columbia
- H5N2, the cause of a 2004 outbreak in poultry in Texas

The 2004 outbreak in Texas was the first HPAI outbreak in the United States since a previous outbreak of H5N2 in 1983-84 in the northeastern United States. The 1983-1984-disease control effort involved the destruction of approximately 17 million birds and cost more the $70 million.

Although avian influenza A viruses do not usually infect humans, several instances of human infections of avian influenza have been reported since 1997. Cases of avian influenza infection in humans are apparently caused by contact with infected poultry, or with surfaces contaminated with avian influenza virus. The few instances of apparent human-to-human transmission have been associated with very close contact to the sick person such as seen in patient care.

**LPAI strains associated with human infection include:**
- H9N2, which caused three cases of human illness in Hong Kong between 1999 and 2003 and other cases in China in 1998-1999.
- H7N2, which was detected serologically in one person involved in culling chickens during the response to a poultry outbreak in Virginia in 2002, and also was isolated from a New York resident in 2003 (exposure unknown).

**HPAI strains associated with human infection include:**
- H5N1, which has caused several hundred deaths in Southeast Asia and elsewhere and is still causing sporadic human illness in certain countries.
- H7N7, which caused the death of a veterinarian as well as 83 cases of mild human disease (including conjunctivitis) during the 2003 poultry outbreak in the Netherlands.
- H7N3, which caused 2 cases of very mild human disease (conjunctivitis, headache) in persons culling sick poultry in British Columbia in 2004.

LPAI and HPAI viruses are illnesses of birds and their pathogenicity status is based on the ability of the virus to infect and kill birds and is not related to human infection (even if the virus can infect humans on a sporadic basis).
Appendix 1

Influenza diagnostic assays

Among the several types of assays used to detect influenza, rapid antigen tests, reverse-transcription polymerase chain reaction (RT-PCR), viral isolation, immunofluorescence assays (IFA), and serology are the most commonly used. The sensitivity and specificity of any test for influenza will vary by the laboratory that performs the test, the type of test used, the type and manner of specimen collected, and the shipping and storage of specimens before testing. The World Health Organization has a comprehensive list of many FDA approved rapid influenza test kits at http://www.who.int/csr/disease/avian_influenza/guidelines/RapidTestInfluenza_web.pdf

When using a laboratory report to determine if a patient has influenza, it is important to know what methodology was used in the testing and what exactly was looked for in the test (e.g. was a rapid kit used that only detected current circulating subtypes of influenza A virus H1 and H3 and is not able to detect novel strains such as H5).

Virus Isolation

*Biocontainment level: BSL-3 with enhancements during the Interpandemic and Pandemic Alert periods; Pandemic period- BSL-2 may be used.*

Virus isolation is a highly sensitive and very useful technique when the clinical specimens are of good quality and have been collected in a timely manner (optimally 3 days from within the start of illness). Isolation of a virus in cell culture along with the subsequent identification of the virus by immunologic or genetic techniques are standard methods for virus diagnosis. Virus isolation amplifies the amount of virus from the original specimen, making a sufficient quantity of virus available for further antigenic and genetic characterization and for drug-susceptibility testing if required. Virus isolation is considered the "gold standard" for diagnosis of influenza virus infections.

Highly pathogenic avian influenza (HPAI) viruses are BSL-3 agents. During the Interpandemic and Pandemic Alert Periods, laboratories should only attempt to isolate the virus under BSL-3 enhanced conditions to optimally reduce the risk of novel influenza virus subtypes spreading to persons or animals. During the Pandemic Period, BSL-2 is appropriate to prevent laboratory-acquired infection and the virus is already widespread.

In recent years, the use of cell lines has surpassed the use of embryonated eggs for culturing of influenza viruses, although only viruses grown in embryonated eggs are used as seed viruses for vaccine production (this may be changing as genetic engineering techniques become useful for mass production). Because standard isolation procedures require several days to yield results, these assays should be used in combination with the spin-amplification
shell-vial method. The results of these assays can be obtained in 24-72 hours, compared to an average of 4-5 days using standard culture techniques. Spin-amplification should not be performed using 24-well plates because of increased risk of cross-contamination. The most effective combination of cell lines recommended for public health laboratories is primary rhesus monkey for standard culture, along with Madin Darby Canine Kidney (MDCK) in shell vial. The use of these two cell lines in combination has demonstrated maximum sensitivity over time for recovery of evolving influenza strains. Some clinical laboratories have recently reported good isolation rates using commercially available cell-line mixed-cell combinations, however data is lacking on performance of these mixed cells with new subtypes of Influenza A viruses. Appropriate clinical specimens for virus isolation include nasal washes, nasopharyngeal aspirates, nasopharyngeal swabs, oropharyngeal swabs, tracheal aspirates and bronchoalveolar lavage. Throat swabs may be appropriate depending on the pathophysiology of the pandemic strain virus (e.g. the current H5N1 seems to have a high viral load in the throat and oropharyngeal specimens are the preferred specimen but throat swabs may also be used). Consideration as to specimen collection method should include thought to infection control if collection techniques are invasive and likely to generate aerosols. Ideally, specimens should be collected within 72 hours of the onset of illness. Viral culture isolates are used to provide specific information regarding circulating influenza subtypes and strains. This information is needed to compare current circulating influenza strains with vaccine strains for the coming year. Virus isolates are also needed to monitor the emergence of antiviral resistance and of novel influenza A subtypes that might pose a pandemic threat. During outbreaks of influenza-like illness, viral culture may help identify other causes of illness when influenza is not the etiology (except when using MDCK cells or the MDCK shell-vial technique).

**Immunofluorescence Assays**

*Biocontainment level: BSL-2 when performed directly on clinical specimens; if used on cultures for earlier detection of virus, biocontainment levels for viral culture apply.*

Direct (DFA) or indirect (IFA) immunofluorescence antibody staining of virus-infected cells is a rapid and sensitive method for diagnosis of influenza and other viral infections. DFA and IFA can also be used to type and subtype influenza viruses using commercially available monoclonal antibodies specific for the influenza virus HA. The sensitivity of these methods is greatly influenced by the quality of the isolate, the specificity of the reagents used, and the experience of the person(s) performing, reading, and interpreting the test.

Although IFA can be used to stain smears of clinical specimens directly, when rapid diagnosis is needed, it is preferable to first increase the amount of virus through growth in cell culture. For HPAI isolates, attempts to culture the virus should be made only under BSL-3 enhanced conditions.
Reverse-Transcription Polymerase Chain Reaction (RT-PCR)

*Biocontainment level: BSL-2*

PCR can be used for rapid detection and subtyping of influenza viruses in respiratory specimens. Because the influenza genome consists of single-stranded RNA, a complementary DNA (cDNA) copy of the viral RNA must be synthesized using the reverse-transcriptase (RT) enzyme prior to the PCR reaction.

APHL and LRN members (including UPHL) can obtain CDC protocols and sequences of primers and probes for rapid RT-PCR detection of human and avian influenza subtypes of current concern. These protocols use real-time RT-PCR methods with fluorescent-labeled primers that allow automatic, semi-quantitative estimation of the input template. The RT-PCR results are analyzed and archived electronically, without the need for gel electrophoresis and photographic recording. A large number of samples may be analyzed at the same time, reducing the risk of carry-over contamination. As with all PCR assays, interpretation of test results must account for the possibility of false-negative and false-positive results. False-negative results can arise from poor sample collection or degradation of the viral RNA during shipping or storage. Application of appropriate assay controls that identify poor-quality samples (e.g. an extraction control and an inhibition control) can help avoid most false-negative results. The most common cause of false-positive results is contamination with previously amplified DNA. The use of real-time RT-PCR helps mitigate this problem by operating as a contained system. A more difficult problem is the cross-contamination that can occur between specimens during collection, shipping, and aliquating in the laboratory. Use of multiple negative control samples in each assay and a well-designed plan for confirmatory testing can help ensure that laboratory contamination is detected and the negative specimens are not inappropriately identified as influenza-positive.

Specimens that test positive for a novel subtype of influenza virus should be forwarded to CDC for confirmatory testing and further characterization of the virus. (Because of the possibility of contamination, it is important to provide original clinical material). All laboratory results should be interpreted in the context of the clinical and epidemiological information available on the patient.

Rapid Diagnostic Tests

*Biocontainment level: BSL-2*

Commercial rapid diagnostic tests can be used in outpatient settings to detect influenza viruses, sometimes within 30 minutes. These rapid tests differ in the types of influenza viruses they can detect and in their ability to distinguish among influenza types. Different tests can 1) detect influenza A viruses only (including avian strains); 2) detect both influenza A and B viruses, without distinguishing between them; or 3) detect both influenza A and B viruses and distinguish between them.
The types of specimens acceptable for use (i.e. nasal wash/aspirate, nasopharyngeal swab, or throat swab) also vary by test kit used. The specificity and, in particular, the sensitivity of rapid tests are lower than for viral culture and vary by test and specimen tested. The majority of rapid tests are >70% sensitive and >90% specific. Thus, as many as 30% of samples that would be positive for influenza by viral culture may give a negative rapid test result with these kits. When interpreting results of a rapid influenza test, physicians should consider the level of influenza activity in the community. When influenza prevalence is low, positive rapid test results should be independently confirmed by culture or RT-PCR. When influenza is known to be circulating, clinicians should consider confirming negative tests with viral culture or other means because of the lower sensitivity of the rapid tests. Package inserts and the laboratory performing the test should be consulted for more details regarding use of rapid diagnostic tests. (see Appendix 6 for more information on rapid testing).

Serologic Tests

Hemagglutination Inhibition (HAI)

Biocontainment level: BSL-2

Serologic testing can be used to identify recent infections with influenza viruses. It can be used when the direct identification of influenza viruses is not feasible or possible (e.g., because clinical specimens for virus isolation cannot be obtained, cases are identified after shedding of virus has stopped, or the laboratory does not have the resources or staff to perform virus isolation). Since most human sera contain antibodies to influenza viruses, serologic diagnosis requires demonstration of a four-fold or greater increase in antibody titer using paired acute and convalescent serum samples. HAI is the preferred diagnostic test for determining antibody rises. In general, acute-phase sera should be collected within one week of illness onset, and convalescent sera should be collected 2-3 weeks later.

There are two exceptions in which the collection of single serum samples can be helpful in the diagnosis of influenza. In investigations of outbreaks due to novel viruses, testing of single serum samples has been used to identify antibody to the novel virus. In other outbreak investigations, antibody test results from single specimens collected from persons in the convalescent phase of illness have been compared with results either from age-matched persons in the acute phase of illness or from non-ill controls. In such situations, the geometric mean titers between the two groups to a single influenza virus type or subtype can be compared. In general, these approaches are not optimal, and paired sera should be collected whenever possible.
Because HAI titers of antibodies in humans infected with avian influenza viruses are usually very low or even undetectable, more sensitive serologic tests, such as microneutralization, may be needed.

**Microneutralization Assay**

*Biocontainment level: Interpandemic and Pandemic Alert periods-BSL-3 with enhancements; Pandemic period-BSL-2.*

The virus neutralization test is a highly sensitive and specific assay for detecting virus-specific antibody in animals and humans. The neutralization test is performed in two steps: 1) a virus-antibody reaction step, in which the virus is mixed with antibody reagents, and 2) an inoculation step, in which the mixture is inoculated into a host system (e.g. cell cultures, embryonated eggs, or animals). The absence of infectivity constitutes a positive neutralization reaction and indicates the presence of virus-specific antibodies in human or animal sera. The virus neutralization test gives the most precise answer to the question of whether or not a person has antibodies that can neutralize the infectivity of a given virus strain. The neutralization test has several additional advantages for detecting antibody to influenza virus. First, the assay primarily detects antibodies to the influenza virus HA and thus can identify functional, strain-specific antibodies. Second, since infectious virus is used, the assay can be developed quickly upon recognition of a novel virus and before suitable purified viral proteins become available for use in other assays.

The microneutralization test is a sensitive and specific assay for detecting virus-specific antibody to avian influenza A (H5N1) in human serum and potentially for detecting other avian subtypes. Microneutralization can detect H5-specific antibody in human serum at titers that cannot be detected by HAI. Because antibody to avian influenza subtypes is presumably low or absent in most human populations, single serum samples can be used to screen for the prevalence of antibody to avian viruses. However, if infection of humans with avian viruses is suspected, the testing of paired acute and convalescent sera in the microneutralization test would provide a more definitive answer regarding the occurrence of infection. Conventional neutralization tests for influenza viruses based on the inhibition of cytopathogenic effect (CPE)-formation in MDCK cell cultures are laborious and slow, but in combination with rapid culture assay principles the neutralization test can yield results within 2 days. For HPAI viruses, neutralization tests should be performed at BSL-3 enhanced conditions. (This test is not available at UPHL but is available at CDC).
Appendix 2
Interim CDC recommendations: enhanced U.S. surveillance and diagnostic evaluation to identify cases of human infection with avian influenza A (H5N1).

NOTE: This guidance pertains to the avian influenza A (H5N1) situation in October 2005. CDC will provide updated guidance for new situations as needed through the Health Alert Network (HAN).

Enhanced surveillance efforts by state and local health departments, hospitals, clinicians and other partners are needed to identify patients at increased risk for influenza A (H5N1). Interim recommendations include the following:

Testing for avian influenza A (H5N1) is indicated in hospitalized patients with:

Radiographically confirmed pneumonia, acute respiratory distress syndrome (ARDS), or other severe respiratory illness for which an alternative diagnosis has not been established AND history of travel within 10 days of symptoms onset to a country with documented avian influenza A (H5N1) infections in poultry and/or humans.

or

Testing should be considered on a case-by-case basis in consultation with state and local health departments for hospitalized or ambulatory patients with:

- Documented temperature of >100.4°F (>38°C), AND
- One or more of the following: cough, sore throat, or shortness of breath, AND
- History of close contact either with poultry (e.g. visited a poultry farm, a household raising poultry, or a bird market, or associated with cock fighting venues) in an H5N1-infected country, or with a known or suspected human case of influenza A (H5N1) within 10 days prior to onset of symptoms or a laboratory worker known to have worked in a lab where H5N1 viruses were actively being researched.
Appendix 3
Reference testing guidelines for potential pandemic strains of influenza

State and local laboratories may conduct initial testing on patient specimens for influenza A or potential highly pathogenic strains, if laboratory capacity is available. Due to the spread of avian influenza A (H5N1) in poultry in Asia and other countries, laboratories should be on the alert for avian and human H5 viruses. Procedures for diagnosis of human cases are provided in Appendix 2. Influenza A viruses other than currently circulating H1 and H3 subtypes should also be considered as potentially pandemic if detected in humans.

UPHL will send or coordinate sending specimens to CDC if a sample tested is positive for H5 or another novel subtype.

Note: A laboratory should test for influenza A (H5) only if it is able to do so by PCR or has a BSL-3 enhanced facility. (UPHL is able to test by PCR).

or

A sample from a patient who meets the clinical and epidemiologic criteria for possible infection with a potentially pandemic virus is positive for influenza A by RT-PCR or rapid antigen detection, is negative for influenza A (H1) and (H3), and the referring jurisdiction is not equipped to test for the specific strain.

Shipping procedures for potential pandemic strains of influenza are provided in Appendix 5.
Appendix 4
Laboratory biosafety guidelines for handling and processing specimens or isolates of novel influenza strains

Key Messages:

- Commercial antigen detection testing for influenza may be conducted under BSL-2 containment conditions if a Class II biological safety cabinet is used.
- Clinical specimens from suspected novel influenza cases may be tested by RT-PCR using standard BSL-2 work practices in a Class II biological safety cabinet for initial processing of patient specimens.
- If a specimen is confirmed positive for influenza A (H5N1) by RT-PCR, additional testing should be performed only under BSL-3 enhanced conditions.
- CDC's Influenza Branch should be informed immediately by contacting the CDC director's Emergency Operations Center.
- Other partners should be notified as outlined in Appendix 8.
- A detailed description of recommended facilities, practices, and protective equipment for the various laboratory biosafety levels can be found in the CDC/NIH Biosafety in Microbiological and Biomedical Laboratories (MBML) manual (5th Ed.) at: http://www.cdc.gov/od/ohs/biosfty/bmbl5/bmbl5toc.htm
- BSL-3 with enhancements and Animal Biosafety Level 3 include: all BSL-3 practices and facilities, plus the use of negative-pressure, HEPA-filtered respirators or positive air-purifying (PAPR) respirators, and clothing change with personal showering protocols. Additional practices and/or restrictions may be added as conditions of USDA-APHIS permits.
- Registration of personnel and facilities with the Select Agent Program is required for work with HPAI viruses, which are classified as agricultural select agents.
- UPHL will test clinical specimens from suspected novel influenza cases by RT-PCR using standard BSL-2 work practices in a Class II biological safety cabinet. DFA testing will also be performed at UPHL using BSL-2 conditions.
- HPAI (H5) and (H7) viruses are classified as select agents. USDA regulations require these viruses (as well as exotic LPAI viruses) be handled under BSL3 laboratory containment conditions, with enhancements (i.e. controlled-access double-door entry, change room and shower, use of respirators, decontamination of all wastes and showering of all personnel). Laboratories that work with these viruses must be certified by USDA.
- Laboratories should not perform virus isolation on respiratory specimens from patients who may be infected with avian influenza unless stringent BSL-3 enhanced containment conditions can be met and diagnostic work
can be kept separate from studies with other human influenza A viruses (i.e. H3 & H1). Therefore, respiratory virus cultures should not be performed in most clinical laboratories.

- Cultures for patients suspected of having influenza A (H5N1) infection should be sent only to state laboratories that have enhanced BSL-3 facilities. UPHL does not have such facilities and will coordinate the transfer of specimens to CDC if viral culture is needed.

Key Messages

- Appropriate specimens for influenza testing vary by type and test.
- Check with the laboratory, which will do the actual testing, before specimens are collected to ensure the correct ones are collected using the appropriate materials (e.g. do not use calcium alginate or swabs with wooden sticks if RT-PCR testing is desired. These swabs have substances that inhibit the PCR reaction.
- Use Dacron or Rayon swabs or whichever material is recommended by the testing laboratory).
- Before collecting specimens, review infection control precautions to minimize the spread of virus.

I. RESPIRATORY SPECIMENS

At least nine types of respiratory specimens may be collected for viral and/or bacterial diagnostics: 1) nasopharyngeal wash/aspirates, 2) nasopharyngeal swabs, 3) oropharyngeal swabs, 4) bronchealveolar lavage, 5) tracheal aspirate, 6) pleural fluid tap, 7) sputum, 8) autopsy specimens, and 9) throat swabs. Nasopharyngeal wash/aspirates are the specimen of choice for detection of most respiratory viruses and are the preferred specimen type for children aged<2 years. For the current H5N1 virus, an oropharyngeal swab is the preferred specimen. Respiratory specimens for the detection of most respiratory pathogens, and influenza in particular, are optimally collected within the first 3 days from the onset of illness.

A. Collecting specimens from the upper respiratory tract

1. Nasopharyngeal wash/aspirate
   - Have the patient sit with head tilted slightly backward
   - Instill 1-1.5 mls. of nonbacteriostatic saline (pH 7.0) into one nostril.
   - Flush a plastic catheter or tubing with 2-3 mls. of saline. Insert the tubing into the nostril parallel to the palate. Aspirate nasopharyngeal secretions. Repeat this procedure for the other nostril. Collect the specimen in sterile vials. Label each specimen container with the patient's name and date collected.
   - If shipping domestically, use cold packs to keep the sample at 4º C. If shipping internationally, pack in dry ice (see shipping instructions below).

2. Nasopharyngeal or Oropharyngeal swabs
   - Use only sterile Dacron or Rayon swabs with plastic shafts. Do not use calcium alginate swabs or swabs with wooden sticks, as they may contain substances that inactivate some viruses and inhibit PCR testing.
   - To obtain a nasopharyngeal swab, insert a swab into the nostril parallel to the palate (roof of the mouth). Leave the swab in place for several seconds
so absorb secretions (swab may also be twirled). Swab both nostrils. For testing purposes it may be advantageous to have two swabs, one for each nostril.
- To obtain an oropharyngeal swab, swab the posterior pharynx and tonsillar areas avoiding the tongue.
- Place the swabs immediately into sterile vials containing viral transport media (there should be enough media to cover the swab - about 2 mls.). Break the applicator sticks off near the tip to permit the tightening of the cap. Make sure the cap is on tight to prevent leakage or contamination. Label each individual tube with the patient's name and date of collection.
- If shipping domestically, use cold packs to keep the sample at 4º C. If shipping internationally, pack in dry ice (see shipping instructions below).

(Fresh frozen unfixed tissue specimens may be submitted for RT-PCR)

**B. Collecting specimens from the lower respiratory tract**

1. Bronchoalveolar lavage, tracheal aspirate, or pleural fluid tap
   - During bronchoalveolar lavage or tracheal aspirate, use a double-tube system to maximize shielding from oropharyngeal secretions.
   - Centrifuge half of the specimen, and fix the cell pellet in formalin. Place the remaining unspun fluid in sterile vials with external caps and internal O-ring seals. If there is no internal O-ring seal, then seal tightly with the available cap and secure with Parafilm. Label each specimen container with the patient's name and specimen collection date.
   - If shipping domestically, use cold packs to keep the sample at 4º C. If shipping internationally, ship fixed cells at room temperature and unfixed cells frozen (see shipping instructions below).

2. Sputum
   - Educate the patient about the difference between sputum and oral secretions.
   - Have the patient rinse the mouth with water and then expectorate deep cough sputum directly into a sterile, screw-cap sputum collection cup or sterile, dry container.
   - If shipping domestically, use cold packs to keep the sample at 4º C. If shipping internationally, pack in dry ice (see shipping instructions below).

**II. BLOOD COMPONENTS**

Both acute and convalescent serum specimens should be collected for antibody testing. Collect the convalescent serum specimen 2-4 weeks after the onset of illness. To collect serum for antibody testing:
- Collect 5-10 mls. of whole blood in a serum separator tube (SST). Allow the blood to clot, centrifuge and collect the serum in vials with external caps and internal O-ring seals. If there is not internal O-ring seal, then secure the available cap on tightly and wrap with Parafilm.
- The minimum amount of serum preferred for each test is 200 microliters, which can easily be obtained from 5 mls. of whole blood. A minimum of 1 cc of whole blood is needed for testing pediatric patients. If possible, collect 1 cc in an EDTA tube and also one cc in a clotting tube. If only 1 cc can be obtained, use a clotting tube.
- Label each specimen container with the patient's name and specimen collection date.
- If unfrozen and shipped domestically, ship with cold packs to keep the sample at 4° C.
- If frozen or transported internationally, ship on dry ice.

III. AUTOPSY SPECIMENS

CDC can perform immunohistochemical (IHC) staining for influenza A (H5) viruses on autopsy specimens. Viral antigens may be focal and sparsely distributed in patients with influenza and are most frequently detected in respiratory epithelium of large airways. Larger airways (particularly primary and segmental bronchi) have the highest yield for detection of influenza viruses by IHC staining. Collection of the appropriate tissues ensures the best chance of detecting the virus by IHC stains.

- If influenza is suspected, a minimum total of 8 blocks or fixed-tissue specimens representing samples from each of the following sites should be obtained and submitted for evaluation:
  - Central (hilar) lung with segmental bronchi
  - Right and left primary bronchi
  - Trachea (proximal and distal)
  - Representative pulmonary parenchyma from right and left lung

In addition, representative tissues from major organs should be submitted for evaluation. In particular, for patients with suspected myocarditis or encephalitis - specimens should include myocardium (right and left ventricle) and CNS (cerebral cortex, basal ganglia, pons, medulla, and cerebellum). Specimens should be included from any other organ showing significant gross or microscopic pathology. Specimens may be submitted as:
  - Fixed, unprocessed tissue in 10% buffered formalin, or
  - Tissue blocks containing formalin-fixed, paraffin-embedded specimens, or
  - Unstained sections cut at 3 microns placed on charged glass slides (10 slides per specimen).
- Specimens should be sent at room temperature (NOT FROZEN).
- Fresh-frozen unfixed tissue specimens may be submitted for RT-PCR.
- Include a copy of the autopsy report (preliminary, or final if available), and cover letter outlining a brief clinical history and the submitter's full name, title, complete mailing address, phone, and fax numbers, in the event that CDC pathologists require further information. Referring pathologists may direct specific questions to CDC pathologists.

IV. SHIPPING INSTRUCTIONS
Local health departments, pathologists, or medical examiners should call UPHL, who will coordinate with CDC before sending specimens for influenza A reference testing. CDC hotline staff will notify a member of the Influenza Branch, who will contact UDOH- Epidemiology/UPHL to answer questions and provide guidance. In some cases, UPHL may arrange for a clinical laboratory to send samples directly to CDC.

Specimens should be sent by Priority Overnight Shipping for receipt within 24 hours. Samples (such as fresh-frozen autopsy samples for RT-PCR or other clinical materials) may be frozen at -70°C. if the package cannot be shipped within the specified time (e.g. if the specimen is collected on a Friday but cannot be shipped until Monday).

When sending clinical specimens, include the specimen inventory sheet (see below), include the assigned CDC case ID number, and note "Influenza surveillance" on all materials and specimens sent.

Include the CDC case ID number on all materials forwarded to CDC. Protocols for standard interstate shipment of etiologic agents should be followed, and are available at [http://www.cdc.gov/od/ohs/biosfty/shipregs.htm](http://www.cdc.gov/od/ohs/biosfty/shipregs.htm). All shipments must comply with current Department of Transportation (DOT) and International Air Transport Association (IATA) shipping regulations.

**Influenza Specimen Inventory Sheet**

**CDC Case ID:**

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List specimens sent to the CDC

Select a SOURCE* from the following list for each specimen: Serum (acute), serum (convalescent), NP swab, NP aspirate/wash, bronchoalveolar lavage specimen (BAL), OP swab, tracheal aspirate, or tissue.

| Specimen Type #1: | Source*: ___________________________ | Collected: __ __ / __ __ / __ __ (mm/dd/yyyy) |
|                  |                                    | Date Sent: __ __ / __ __ / __ __ (mm/dd/yyyy) |
|   • Clinical Material |                           |                                           |
|   • Extracted RNA     |                           |                                           |
|   • Virus Isolate     |                           |                                           |
| Specimen Type #2: | Source*: ___________________________ | Collected: __ __ / __ __ / __ __ (mm/dd/yyyy) |
|                  |                                    | Date Sent: __ __ / __ __ / __ __ (mm/dd/yyyy) |
|   • Clinical Material |                           |                                           |
|   • Extracted RNA     |                           |                                           |
|   • Virus Isolate     |                           |                                           |
| Specimen Type #3: | Source*: ___________________________ | Collected: __ __ / __ __ / __ __ (mm/dd/yyyy) |
|                  |                                    | Date Sent: __ __ / __ __ / __ __ (mm/dd/yyyy) |
|   • Clinical Material < Isolate |                           |                                           |
| Specimen Type #4: | Source*: ___________________________ | Collected: __ __ / __ __ / __ __ (mm/dd/yyyy) |
|                  |                                    | Date Sent: __ __ / __ __ / __ __ (mm/dd/yyyy) |
|   • Clinical Material |                           |                                           |
|   • Extracted RNA     |                           |                                           |
|   • Virus Isolate     |                           |                                           |
| Specimen Type #5: | Source*: ___________________________ | Collected: __ __ / __ __ / __ __ (mm/dd/yyyy) |
|                  |                                    | Date Sent: __ __ / __ __ / __ __ (mm/dd/yyyy) |
|   • Clinical Material |                           |                                           |
|   • Extracted RNA     |                           |                                           |
|   • Virus Isolate     |                           |                                           |

Carrier: Tracking #:  

Appendix 6  
Rapid diagnostic testing for influenza
The following information in this appendix is designed to assist clinicians and clinical laboratory directors in the use of rapid diagnostic tests during interpandemic influenza seasons. During an influenza pandemic, one or more of these tests may be sensitive and specific enough to be used by clinicians to supplement clinical diagnoses of pandemic influenza. However, clinicians should be reminded that a negative test result might not rule out pandemic influenza and should not affect patient management or infection control decisions.

I. INFORMATION FOR CLINICIANS

A. Background

Rapid diagnostic tests for influenza can help in the diagnosis and management of patients who present with signs and symptoms compatible with influenza. They also are useful for helping to determine whether institutional outbreaks of respiratory disease might be due to influenza. In general, rapid diagnostic testing for influenza should be done when the results will affect a clinical decision. Rapid diagnostic tests can provide results in as little as 30 minutes.

B. Reliability and interpretation of rapid test results

The reliability of rapid diagnostic tests depends largely on the conditions under which they are used. Understanding some basic considerations can minimize being misled by false-positives or false-negative results.

Median sensitivities of rapid diagnostic tests are generally ~70%-75% when compared with viral culture, but median specificities of rapid diagnostic tests for influenza are approximately 90%-95%. False-positive (and true negative) results are more likely to occur when disease prevalence in the community is low, which is generally at the beginning and end of the influenza season. False-negative (and true positive) results are more likely to occur when disease prevalence is high in the community, which is typically at the height of the influenza season.

C. Minimizing the occurrence of false results

- Use rapid diagnostic tests that have high sensitivity and specificity.
- Collect specimens as early in the illness as possible (within 4-5 days of symptoms onset).
- Follow the manufacturer's instructions, including those for handling of specimens.
- Consider sending specimens for viral culture when:
  - Community prevalence of influenza is low and the rapid diagnostic test result is positive, or
  - Disease prevalence is high but the rapid diagnostic test result is negative.
- Contact your local health department or Utah Department of Health for information about influenza activity.

II. INFORMATION FOR CLINICAL LABORATORY DIRECTORS

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A. Background

Rapid diagnostic tests for influenza are screening tests for influenza virus infection; they can provide results within 30 minutes. These are to be distinguished from more complex test done by DFA or PCR, which yield results in 2-4 hours. The use of commercial influenza rapid diagnostic tests by laboratories and clinics has increased substantially in recent years. The World Health Organization has a comprehensive list of FDA approved rapid influenza test kits, and a comparison of features at

Rapid tests differ in some important aspects. Some can identify influenza A and B viruses and distinguish between them; some can identify influenza A and B viruses but cannot distinguish between them. Some tests are waived from requirements under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). Most tests can be used with a variety of specimen types, but sensitivity and specificity can vary with specimen type. Rapid tests vary in terms of sensitivity and specificity when compared with viral culture. Product insert information and research publications indicate that median sensitivities are approximately 70-75% and median specificities are 90-95%. Specimens to be used with rapid tests generally should be collected as close as possible to the start of symptoms and usually no more than 4-5 days later in adults. In very young children, influenza viruses can be shed for longer periods; therefore, in some instances, testing for a few days after this period may still be useful. Test sensitivity will be greatest in children, who generally have higher viral titers, if the specimen is obtained during the first 2 days of illness, and if the clinician or laboratory has more experience performing the test. The quality of the specimen tested also is critical for test sensitivity.

B. Accuracy depends on disease prevalence

The positive and negative predictive values of rapid tests vary considerably depending on the prevalence of influenza in the community. False-positive (and true negative) influenza test results are more likely to occur when disease prevalence is low, which is generally at the beginning and end of the influenza season. False-negative (and true positive) influenza test results are more likely to occur when disease prevalence is high, which is typically at the height of the influenza season.

1. Clinical considerations when influenza prevalence is low

When disease prevalence is low, the positive-predictive value (PPV) is low and false-positive test results are more likely. By contrast, the negative-predictive value (NPV) is high when disease prevalence is low, and negative results are likely to be truly negative.

If flu prevalence is... and specificity is... then PPV is... false-positive rate is...

<table>
<thead>
<tr>
<th>Flu Prevalence</th>
<th>Specificity</th>
<th>PPV</th>
<th>False-Positive Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>VERY LOW (2.5%)</td>
<td>POOR (80%)</td>
<td>VERY POOR (6-12%)</td>
<td>VERY HIGH (88-94%)</td>
</tr>
<tr>
<td>VERY LOW (2.5%)</td>
<td>GOOD (98%)</td>
<td>POOR (39-56%)</td>
<td>HIGH (44-61%)</td>
</tr>
</tbody>
</table>

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Interpretation of positive results should take into account the clinical characteristics of the case-patient. If an important clinical decision is affected by the test result, the rapid test result should be confirmed by another test such as viral culture or PCR.

2. Clinical considerations when influenza prevalence is high

When disease prevalence is relatively high, the NPV is low and false-negative results are more likely. By contrast, when disease prevalence is high, the PPV is high and positive results are more likely to be true.

If flu prevalence is... and sensitivity is... then NPV is... false-negative rate is...
MODERATE (20%) POOR (50%) MODERATE (86-89%) MODERATE (88-94%)
MODERATE (20%) HIGH (90%) VERY GOOD (97-99%) VERY LOW (2-3%)
HIGH (40%) POOR (50%) MODERATE (70-75%) MODERATE (25-30%)
HIGH (40%) HIGH (90%) VERY GOOD (93-94%) LOW (6-7%)

Interpretation of negative results should take into account the clinical characteristics of the case-patient. If an important clinical decision is affected by the test result, the rapid test result should be confirmed by another test such as viral culture or PCR.

C. Selecting tests

Selection of a test should take into consideration several factors, such as the types of specimens that are considered optimal for that test, storage conditions and expiration date of kits. Also, tests with high sensitivity and specificity will provide better positive and negative predictive values. Information about test characteristics is provided in product inserts, scientific articles and by the manufacturer.

D. Changes in recommended procedures can affect test results

Modification by the user can affect test performance and increase false-positive and/or false-negative rates. Such modifications include using specimen types for which the test is not optimized or using swabs that did not come with the rapid test kit (unless allowed by the manufacturer). Temperature requirements for storage of the kit and the specimen, as well as running the test should be followed.

E. Conditions for when rapid diagnostic test may be beneficial

Uses of rapid diagnostic tests are beneficial in situations such as the following:
- To test cases during an outbreak of acute respiratory disease to determine if influenza is the cause, or
- To test selected patients during the influenza season, or

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- In the fall or winter, to test selected patients presenting with respiratory illnesses compatible with influenza to help establish whether influenza is present in a specific population and to guide healthcare providers in diagnosing and treating respiratory illness.

In general, the exclusive use of rapid tests does not address the public health need for obtaining viral isolates so that influenza virus strain subtyping and characterization can be conducted to monitor antigenic and genetic changes.

During an influenza pandemic, some rapid diagnostic tests may be able to detect the pandemic strain with adequate sensitivity and specificity. Rapid tests can be used by physicians to supplement clinical diagnoses of pandemic influenza.

Physicians should be reminded that a negative test result might not rule out influenza and should not affect patient management or infection control decisions.
Appendix 7
Guidelines for medical surveillance of laboratory/research personnel working with novel strains of influenza, including avian strains and other strains with pandemic potential.

Key Messages
- Laboratory workers should receive training on the appropriate biosafety level for the type of work being performed.
- Before working with avian influenza A viruses, including highly pathogenic strains, laboratory workers should have a baseline serum sample obtained and stored for future reference.
- Workers in laboratories that contain avian influenza A viruses should report any fever or lower respiratory symptoms to their supervisors. Workers should be evaluated for possible exposures, and the clinical features and course of the illness should be closely monitored.
- Laboratory workers who are believed to have had a laboratory exposure to an avian influenza A virus or other highly pathogenic strain should be evaluated, counseled about the risk of transmission to others, and monitored for fever or lower respiratory symptoms as well as any of the following: sore throat, rhinorrhea, chills, rigors, myalgia, headache, and diarrhea.
- UDOH and/or local health districts should be notified promptly of laboratory exposures and illnesses in exposed laboratory workers. Medical surveillance of laboratory personnel can help to ensure that workers who are at risk of occupational exposure to avian influenza viruses or other novel animal or human influenza strains and who develop symptoms of illness receive appropriate medical evaluation and treatment, both for the benefit of their health and to prevent further transmission for the public's health.

I. PREREQUISITES FOR WORKING WITH NOVEL AVIAN OR HUMAN INFLUENZA VIRUSES

A. Baseline serum samples

Before working with novel avian or human (animal) influenza viruses, laboratory workers should have a baseline serum sample obtained and stored for future reference.

B. Influenza vaccine

Laboratories should offer the current inactivated influenza vaccine to laboratory personnel. Its use is especially encouraged for personnel working with avian viruses in BSL-3 enhanced laboratory conditions and for those who may be exposed to these viruses in the field. Immunization might reduce the chance of illness from exposure to human influenza viruses currently circulating in the community that could lead to confusion in monitoring for avian influenza A
infection. Vaccines against novel influenza A viruses (e.g. H5N1) are undergoing clinical trials and might be available in the future.

C. Oseltamivir prophylaxis

- It is not necessary to require oseltamivir for laboratory research personnel working with highly pathogenic influenza strains. It is encouraged for those doing animal experiments only for the time they are working with animals, especially ferrets.
- When considering oseltamivir prophylaxis, be sure to evaluate appropriate candidates for contraindications, answer their questions, review adverse effects, and explain the benefits.
- Maintain a log of persons on oseltamivir, persons evaluated and not on oseltamivir, doses dispensed, and other adverse effects.
- Periodically evaluate and update oseltamivir policies and procedures.

D. Post-exposure prophylaxis

Conditions for use of oseltamivir for post-exposure prophylaxis include a known or suspected laboratory exposure to live avian influenza virus, including highly pathogenic strains, for a person not on oseltamivir. Appropriate healthcare personnel should be available to evaluate immediately and dispense oseltamivir if the exposure occurs during working hours. If exposure occurs after working hours, an exposed laboratory person should present to the Emergency Department and, after evaluation, communicate with UDOH or CDC for recommendations.

II. MANAGEMENT OF INFLUENZA-LIKE ILLNESS IN PERSONNEL WITH POSSIBLE EXPOSURE TO NOVEL AVIAN OR HUMAN INFLUENZA VIRUSES.

A. General procedures

- Maintain a daily sign-in/out sheet to record name, date, time in/out, use of oseltamivir, and brief description of job tasks. This record will facilitate retrospective documentation if an illness occurs.
- Workers should report any influenza-like illness and any potential laboratory exposures to the supervisor.

B. Evaluation and treatment

1. During regular working hours

- The affected employee should notify the supervisor. The supervisor should immediately contact the appropriate healthcare personnel and facility contacts (e.g. occupational health, infection control or designee).
• Upon arrival at the designated clinic, the employee should be placed in a private room for isolation where a healthcare provider can provide consultation and evaluation.

• The healthcare provider should obtain respiratory specimens (e.g. nasopharyngeal swab or aspirate) for viral culture. A rapid antigen test, with the ability to differentiate between influenza A and B, should be used for initial diagnosis, followed by virus isolation.

• Based on: 1) the rapid test results (if influenza A positive), 2) the status of oseltamivir prophylaxis, and 3) the clinical evaluation, the healthcare provider should determine whether the patient will return to work, be sent home, or be sent to an infectious disease consultant.

2. During working hours when the employee calls from home
   • The employee should notify the supervisor. The supervisor should discuss the situation with the appropriate healthcare personnel and determine where and by whom the employee will be evaluated and specimens for viral culture will be obtained.
   • The employee may come to an on-site clinic for evaluation or may elect to see a personal physician. If the employee chooses to see a personal physician, the on-site clinician should discuss with the personal physician the likelihood of a laboratory-acquired infection. The personal physician should be asked to collect specimens for antigen detection and viral culture.
   • An employee who is not sick enough to be admitted to a hospital should remain at home under the care of a personal physician, pending results from the viral culture. If influenza A (H3N2) or A (H1N1) is identified, the employee should be advised and can resume normal activities as soon as symptoms subside.
   • If avian influenza A (e.g. H5, H7, H9) is identified, the family and other contacts should be monitored for illness.
   • Local public health officials should be notified about any confirmed avian influenza infections.

3. After working hours
   • The employee should notify the supervisor. The supervisor should inform other persons as the situation dictates.
   • If the employee is acutely ill with symptoms consistent with influenza, the employee and/or supervisor should contact the appropriate healthcare provider for instructions. The healthcare provider should conduct the initial evaluation and patient management.
   • The supervisor should immediately ask the healthcare provider to collect specimens for rapid testing and viral culture.
   • The employee should follow the advice of the healthcare provider with regards to further evaluation/treatment.
   • Public health officials should be notified as appropriate by the situation.
Appendix 8
Contact Information and Resources

I. NOTIFICATION AND COMMUNICATION ALGORITHM FOR AVIAN OR NOVEL PANDEMIC STRAIN OF INFLUENZA VIRUS DETECTION IN A LABORATORY

For pandemic surveillance purposes it is essential the proper risk communication and notification be done for public health response and intervention when a novel strain of influenza virus is detected. Laboratories should be familiar with and adhere to all regulatory requirements addressing disease reporting and/or specimen submission for influenza. UDOH currently has no means of electronic laboratory reporting by transfer of medical records or lab test results. Work is moving forward to develop an electronic reporting system starting with an exchange between Intermountain Health Care Institutions and UDOH. Until that system is complete and expanded to other hospital chains, reporting is done by phone, email, fax or mailed report.

A. Clinical Laboratories
- Clinical laboratories should develop their own internal notification and communication protocols that ensure proper notice is given to management, infection control personnel, safety officers and public information officers (if appropriate).
- Local health departments and/or the Utah Department of Health Epidemiologists should receive notification as soon as a novel strain of influenza is detected (or if available to the lab, a medical history/investigation implicates a suspect novel or avian influenza A).
- Appropriate specimens should be sent to UPHL as soon as a novel influenza virus is detected. UPHL should be notified (24/7) that a specimen is being sent, by what means (e.g. courier, Fed Ex) and what time it is expected to arrive.
- Local health departments and/or UDOH Epidemiology may assist in coordinating notification of UPHL staff and specimen shipping.
- It is desirable that any communications with outside media/press be coordinated with partner laboratories and parent agencies.

B. Veterinary Laboratories
- Veterinary laboratories should develop their own internal notification and communication protocols that ensure proper notice is given to management, infection control personnel, safety officers and public information officers (if appropriate).
- The Department of Agriculture and the Veterinary Laboratory will take the lead in notifying partner laboratories and parent agencies in a timely manner of any novel influenza A viruses detected in the laboratory that poses a threat to human, domestic animal or wildlife.
- Veterinary laboratories should report to local health districts and/or UDOH Epidemiology any influenza A viruses detected that was involved in a mass poultry die-off and/or culling event.
- UPHL may be notified as a courtesy to a partner lab that could be impacted by the detection of a novel influenza virus.
- It is desirable that any communications with outside media/press be coordinated with partner laboratories and parent agencies.

C. Utah Public Health Laboratories
- UPHL staff will follow all internal policies for notification and communication when a novel or avian strain of influenza A is detected. This includes communication with UDOH Epidemiology (who will notify local health and CDC).
- UPHL will work with UDOH Epidemiology and UDOH Public Information to coordinate notification to all laboratory partners.
- Notification may be done by phone, email, fax or incorporate all these means of communication through the Utah Notification Information System (UNIS).
- UPHL will notify appropriate laboratory personnel at CDC, such as the Laboratory Response Network (LRN). Use of LRN Messenger will be used until the appropriate, corresponding module [PHLIP & NEDSS] is built into UPHL’s Lab LIMS (estimated completion 2008).
- UPHL will assist in coordinating reports to all partner laboratories as appropriate so that clinical labs and veterinary labs are informed of any novel influenza virus detections. Clinical labs may use UPHL to notify the vet lab and the veterinary lab may use UPHL to notify the clinical labs.
Bench Tech identifies H5N1 Avian Strain of Influenza A or other novel influenza strain.

For UPHL Supervisor & Bureau Director Notified

For Other Labs Supervisor or Director is Notified & Client

Local Health Dept. is Notified

UDOH Epidemiology is Notified

UDOH Epidemiology assists with Local Health and Other Labs to get specimen to UPHL for confirmation testing

UDOH Epidemiology coordinates contact of CDC Epidemiology, UDOH PIO, UDOH Director, State Epidemiologist, & Other Local Health Departments.

UPHL coordinates messages to go back to all partner labs as authorized by lab director and UDOH directors.

UDOH, UPHL, Local Health, PIOs and Appropriate Partners prepare unified message for release to media & public as warranted.