



Center for Infectious
Disease Research & Policy

UNIVERSITY OF MINNESOTA

MCEIRS AVIAN INFLUENZA TRAINING

Individual Study Guide

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Avian Influenza in Humans: Detection, Prevention and Control

**Minnesota Center of Excellence for Influenza
Research and Surveillance**

CONTENTS

Avian Influenza in Humans: Detection, Prevention and Control

Introduction

Lesson 1: Background

Lesson 2: Avian Influenza Surveillance Overview

Lesson 3: Diagnostic Testing for Avian Influenza in Humans

Lesson 4: Avian Influenza Case Identification

Lesson 5: Avian Influenza Case Investigation and Contact Management

Lesson 6: Preventing Disease in the Community

Lesson 7: Preventing Avian Influenza in Medical Settings

Lesson 8: Preventing Avian Influenza Among Poultry Workers

Glossary

Resources

INTRODUCTION

AVIAN INFLUENZA IN HUMANS: DETECTION, PREVENTION, AND CONTROL

This course will review the status of detection, prevention, and control of avian influenza in humans. Surveillance methods are described, as well as case investigation and contact management principles used to control the spread of avian influenza.

Background on the role of avian influenza in past pandemics and the current status of avian influenza in humans are also addressed, as will case definitions, specimen collection, laboratory testing, and prevention and control measures.

LESSON 1: BACKGROUND

In this lesson we will cover

- Influenza Pandemics
- Impact of Influenza Pandemics
- Current Status of Avian Influenza Viruses in Humans
- Adaptability of Avian Influenza Viruses in Humans
- WHO Risk Status for H5N1 and H7N9

INFLUENZA PANDEMICS

Three pandemics occurred during the 20th century and one in the 21st century. These were caused by an H1, an H2, an H3, and an H1 strain, respectively. Currently, H1 and H3 influenza strains are circulating in the human population.

Influenza pandemic strains can emerge from the avian lineage either through the process of genetic reassortment between human and animal strains (referred to as "antigenic shift") or through "antigenic drift" and gradual adaptation to humans.

Influenza pandemics occurring during the 20th century apparently all arose from the Eurasian avian lineage of viruses. The 2009 pandemic influenza strain also contained genes of avian influenza origin.

Influenza Pandemics of the 20 th and 21 st Century: Impact in the United States*			
Date	Strain	Estimated No. of Deaths in US	Comments
1918-19 (Spanish Flu)	H1N1	500,000	Global mortality may have been as high as 100 million. The virus likely originated in the US and then spread to Europe.
1957-58 (Asian Flu)	H2N2	60,000	The virus was first identified in China; approximately 1 million people died globally during this pandemic.
1968-69 (Hong Kong Flu)	H3N2	40,000	The death rate from this pandemic may have been lower because the strain had a shift in the hemagglutinin (HA) antigen only and not in the neuraminidase (NA) antigen.
2009-10	H1N1	18,500	The first case occurred in Mexico in March 2009 and quickly spread worldwide. In June 2012, researchers estimated that the pandemic virus caused between 151,700 and 575,400 deaths worldwide. The death rate was lower compared with other pandemics, but severe and fatal cases occurred more often in younger age-groups.
*All four pandemics were characterized by a shift in age distribution of deaths to younger populations under age 65 (at least initially); shift was particularly dramatic during the 1918 pandemic.			

1918 (SPANISH FLU)

Recent genetic sequencing of the 1918 strain indicates that the strain was of avian origin and that the strain did not reassort with a human strain (unlike later pandemics), but rather gradually adapted to humans until it could be efficiently transmitted person to person. Current evidence indicates that the 1918 virus was an avian-like virus derived in toto from an unknown source. A two-amino-acid change in the hemagglutinin (HA) of the 1918 virus was recently shown to abolish transmission among ferrets, confirming the essential role of HA receptor specificity for the transmission of influenza viruses in mammals.

1957-58 (ASIAN FLU)

The Asian flu was caused by an H2N2 strain and originated in China. The virus was initially isolated in Singapore in February 1957 and in Hong Kong in April of that year. The pandemic spread to the Southern Hemisphere during the summer of 1957 and reached the United States in June 1957. The pandemic strain acquired three genes from the avian influenza gene pool in wild ducks by genetic reassortment and obtained five other genes from the then-circulating human strain.

1968-69 (HONG KONG FLU)

The Hong Kong flu was caused by an H3N2 strain. The strain acquired two genes from the duck reservoir by reassortment and kept six genes from the virus circulating at the time in humans.

2009-10 (PANDEMIC H1N1)

The pandemic that began in 2009 was caused by an H1N1 strain. This triple reassortant virus contained genes from viruses of avian, swine, and human origin.

CURRENT STATUS OF THE AVIAN INFLUENZA VIRUS IN HUMANS

Highly pathogenic H5N1 avian influenza has caused sporadic disease in people and continues to cause outbreaks in poultry and, more often, wild birds (particularly in parts of Asia and in Egypt).

At this point, there is no evidence of genetic reassortment between avian H5N1 viruses and human strains; however, if H5N1 continues to circulate widely among poultry, the potential for emergence of a reassorted pandemic strain remains a concern. For example, H5N1 viruses have been found in pigs in southern China and in Indonesia, and human H3N2 influenza viruses are endemic in pigs in China. Thus, the conditions exist for exchange of genetic material between the different viruses in the pig host.

Highly pathogenic avian influenza H5N6 has been circulating in poultry in China, becoming more prevalent in poultry than avian influenza H5N1. As of January 2017, 16 human cases of influenza A H5N6, with 6 deaths, had been reported in China. HPAI H5N6 has also been seen in South Korea, Vietnam, Laos, and Hong Kong. From 2014-17, other H5 viruses (including H5N2 and H5N8) have been circulating in poultry and wild birds in North America, Europe, Asia, and Africa. No human cases associated with these viruses have been detected.

An H7N9 avian influenza virus is causing an outbreak of causing ongoing disease in humans in China. Initial cases were first recognized in the spring of 2013 and have continued to occur, generally following a seasonal pattern with most illnesses occurring during winter or early spring months. According to FAO, as of January 2017, more than 1000 illnesses and at least 360 deaths have been reported. Public health officials also are concerned about the pandemic potential of this avian influenza virus. The fact that the virus does not cause clinical signs in birds makes detection of the virus in animals more difficult. In addition, the virus has been shown to spread efficiently via the aerosol route (although as of January 2017, human-to-human transmission appears to be minimal).

ADAPTABILITY OF AVIAN INFLUENZA VIRUSES IN HUMANS

- The potential for gradual adaptation of avian influenza viruses, such as H5N1 or H7N9, to humans over time with evolution into a pandemic strain remains a possibility.
- This is potentially more likely to occur as more humans become infected with the avian strain, which allows the possibility for the avian strain to share genetic material and reassort with existing human strains.
- Influenza viruses that are adapted to humans have hemagglutinin proteins (HAs) (ie, virus surface proteins) that bind specifically to the long alpha 2-6 glycan receptors of epithelial cells in the human upper respiratory tract. If a novel avian strain acquires this ability, it will be more suited to human hosts, and therefore will be more likely to cause a pandemic.

WHO RISK STATUS OF H5N1 AND H7N9 AS OF JANUARY 2017

Risk Assessment for H5N1:

According to the World Health Organization (WHO), at this time the pandemic alert level for H5N1 influenza is “Alert,” which is described as “the phase at which influenza caused by a new subtype has been identified in humans.” This phase calls for increased vigilance and careful risk assessment at the local, national, and global levels. In January 2015, the WHO indicated that “the H5N1 virus does not currently appear to transmit easily among people. As such, the risk of community-level spread of this virus remains low.”

Risk Assessment for Avian Influenza H5 Subtypes

Avian Influenza H5 subtypes in addition to H5N1, such as H5N8, H5N2, H5N3, H5N6, and H5N9, have been circulating in poultry populations in Asia, Africa, Europe, and North America in 2014-17. Other than the H5N6 virus in China, these viruses have not yet caused illness in people. However, WHO states that there is a “need to increase vigilance in the animal and public health sectors.”

Risk Assessment for H7N9:

The WHO provided a risk assessment in December 2013: “Although 5 small family clusters have been reported, evidence does not support sustained human-to-human transmission of this virus; therefore, the current likelihood of community-level spread of this virus is considered to be low. Continued vigilance is needed within China and neighboring areas to detect infections in animals and humans. WHO advises countries to continue surveillance and other preparedness actions, including ensuring appropriate laboratory capacity.” This risk assessment has not changed as of January 2017.

LESSON 2: AVIAN INFLUENZA SURVEILLANCE OVERVIEW

In this lesson we will cover:

- Importance of Surveillance
- Surveillance Methods
- Review of Avian Influenza Surveillance Data for Humans
- Surveillance for Novel AI H5 Viruses in the US

IMPORTANCE OF SURVEILLANCE

Surveillance for and management of outbreaks of avian influenza in animals are important for minimizing the risk for transmission to humans, particularly in areas where animals and humans closely interact.

Surveillance for and management of human cases of avian influenza and their contacts are also essential for minimizing the risk of an avian influenza virus entering, adapting to, and/or spreading through the human population.

The primary public health objectives for surveillance of avian influenza in humans are to:

- Monitor trends in the occurrence of disease, including the detection of epidemics and pandemics
- Guide the planning, implementation, and evaluation of programs to prevent and control avian influenza in humans
- Understand the natural history of avian influenza, including the identification of populations at high risk for disease or complications
- Monitor changes in avian influenza virus strains that infect humans

Effective surveillance through rapid case identification and reporting allows more time to follow up with the contacts of cases and possibly prevent ongoing transmission of the virus among humans.

Effective disease surveillance requires rapid detection of cases through efficient and accurate diagnostic tests, detailed case definitions, and rapid reporting. Data gathered during surveillance activities can then be used to guide and assess public health actions.

SURVEILLANCE METHODS

Surveillance for avian influenza in humans can be conducted through a number of methods. These are outlined below.

- Laboratory-based surveillance
 - Laboratory-based surveillance is particularly useful when an objective of the system is to monitor changes in influenza virus strains that infect humans.
 - Laboratory tests are widely used to identify influenza virus at the genus level (influenza A/B) or at the H-type level (H1, H3, and H5).
- Passive reporting of clinically diagnosed cases directly to public health authorities through routine disease-reporting channels
- Active surveillance during periods of heightened disease activity
 - Active surveillance involves routine outreach by health department staff to potential disease reporters to increase the completeness and/or timeliness of disease reporting.
 - Following the first identification of a human case of H5N1 avian influenza in Hong Kong in 1997, public health officials intensified disease surveillance activities at outpatient clinics and hospitals. An additional 17 cases were eventually identified.
- Investigation of outbreaks of highly pathogenic avian influenza in birds with follow-up of exposed human populations
 - During an outbreak of highly pathogenic avian influenza A virus subtype H7N7 that began in 2003 in commercial poultry farms in the Netherlands, an outbreak investigation was launched to assess the extent of transmission of H7N7 from chickens to humans. A total of 89 cases, including 1 death, were identified in humans as part of this investigation.
 - Because birds infected with low-pathogenic avian influenza rarely show clinical signs, surveillance for viruses such as H7N9 in animals becomes more difficult.
- Contact investigations for confirmed cases of avian influenza (particularly H5N1 and H7N9)
- Serologic surveys that obtain information regarding past exposure to avian influenza viruses
 - These are generally outside the purview of public health and are usually conducted as investigative studies, but they provide valuable information on potential for exposure of people who work or recreate at the human-animal interface.

REVIEW OF AVIAN INFLUENZA SURVEILLANCE DATA FOR HUMANS

HUMAN CASES OF AVIAN INFLUENZA

The table below provides examples of occurrences of human disease caused by avian influenza virus subtypes. The cases outlined below have primarily been detected through the following surveillance activities:

- Passive reporting of clinically diagnosed cases to public health authorities
- Active case finding and contact investigations by public health authorities during periods of increased activity
- Investigation of specific outbreaks in poultry and follow-up of potentially exposed persons

Illustrative Examples of Human Avian Influenza Cases				
Year	Subtype	No. of Cases	Location	Comments
1996	H7N7	1	United Kingdom	The case-patient developed conjunctivitis after cleaning a duck house.
1997	H5N1	18 (6 deaths)	Hong Kong	Case-patients were linked to an outbreak of H5N1 in poultry. Sustained person-to-person transmission did not occur, and the outbreak stopped when all birds in the Hong Kong commercial poultry industry (about 1.4 million) were slaughtered.
1999	H9N2	2 (children ages 4 yr, 13 mo)	Hong Kong	Both case-patients had been hospitalized with influenza-like illness and both recovered uneventfully. No additional cases of person-to-person transmission occurred. Further investigation demonstrated that H9N2 strains were circulating in poultry in Hong Kong and China, although the viruses were not highly pathogenic for birds.
2002	H7N2	1	United States (Virginia)	Evidence of infection was found in one person in Virginia following a poultry outbreak.
2003	H7N7	89 (1 death)	The Netherlands	During an outbreak of H7N7 avian influenza in poultry, infection spread to poultry workers and their families in the area. Most patients had conjunctivitis, and several reported influenza-like illness. The death occurred in a 57-year-old veterinarian. Subsequent serologic testing demonstrated that additional case-patients had asymptomatic infections.
2004	H10N7	2 (infants)	Egypt	One child's father was a poultry merchant.
2006	H7N3	1	United Kingdom	Although a number of exposed persons had symptoms of conjunctivitis or influenza-like illness, only one poultry worker had a laboratory-confirmed infection.
2007	H7N2	4	United Kingdom	Case-patients were associated with a

				poultry outbreak of H7N2 in Wales. The case-patients had conjunctivitis and influenza-like illness.
2008	H9N2	1 (infant)	China	The source of infection is unknown.
2009	H9N2	1 (47 year old)	Hong Kong SAR	Reported travel history to mainland China; patient had mild disease and recovered.
2010	H5N1	48 total cases/ 24 deaths	Cases/deaths in 2010: • Cambodia (1/1) • China (2/1) • Indonesia (9/7) • Vietnam (7/2) • Egypt (29/13)	Since 2003 the WHO has officially recognized more than 530 human cases of H5N1 influenza, with more than 310 deaths and a case-fatality rate (CFR) of 59%. Cases have been reported from Azerbaijan, Bangladesh, Cambodia, China, Djibouti, Egypt, Indonesia, Iraq, Lao PDR, Myanmar, Nigeria, Pakistan, Thailand, Turkey, and Vietnam. As of early 2011, sporadic cases continue in Egypt and southeast Asia.
2012	H7N3	2	Jalisco, Mexico	Two poultry workers developed conjunctivitis caused by H7N3 in association with an outbreak in poultry.
2013-17	H7N9	1000	China	According to FAO, over 1000 cases had occurred through the January 2017 with a total of over 360 deaths.
2014-17	H5N6	16	China	According to WHO, 16 cases and 6 deaths had occurred through January 2017.

SURVEILLANCE FOR NOVEL AI H5 VIRUSES IN THE US

In late 2014, an H5N8 HPAI virus that had been circulating in Europe and Asia was detected in the Pacific flyway. This virus then mixed with other North American lineage viruses resulting in reassortant H5N2 and H5N1 viruses. All 3 viruses were subsequently detected in wild birds, backyard poultry, and commercial poultry in North America in 2015. The HPAI H5N2 reassortant virus caused 219 cases of HPAI in domestic poultry in the United States (predominantly in the Upper Midwest), which resulted in the death or destruction of over 48 million birds.

During the winter of 2016-17, the H5N8 virus previously circulating in Europe and Asia returned, and was detected in wild birds or poultry in more than 35 countries in Europe, Asia, the Middle East, and Africa. At least 4 other HPAI H5 subtypes, including H5N6 and H5N5, were also detected in birds in 2016.

While no human infections associated with these H5 viruses have been detected in North America, because of the relationship to the Eurasian H5N1 virus, the CDC is concerned about the potential for these viruses to cause severe human disease; therefore, the CDC recommends that clinicians consider infection with novel H5 viruses for persons with compatible illness who have an appropriate exposure history (see Lesson 4 for the current case definition).

LESSON 3: DIAGNOSTIC TESTING FOR AVIAN INFLUENZA IN HUMANS

In this lesson we will cover:

- Rapid Antigen Testing
- Immunofluorescence
- PCR Assays
- Virus Isolation by Cell Culture
- Susceptibility Testing

Diagnostic tests to identify avian influenza infection are essential for all types of influenza surveillance systems. There are multiple types of tests used to directly identify the virus or the antibodies produced by the human immune system in response to the virus.

Tests for influenza include: rapid antigen testing, immunofluorescence, polymerase chain reaction (PCR), and viral culture.

Laboratory tests are widely used to identify influenza virus at the genus level (influenza A/B) or at the H-type level (such as H1, H3, and H5). H-subtype-specific tests must be used to identify potential avian strains, including H5N1 and H7N9.

The WHO recommends forwarding all H5-, H7-, and H9-positive isolates to an approved influenza reference laboratory for confirmation and N-typing.

RAPID ANTIGEN TESTING

- Rapid tests detect viral antigen (generally nucleoprotein) or enzymatic activity (neuraminidase, or NA) directly on patient specimens using a variety of platforms. Rapid tests are designed to identify influenza A only, influenza A or B without identifying the type, or influenza A or B with type-specific identification.
- Reported sensitivities range from 40% to 80%. Sensitivity is generally greater in children than adults and is greater early in the course of illness.
- The predictive value of rapid assays without confirmation by a reference test is strongly correlated with disease prevalence in the community, as is clinical diagnosis without laboratory testing.
 - When the disease prevalence is low, the tests' positive predictive value decreases; therefore, positive results should be confirmed by culture or real-time PCR (RT-PCR) if a definitive diagnosis is needed.
 - When the disease prevalence is high, the negative predictive value of the tests will be lower and clinicians should consider confirming negative tests with culture or RT-PCR as necessary for clinical confirmation. Similarly,

the diagnostic predictive value increases when the patient's symptoms are strongly suggestive of influenza.

- While the sensitivity and specificity of rapid tests has been evaluated for circulating strains, these measures are largely unknown for detection of emerging strains (including pandemic strains). For example, in a 2005 study by Chotpitayasunondh et al, only 4 (36%) of 11 culture-positive H5N1 influenza A specimens from patients in Thailand were positive by rapid antigen tests.
- The WHO, in its Checklist for Influenza Pandemic Preparedness Planning, recommends against routine use of commercial rapid antigen detection kits and suggests they be used for outbreak investigation only when no other options exist.

IMMUNOFLUORESCENCE

- Immunofluorescence assay (IFA) methods may be used to identify influenza to the species level (influenza A or B) or specific H subtypes (including H5) directly from specimens or cell culture. The US Centers for Disease Control and Prevention (CDC) distributes IFA typing and subtyping reagents to WHO-collaborating laboratories, including many health department laboratories. If highly pathogenic avian influenza (HPAI) strains are suspected, enhanced biosafety level-3 (BSL-3) containment should be used.
- Direct immunofluorescence (DFA) methods are faster and less labor intensive than IFA but are less sensitive and are currently only available for genus-specific detection.

PCR ASSAYS

- PCR assays use conserved targets such as the matrix (M) protein for genus-level identification. HA and NA targets are used for specific identification of avian subtypes. PCR generally is not used for strain-level identification, which is based on serologic markers.
- The sensitivity of PCR assays has been reported to be in the range of 90% to 100% when compared with cell culture; however, several researchers have reported significantly higher numbers of total positive specimens with PCR, possibly reflecting its ability to detect nonviable virions.
- Since 2006, the US Food and Drug Administration (FDA) has approved several influenza A/H5 (Asian Lineage) virus real-time reverse transcription–polymerase chain reaction (RT-PCR) diagnostic tests for use in the United States (in Laboratory Response Network [LRN] laboratories). Samples positive for influenza A/H5 by RT-PCR should be forwarded to the CDC for confirmation.
- The CDC also has developed a real-time RT-PCR diagnostic panel for influenza A/H7 (Eurasian Lineage). In April 2013, the FDA issued an Emergency Use Authorization (EUA) for this assay.
- The WHO accepts positive RT-PCR test results of H5 infection in humans from a number of laboratories around the globe. In addition, a protocol for RT-PCR testing for A/H7 is available on the WHO web site. The WHO recommends that

all unsubtypeable influenza A specimens be immediately sent to one of the six WHO Collaborating Centers for Influenza in the Global Influenza Surveillance and Response System (GISRS) for testing and analysis

VIRUS ISOLATION BY CELL CULTURE

Virus isolation is considered the "gold standard" of influenza testing.

- Specimens for culture optimally should be collected within 3 days of illness onset.
- Turnaround time for the standard method is 2 to 14 days.
- The time to detection in culture, as measured in one study conducted during two influenza seasons, ranged from 5 days (>90% of positive specimens) to 7 days (100% of positive specimens).

Isolates obtained from cell culture are required for strain characterization, which is an integral part of global influenza surveillance and monitoring activities during a pandemic.

SUSCEPTIBILITY TESTING

Testing to determine how susceptible a particular influenza strain is to antiviral drugs generally is conducted at specialized laboratories as part of surveillance or research and is considered an integral component of pandemic influenza response.

Understanding the susceptibility profile of an influenza virus helps to inform treatment recommendations for that particular strain.

The types of assays used for susceptibility testing of influenza viruses include:

- Plaque reduction assay
 - The traditional influenza susceptibility testing method for the M2 ion channel inhibitors (amantadine, rimantadine)
 - Can detect a wide range of resistance phenotypes
 - Limited utility for neuraminidase inhibitors
- Enzyme inhibition assays
 - Useful for assay of neuraminidase inhibitors
- Sequence analysis
 - Used to detect mutations in genes known or suspected to be responsible for resistance

LESSON 4: AVIAN INFLUENZA CASE IDENTIFICATION

In this lesson we will cover:

- H5N1 and H7N9 Case Definitions and Case Evaluations
- Avian Influenza H5 Case Definition
- Specimen Collection from Suspected Novel AI Cases

H5N1 and H7N9 CASE DEFINITIONS

In August 2006, the WHO released case definitions for H5N1 influenza. The following case definitions apply to the current pandemic phase (alert) and may change as new information about the disease or its epidemiology becomes available. The current case definitions are:

- **Person under investigation:** A person whom public health authorities are investigating for possible H5N1 infection.
- **Suspected H5N1 case:** A patient who has unexplained acute lower respiratory illness with a fever higher than 100.4°F (38°C) and cough, shortness of breath, breathing difficulty, and one or more of the following exposures 7 days before symptom onset:
 - Close contact (within 1 meter, e.g., caring for, speaking with, or touching) with a person who is a suspected, probable, or confirmed H5N1 case
 - Exposure to (e.g., handling, slaughtering, defeathering, butchering, or preparing for consumption) poultry or wild birds, their remains, or their feces where H5N1 infections in animals or humans have been suspected or confirmed in the last month
 - Consumption of raw or undercooked poultry where H5N1 infections in animals or humans have been suspected or confirmed in the last month
 - Close contact with a confirmed H5N1-infected animal other than poultry or wild birds (e.g., cat or pig)
 - Handling human or animal samples suspected of containing the H5N1 virus in a laboratory or other setting
- **Probable H5N1 case** (the WHO should be notified):
 - *Definition 1:* A person who meets the criteria for a suspected case and has either (1) evidence of acute pneumonia on a chest radiograph plus respiratory failure (hypoxemia, severe tachypnea) or (2) laboratory confirmation of influenza A but insufficient laboratory evidence for H5N1.

- *Definition 2:* A person dying of an unexplained respiratory illness who is epidemiologically linked by time, place, and exposure to a probable or confirmed H5N1 case.
- **Confirmed H5N1 case** (notify the WHO): A patient who meets the criteria for a suspected or probable case and has had one of the following test results from a national, regional, or international influenza laboratory whose H5N1 test results are accepted by the WHO:
 - Isolation of an H5N1 virus
 - Positive H5 PCR results from tests using two different PCR targets (e.g., primers specific for influenza A and H5)
 - A fourfold or greater rise in neutralization antibody titer for H5N1 based on testing of an acute serum specimen (collected 7 days or less after symptom onset) and a convalescent serum specimen; the convalescent neutralizing antibody titer must be 1:80 or higher
 - A microneutralization antibody titer for H5N1 of 1:80 or greater in a single serum specimen collected at day 14 or later after symptom onset and a positive result using a different serologic assay, such as a horse red blood cell HA inhibition titer of 1:160 or more or an H5-specific Western blot positive result

H5N1 CASE EVALUATION

Recommendations from the CDC for evaluation of suspected H5N1 cases were published in February 2004; these have been revised slightly over time.

According to current CDC recommendations, testing for H5N1 of patients hospitalized in the United States is indicated for patients who have both of the following conditions:

- Radiographically confirmed pneumonia, acute respiratory distress syndrome (ARDS), or other severe respiratory illness for which an alternative diagnosis has not been established
- A history of travel within 10 days of symptom onset to a country with documented recent H5N1 avian influenza infection in poultry or humans or where H5N1 viruses are known to be endemic in poultry (as of January 2017, these include Bangladesh, China, Egypt, India, Indonesia, and Vietnam) OR recent close contact with a suspected or confirmed case of H5N1 influenza Testing for influenza A (H5N1) also should be considered for patients with all of the following:

H7N9 CASE DEFINITIONS

Diagnosis of H7N9 is confirmed using real-time reverse transcriptase polymerase chain reaction (RT-PCR) and viral culture.

The CDC has developed diagnostic material for H7N9 influenza, but patients should not be tested unless they meet one of the case definitions for H7N9 influenza A infection.

CDC Case Definitions:

CASE UNDER INVESTIGATION

Influenza-like illness in a patient who within the past 10 days has been to an area where human cases of H7N9 have been diagnosed or where H7N9 has been circulating in animal populations OR the patient has been in close contact with a person with a confirmed H7N9 infection in the past 10 days AND for whom laboratory results are not known or are pending.

PROBABLE CASE

A case in a patient that meets the exposure criteria for a case under investigation and is positive for influenza A, but for whom the influenza subtype is not able to be determined.

CONFIRMED CASE

An H7N9 case that has been confirmed by a CDC-approved laboratory test done in a CDC-approved laboratory.

H7N9 CASE EVALUATION

The CDC recommends testing for H7N9 for persons who have an illness compatible with influenza and who meet the appropriate exposure criteria:

- Patients with recent travel (within <10 days of illness onset) to areas where human cases of avian influenza A (H7N9) virus infection have occurred or to areas where avian influenza A (H7N9) viruses are known to be circulating in animals (poultry).

OR

- Patients who have had recent close contact (within <10 days of illness onset) with confirmed or suspected cases of human infection with avian influenza A (H7N9) virus. Close contact may be regarded as coming within about 6 feet (2 meters) of a confirmed or suspected case while the case was ill (beginning 1 day prior to illness onset and continuing until resolution of illness). This includes healthcare personnel providing care for a confirmed case, family members of a confirmed case, persons who lived with or stayed overnight with a confirmed or suspected case, and others who have had similar close physical contact.

CASE DEFINITION FOR HUMAN INFECTIONS WITH HPAI H5

Case Under Investigation: Illness compatible with influenza in a patient meeting any of the exposure criteria below and for whom laboratory test results are not known or are pending.

Exposure Criteria

- Patients who have had recent contact (within <10 days of illness onset) with birds potentially infected with HPAI H5 virus (i.e., sick or dead birds, or flocks where HPAI H5 virus infection has been confirmed).

OR

- Patients who have had recent close contact (within <10 days of illness onset) with confirmed or suspected cases of human infection with HPAI H5 virus. Close contact may be regarded as coming within about 6 feet (2 meters) of a confirmed or suspected case while the case was ill (beginning 1 day prior to symptom onset and continuing until resolution of illness). This includes healthcare personnel providing care for a confirmed or suspected case, family members of a confirmed or suspected case, persons who lived with or stayed overnight with a confirmed or suspected case, and others who have had similar close physical contact in a community or workplace environment.

OR

- Unprotected exposure to live HPAI A H5 virus in a laboratory.

Probable Case: Illness compatible with influenza in a patient meeting any of the exposure criteria below and for whom laboratory test results indicate influenza but do not provide a sufficient level of detail to confirm HPAI A H5 virus infection. Examples of such test results include: results that are presumptive positive for HPAI H5 virus (see Confirmed Case definition tab), an influenza RT-PCR test that is positive for influenza A but cannot be subtyped (i.e., an influenza RT-PCR test that is positive for influenza A, negative for H1, negative for H1pdm09, and negative for H3); and a rapid influenza diagnostic test that is positive for influenza A. Specimens from probable cases should be sent to the CDC for confirmatory testing.

Confirmed Case: HPAI A H5 virus infection in a person that is confirmed by CDC's Influenza Division Laboratory. Presumptive positive identification of infection with HPAI A H5 viruses may be made by public health laboratories using the CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel for detection of Asian-origin HPAI A/H5 viruses; however, specimens from presumptive positive cases should be sent to the CDC for confirmatory testing.

SPECIMEN COLLECTION FROM SUSPECTED NOVEL AI CASES

The CDC recommends the following for laboratory testing of clinical specimens from patients with suspected novel influenza A virus infection (including H5N1 and H7N9):

- Specimens should be obtained as soon as possible after illness onset, ideally within 7 days.
- Standard, contact, and airborne precautions are recommended for patient management.
- The following should be collected as soon as possible after illness onset: (1) a nasopharyngeal swab, or (2) a nasal aspirate or wash, or (3) two swabs combined into one viral transport media vial (eg, nasal or nasopharyngeal swab combined with an oropharyngeal swab). If these specimens cannot be collected, a single nasal, or oropharyngeal swab is acceptable. For patients with lower respiratory tract illness, a lower respiratory tract specimen (eg, an endotracheal aspirate or bronchoalveolar lavage fluid) is preferred because of higher yield.
- Testing should be performed at state public health laboratories and sent to the CDC for confirmatory testing.

LESSON 5: H5N1 and H7N9 AVIAN INFLUENZA CASE INVESTIGATION AND CONTACT MANAGEMENT

In this lesson we will cover:

- Types of Contacts
- Follow-Up Period
- Treatment of Close Contacts

Rapid case identification and contact tracing and management can reduce the number and severity of secondary cases. Public health workers play a critical role in helping identify and offer treatment to contacts of persons with suspected, probable, or confirmed H5N1 or H7N9 infection. The information in this lesson is taken from CDC guidance for use of antiviral chemoprophylaxis of close contacts of persons with novel influenza A viruses associated with human disease (<http://www.cdc.gov/flu/avianflu/novel-av-chemoprophylaxis-guidance.htm>).

TYPES OF CONTACTS

Close contacts are defined as persons within approximately 6 feet (2 meters) or within the room or care area of a confirmed or probable novel influenza A case patient for a prolonged period of time, or with direct contact with infectious secretions while the case patient was likely to be infectious (beginning 1 day prior to illness onset and continuing until resolution of illness).

Decisions to initiate antiviral chemoprophylaxis should be guided by the following risk stratification:

- Highest-risk exposure groups (recognized risk of transmission): Household or close family member contacts of a confirmed or probable case
- Moderate-risk exposure groups (unknown risk of transmission): Healthcare personnel with unprotected close contact with a confirmed or probable case
- Low-risk exposure groups (transmission unlikely): Others who have had social contact of a short duration with a confirmed or probable case in a non-hospital setting (e.g., in a community or workplace environment)

Persons with an unprotected exposure to novel influenza A virus associated with severe human disease in a laboratory setting may have a high-risk or moderate-risk exposure, and need to be evaluated case by case.

FOLLOW-UP PERIOD

According to the CDC, all identified close contacts should be monitored daily for 10 days after the last known exposure to a confirmed or probable case. The following should be assessed each day during this period:

- Measured temperature
- Presence of any respiratory symptoms

Any close contacts who have a temperature higher than 100.4 (38°C) or any respiratory symptoms should be referred for prompt medical evaluation and possible testing for novel influenza viral infection.

H5N1 can be ruled out when laboratory testing by RT-PCR of appropriately collected respiratory specimens at a state health department laboratory or at the CDC has excluded infection with H5N1 virus or upon absence of any illness symptoms among contacts during the 7-day follow-up.

CHEMOPROPHYLAXIS FOR ASYMPTOMATIC CLOSE CONTACTS

A daily antiviral drug regimen with a neuraminidase inhibitor (oseltamivir or zanamivir) should be provided to close contacts for 5 to 10 days after the last known exposure. If the exposure was time limited and not ongoing, 5 days is recommended. If exposure is likely to be ongoing, 10 days is recommended. Administration of chemoprophylaxis should begin as soon as possible (within 48 hours) after first exposure to the confirmed or probable case.

Chemoprophylaxis should be provided to close contacts according to the risk of exposure:

- Highest-risk exposure groups: Administer chemoprophylaxis
- Moderate-risk exposure groups: Consider chemoprophylaxis, based on clinical judgment
- Low-risk exposure groups: Chemoprophylaxis is not routinely recommended, but decisions should be based on clinical judgment.

The CDC recommends one dose twice daily treatment frequency dosing for oral oseltamivir or inhaled zanamivir, instead of the typical antiviral chemoprophylaxis regimen (once daily).

LESSON 6: PREVENTING DISEASE IN THE COMMUNITY

In this lesson we will cover:

- Public Health Practices
- Role of Influenza Vaccines in Disease Prevention
- Food Safety Issues

PUBLIC HEALTH PRACTICES

HIGH-RISK GROUPS

Some groups of people are at greater risk for exposure to avian influenza viruses. Particularly in geographic areas where H5N1, H5N6, H7N9 (or another avian influenza virus) is known or suspected to be circulating among domestic birds, the following groups should be targeted with information about how to protect themselves and their families:

- Poultry farm workers, including those involved with culling birds during depopulation efforts
- Backyard/smallholder poultry owners
- Live-bird wet market workers
- Medical and laboratory workers
- Public health teams
- First responders

This remainder of this lesson addresses general disease prevention measures aimed at the community level. Lessons 7 and 8 provide more detail about preventing exposure to avian influenza in medical and other high-risk occupational settings.

GENERAL PUBLIC

Education for the general public in areas where H5N1, H5N6, H7N9, or other avian influenza strain is circulating among birds emphasizes that people should avoid:

- Slaughtering, butchering, defeathering, and preparing sick birds
- Playing with or holding sick or dead birds
- Touching or accidentally ingesting droppings from sick birds
- Eating raw or undercooked meat from sick birds

Sometimes cultural values and practices make delivering these messages difficult. For example, in some cultures, a bird is eaten once it becomes sick.

ROLE OF INFLUENZA VACCINES IN DISEASE PREVENTION

SEASONAL INFLUENZA VACCINE

Seasonal influenza vaccines help protect individuals, families, and communities from seasonal influenza. By decreasing the occurrence of seasonal influenza, the vaccine is also diminishing the potential for a new pandemic strain to develop. Reducing the number of people with seasonal influenza also means fewer opportunities for an avian influenza virus to reassort with a circulating human strain.

PREPANDEMIC H5N1 AND H7N9 VACCINES

H5N1 viruses have diversified genetically and antigenically, which necessitates the need for multiple candidate vaccine viruses. In April 2004, the WHO made the prototype seed strain for an H5N1 vaccine available to manufacturers. Over time, the WHO has added additional strains as candidate vaccine viruses.

To date, several H5N1 vaccines have been developed for use during an influenza pandemic and a certain quantity of H5N1 vaccines have been added to the US Strategic National Stockpile.

Prepandemic H5N1 influenza vaccines intended for use prior at the onset of a pandemic are an important milestone in efforts to address this threat globally.

Vaccines against H7N9 also are under development and have entered clinical trials. Results of one H7N9 vaccine trial from an American vaccine manufacturer suggest that an adjuvant may be required for an effective immune response to the vaccine.

VACCINE DEVELOPMENT ISSUES

Even though progress is being made, a number of barriers exist to actually having effective vaccines against H5N1 influenza available for practical use. These barriers also apply to the development of vaccines against other avian influenza viruses such as H7N9.

Study of candidate vaccines is hampered by a lack of established correlates of immunity in animals and humans. Developing consistent immunologic end points for clinical trials remains an important challenge.

The global annual production capacity for pandemic influenza vaccines in 2015 was estimated at 6.4 billion (for a monovalent vaccine). Much of the production capacity resides in high-income countries. This predicted capacity represents enough vaccine to immunize roughly 43% of the global population with two doses of vaccine or 86% of the population with a single dose (2015 population estimates).

Challenges remain in maintaining and expanding manufacturing capacity for influenza vaccines, and ensuring equitable access to vaccines in under-resourced regions of the world in the event of a global pandemic. Developing an effective vaccine may require having the pandemic strain in hand, which will mean that a vaccine cannot be produced until the onset of the pandemic. Once a pandemic virus is identified, it will take 5 to 6 months to prepare and verify the vaccine strain, develop reagents to test the vaccine, manufacture bulk vaccine, complete the finish and fill process, conduct clinical trials, and obtain regulatory approval.

One strategy for dealing with the current limitations in influenza vaccine production involves developing vaccines that focus on conserved regions of the viral genome (i.e., regions of the genome that do not change over time and are consistent across various virus strains). Such vaccines could offer cross-protection to multiple virus subtypes, including novel strains. Research in this area is ongoing.

FOOD SAFETY ISSUES

CONCERNS

- Several human cases of H5N1 apparently have resulted from consumption of improperly cooked or raw poultry products. In September 2007, German officials reported that they had found H5N1 virus in 18 frozen ducks from a batch sample at a poultry company slaughterhouse, but no cases were traced to consumption of the contaminated ducks.
- Concerns also have been raised about the potential for contamination of water sources with H5N1 virus. A 2007 study, however, found that free chlorine concentrations typically used in drinking water treatment are sufficient to inactivate the virus by >3 orders of magnitude.

INFORMATION AND RECOMMENDATIONS

In November 2005, the WHO issued published a statement on food safety issues related to H5N1. These same principles related to food safety also apply to poultry potentially infected with other avian influenza viruses (such as H7N9). The 2005 statement on H5N1 includes the following information:

- The H5N1 avian influenza virus is not transmitted to humans through properly cooked food. The virus is sensitive to heat, and normal temperatures used for cooking (so that food reaches 70°C in all parts) will kill the virus.
- To date, no evidence indicates that any person has become infected with the H5N1 virus following the consumption of properly cooked poultry or poultry products, even when the food item contained the virus prior to cooking. However,

several cases have involved consumption of raw poultry ingredients, such as uncooked duck blood.

- Poultry and poultry products from areas free of the disease can be prepared and consumed as usual, with no fear of acquiring avian influenza infection.
- Most strains of avian influenza virus are found only in the respiratory and gastrointestinal tracts of infected birds, not in meat. However, available studies indicate that highly pathogenic viruses, including the H5N1 virus, spread to virtually all parts of an infected bird, including meat. For this reason, proper handling of poultry and poultry products during food preparation and proper cooking are extremely important in areas experiencing outbreaks of highly pathogenic avian influenza (including H5N1) in poultry.
- Consumers in areas with outbreaks need to be aware of the risks of cross-contamination between raw poultry and other foods that will not be cooked prior to their consumption. Juices from raw poultry or poultry products should never be allowed during food preparation to touch or mix with items eaten raw. When handling raw poultry or raw poultry products, persons involved in food preparation should wash their hands thoroughly and clean and disinfect surfaces in contact with the poultry products. Soap and hot water are sufficient for this purpose.
- In countries with outbreaks, thorough cooking is imperative. Consumers need to be sure that all parts of the poultry are fully cooked (no "pink" parts) and that eggs, too, are properly cooked (no "runny" yolks).
- The H5N1 virus can survive for at least 1 month at low temperatures. For this reason, common food preservation measures, such as freezing and refrigeration, will not substantially reduce the concentration of virus in contaminated meat or kill the virus. In countries with outbreaks, poultry stored under refrigeration or frozen should be handled and prepared with the same precautions as fresh products.
- In countries with outbreaks, eggs may contain virus both on the outside (shell) and inside (white and yolk). Eggs from areas with outbreaks should not be consumed raw or partially cooked. Raw eggs should not be used in foods that will not be treated by heat high enough to kill the virus (70°C or higher).
- To date, a large number of human infections with the H5N1 virus have been linked to the home slaughter and subsequent handling of diseased or dead birds prior to cooking. These practices represent the highest risk of human infection and are the most important to avoid. Proper handling and cooking of poultry and poultry products can further lower the risk of human infections.

In May 2010, the US Department of Agriculture released a risk assessment tool for contracting HPAI from eating poultry products, shell eggs, and egg products. The tool is intended to be used by risk managers for decision-making when determining possible interventions following detection of HPAI in a poultry flock in the United States. The risk assessment also can be used to target risk communication messages, identify and prioritize research needs, and provide a framework for coordinating prevention and control efforts with stakeholders.

LESSON 7: PREVENTING AVIAN INFLUENZA IN MEDICAL SETTINGS

In this lesson we will cover:

- Infection Control Recommendations for Healthcare Settings
- Worker Safety Recommendations for Diagnostic Laboratories

INFECTION CONTROL RECOMMENDATIONS FOR HEALTHCARE SETTINGS

In 2014, the CDC released interim guidance for “Infection Control Within Healthcare Settings When Caring for Confirmed Cases, Probable Cases, and Cases Under Investigation for Infection with Novel Influenza A Viruses Associated with Severe Disease” including H5N1 and H7N9. This document describes the fundamental elements to prevent transmission of these viruses. The CDC recommends a higher level of protection when working with patients infected with the H5N1 or H7N9 AI viruses than those patients infected with seasonal influenza viruses, including the use of eye protection and respiratory protection.

Isolation Precautions for Patients With H5N1 Avian Influenza	
CDC Recommendations	
Standard Precautions Pay careful attention to hand hygiene before and after all patient contact or contact with items potentially contaminated with respiratory secretions.	
Contact Precautions — Use gloves and gown during all patient contact. — Use dedicated equipment such as stethoscopes, disposable blood pressure cuffs, and disposable thermometers.	
Eye protection (i.e., goggles or face shields) Wear when entering patient care room or area	
Airborne Precautions — Place patient in an AIIR. Such rooms should have monitored negative air pressure in relation to corridor, with 6 to 12 ACH, and should exhaust air directly outside or have recirculated air filtered by a HEPA filter. If an AIR is unavailable, contact the healthcare facility engineer to assist or use portable HEPA filters to augment ACH. — Use a fit-tested respirator, at least as protective as a NIOSH-approved N95 filtering facepiece (i.e., disposable) respirator, when entering room.	
WHO Recommendations	
Standard Precautions Droplet Precautions Contact Precautions Airborne Precautions (including use of high-efficiency masks and negative-pressure rooms when available)	
<i>Abbreviations:</i> ACH, air changes per hour; AIIR, airborne infection isolation room; HEPA, high-efficiency particulate air; NIOSH, National Institute of Occupational Safety and Health.	

A recent study demonstrated that hand hygiene using soap and water or an alcohol-based hand rub is highly effective in reducing influenza A virus on human hands; therefore, good hand hygiene is an important component of influenza A infection control.

In June 2006, researchers in Thailand reported isolating H5N1 virus from the blood of a 5-year-old patient with avian influenza. This finding supports the importance of using Standard Precautions (which include wearing gloves when handling blood or body fluids from any patient).

A recent study analyzed the effectiveness of respirators and safety glasses and the prophylactic use of oseltamivir during the 2003 avian influenza A (H7N7) epidemic in the Netherlands. Prophylactic use of oseltamivir greatly reduced the risk of infection with avian influenza A (H7N7); however, even with oseltamivir use, the risk for infection was considerable. The effectiveness of PPE on the risk of infection was inconclusive.

WORKER SAFETY RECOMMENDATIONS FOR DIAGNOSTIC LABORATORIES

BIOSAFETY RECOMMENDATIONS FOR TESTING CLINICAL SPECIMENS

Recommendations for testing of clinical specimens from patients suspected to have H5N1 influenza (or another HPAI virus) include:

- Culture from patients suspected of having avian influenza, other novel influenza strains, or severe acute respiratory syndrome (SARS) coronavirus should be conducted only under enhanced BSL-3 containment. This includes controlled access, double-door entry with changing room and shower, use of respirators, decontamination of all waste, and showering out of all personnel. These diagnostic activities must be kept separate from routine influenza diagnostic activities (e.g., probable H1 or H3 isolates) to prevent recombination.
- IFA testing of specimens requires BSL-2 containment and practices. Culture biocontainment recommendations should be implemented when IFA is used for culture identification.
- Direct detection methods, including commercial antigen detection assays and RT-PCR, should be conducted under BSL-2 conditions with a class II biological safety cabinet. Serologic methods require BSL-2 containment.
- If H5N1 avian influenza virus is presumptively identified by one of the above direct methods, further work should be conducted using the enhanced BSL-3 procedures described above for culture.
- Any new or re-emergent human influenza strain with suspected pandemic potential should be treated as described for H5N1 avian influenza.
- Additional requirements and recommendations apply for laboratory work involving live animals.

LESSON 8: PREVENTING AVIAN INFLUENZA AMONG POULTRY WORKERS

In this lesson we will cover:

- Guidance to Protect Workers from Avian Influenza Viruses

GUIDANCE TO PROTECT WORKERS FROM AVIAN INFLUENZA VIRUSES

In February 2008, the WHO updated and consolidated available guidance on protection of workers and other individuals at risk of exposure to H5N1 avian influenza. High-contact activities include handling, collecting, transporting, culling, and disposal of birds, and cleaning/disinfection of contaminated areas. According to the WHO, all individuals involved in high-risk activities should perform the following:

- Be registered with the local animal health authority (or by the public health authority in collaboration with the animal health authority).
- Wear appropriate PPE, including protective clothing, heavy gloves and boots, goggles, and masks, and receive adequate training on putting on, taking off, and hygienic disposal/disinfection of PPE.
- Maintain diligence in personal hygiene, including frequent hand washing.
- Receive adequate instruction on disinfection/disposal of potentially contaminated personal clothing and other personal articles.
- Be monitored twice daily for fever ($>38^{\circ}\text{C}$) and influenza-like illness for 7 days after the last day of contact with poultry or contaminated environments. Any person experiencing fever or influenza-like illness should immediately report to health authorities for diagnostic testing and appropriate treatment.

In 2015, the CDC developed “Recommendations for Worker Protection and Use of Personal Protective Equipment to Reduce Exposure to Highly Pathogenic Avian Influenza A H5 Viruses due to the incursion of Eurasian H5 viruses into North America.” Key recommendations are:

- Avoid unprotected direct physical contact with sick birds, poultry carcasses, and poultry feces or litter.
- Wear recommended PPE (properly-fitted safety goggles, disposable gloves, boots, a NIOSH-certified respirator [e.g., N95], and disposable fluid-resistant [\[1\]](#) coveralls) when in direct contact with birds, poultry carcasses, and poultry feces or litter, and when going into any buildings with sick or dead poultry, or carcasses, feces, or litter from potentially-infected poultry.
- Put on and take off PPE in separate clean areas.
- Reusable PPE (e.g. rubber boots, rubber apron) should be:

- Cleaned until visible dirt is removed, and then
 - Disinfected with an EPA approved disinfectant that has label claims against influenza A viruses (<http://www.epa.gov/oppad001/influenza-disinfectants.html>) according to the manufacturer's instructions.
- Avoid touching the eyes, mouth, and nose after touching any contaminated material while wearing PPE.
- Do not eat, drink, smoke, or use the bathroom while wearing PPE.
- Safely remove PPE in sequence:
 1. Remove and dispose of the apron, if worn;
 2. Clean and disinfect boots;
 3. Remove boots;
 4. Remove and dispose of the coverall;
 5. Remove and dispose of gloves;
 6. Wash hands with soap and water;
 7. Remove goggles and respirator;
 8. Clean and disinfect reusable goggles and respirator;
 9. Wash hands with soap and water again.
- Perform good hand hygiene such as hand-washing with soap and water or using an alcohol-based hand rub after removing PPE if soap and water are not immediately available.
- Shower at the end of the work shift and leave all contaminated clothing and equipment at work. Never wear contaminated clothing or equipment outside the work area.

GLOSSARY

Acute Respiratory Distress Syndrome – See ARDS.

Adamantanes – A class of antiviral drugs used to treat influenza. Most H5N1 viruses appear to be resistant to all drugs in this class. This class includes amantadine and rimantadine.

Adaptive Immunity – Specific immunity; The form of immunity that produces protection against infection that is highly specific and long lasting. The adaptive immune system takes time to mobilize following the first exposure to a specific antigen, but subsequent exposures produce a rapid adaptive immune response. Adaptive immunity includes humoral and cell-mediated immunity.

Amantadine – An antiviral drug used to treat or prevent influenza and belongs to the drug class called “adamantanes.”

Antibody – A type of glycoprotein molecule produced during a humoral (adaptive) immune response that binds antigens, often with a high degree of specificity and strength.

Antigen – A molecular substance foreign to the body that binds with antibodies or T-cell receptors. Antigens that produce a specific immune response can also be called “immunogens.” The adaptive immune system may recognize multiple antigens in a single virus.

Antiviral – Drug that is used to prevent or cure a disease caused by a virus, by interfering with the ability of the virus to

multiply in number or spread from cell to cell.

ARDS – Acute Respiratory Distress Syndrome; an emergency caused by failure of the lungs to work.

Atelectasis – An abnormal condition characterized by the collapse of alveoli, preventing the respiratory exchange of carbon dioxide and oxygen in a part of the lungs.

Case-Fatality Rate – The number of registered deaths caused by any specific disease, expressed as a percentage of the total number of reported cases of a specified disease.

Cell-Mediated Immunity – A type of adaptive immune response mediated by T cells of the immune system.

Chemoprophylaxis – The use of chemicals (drugs) to prevent infection or disease.

Clade – A grouping of genetic variants within a single species.

Communicable – See Contagious.

Contagious – communicable; A contagious or communicable disease is one that is spread from one person or animal to another by direct or indirect contact. Direct contact includes touching any discharge from the body that contains the infectious agent. Indirect contact might include contact through something else, such as toys or eating utensils.

Crepitation – An abnormal breathing sound produced at the end of inspiration and caused by air entering collapsed alveoli or just collapsed alveoli and atelectasis that contain fibrous exudate. It occurs in pneumonia, tuberculosis, and pulmonary edema.

Dyspnea – A distressful subjective sensation of uncomfortable breathing that may be caused by many disorders, including certain heart and respiratory conditions, strenuous exercise, or anxiety.

Epidemic – A disease occurring suddenly in humans in a community, region or country in numbers clearly in excess of normal.

Fomite – Any inanimate object or substance capable of carrying infectious organisms (such as bacteria or viruses) and hence transferring them from one individual to another.

Hemagglutinin (HA) – An important surface structure protein of the influenza virus that is an essential gene for the spread of the virus throughout the respiratory tract. This protein enables the virus to attach itself to a cell in the respiratory system and penetrate it. It is used to name influenza A subtypes and is referred to as the "H" in the influenza virus subtype (e.g., H5N1).

Host – An organism on or in which a parasitic organism (e.g., virus, bacteria) lives.

HPAI (Highly Pathogenic form of Avian Influenza) - Often fatal in chickens and turkeys. HPAI spreads more rapidly than LPAI and has a high mortality rate in domestic birds.

ILI – Influenza-like illness.

Humoral Immunity – A type of adaptive immune response mediated by the production of antibodies.

Incubation Period – The time between exposure to a disease-causing organism and the onset of symptoms.

Infection – The invasion of the body by microorganisms that reproduce and multiply.

Infectious – Capable of causing infection.

Infectivity – A pathogen's ability to spread rapidly from one person or animal to another.

LPAI (Low-Pathogenic form of Avian Influenza) – Naturally occurs in wild birds and can spread to domestic birds. In wild birds, LPAI strains generally do not cause signs of infection. In domestic birds, the illness is not severe and mortality rates are low. LPAI H5 and H7 strains have the potential to mutate into HPAI and are therefore closely monitored.

Morbidity – Disease; morbidity rate is the incidence or prevalence of disease in a specific population during a specified interval of time or a specific point in time.

Mortality – Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Myalgia – Diffuse muscle pain, usually accompanied by malaise.

Neuraminidase (NA) – An important surface structure protein of the influenza virus that is an essential enzyme for the spread of the virus throughout the respiratory tract. This protein enables the virus to escape the host cell and infect new cells. It is used to name influenza A subtypes and is referred to as the "N" in the influenza virus subtype (e.g., H5N1).

Neuraminidase Inhibitors – A class of antiviral drugs commonly used to treat or prevent influenza. This class includes oseltamivir and zanamivir.

Oseltamivir – An antiviral drug commonly used to treat or prevent influenza and belongs to the drug class called "neuraminidase inhibitors."

Outbreak – Presence of disease in numbers in excess of normal in a specific geographic area or population.

Pandemic – A worldwide outbreak of a disease in humans in numbers clearly in excess of normal. A global influenza pandemic may occur if two conditions are met:

- A new subtype of influenza A virus emerges for which there is little or no immunity in the human population.
- The virus can spread easily from person to person in a sustained manner.

Panzootic – A worldwide outbreak of a disease in animals in numbers clearly in excess of normal.

Pathogen – A disease-causing agent (e.g., virus, bacteria, fungus).

Pathogenesis – The mechanisms by which an agent causes disease.

Pathogenic – Causing disease or capable of doing so.

Reservoir – A person or animal that serves as a host to a pathogenic agent, generally without visible symptoms of the disease or injury.

Rimantadine – An antiviral drug used to treat or prevent influenza and belongs to the drug class called "adamantanes."

Seasonal Flu ("Common Flu", "Winter Flu") – Influenza caused by one of the common influenza subtypes known to be circulating in the human population; seasonal influenza peaks in the winter months in the Northern and Southern Hemispheres and tends to be year-round in tropical regions.

Specific Immunity – See Adaptive Immunity.

Strain – Influenza virus subtypes are further characterized into strains. New strains of influenza viruses replace older strains through the process of antigenic drift (i.e., small mutations in the genetic material of the virus).

Tachycardia – Rapid heart rate.

Tachypnea – Increased rate of respiration.

Virulence – A pathogen's ability to invade host tissues and cause severe disease.

Virulent – Highly lethal; causing severe illness or death.

Virus – Any of various simple submicroscopic parasites of plants, animals, and bacteria that often cause disease and that consist essentially of a core of RNA or DNA surrounded by a protein coat. Unable to replicate without

a host cell, viruses are typically not considered living organisms.

Zanamivir – An antiviral drug used to treat or prevent influenza and belongs to the drug class called “neuraminidase inhibitors.”

Zoonoses – Diseases that transfer from animals to humans.

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