MCEIRS AVIAN INFLUENZA TRAINING

Individual Study Guide
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Avian Influenza in Humans: Epidemiology, Clinical Features, and Treatment

Minnesota Center of Excellence for Influenza Research and Surveillance
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Avian Influenza in Humans: Epidemiology, Clinical Features, and Treatment

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INTRODUCTION

AVIAN INFLUENZA IN HUMANS: EPIDEMIOLOGY, CLINICAL FEATURES AND TREATMENT

This course will describe how avian influenza (AI) is affecting humans and will enhance your understanding of how AI clinically presents in people and how it is treated. AI terminology, H5N1 occurrence in humans, routes of transmission, and treatment issues are among the topics addressed in this module. The epidemiology, clinical features, and treatment of the H7N9 virus also are discussed.
LESSON 1: AVIAN INFLUENZA BACKGROUND

In this lesson we will cover

- Viral Nomenclature
- Avian Influenza in Birds
- Environmental Survival of Avian Influenza Viruses

VIRAL NOMENCLATURE

Influenza viruses belong to the Orthomyxoviridae family of segmented negative-sense RNA viruses.

The genus influenza A consists of a single species: influenza A virus, which is the cause of type A influenza.

All AI is caused by influenza A virus. Influenza A virus also causes illness in a variety of mammals and is the most common cause of influenza in humans. Influenza B is also an important cause of influenza in humans, whereas influenza C is a relatively uncommon cause of human disease. Influenza D has recently been found in swine and cattle, but is not known at this time to cause disease in humans.

Influenza A virus subtypes are defined by two of the surface proteins that are part of the structure of the virus as shown in Figure 1:

H: Hemagglutinin
N: Neuraminidase

Note: The Matrix 2 protein is not visible from the surface.
There are 18 different HA antigens (H1 to H18) and 11 different NA antigens (N1 to N11) for influenza A. These antigens give rise to the subtype designation. Subtypes H1 to H16 and N1 to N9 are found in birds (mostly wild birds) and some of these subtypes have been found in mammals. H17N10 and H18N11 were discovered in bats in Guatemala in 2009 and in Peru in 2013, respectively. The NA genes in these influenza subtypes are highly divergent from other known influenza NAs and researchers propose that the attachment and activation of these viruses occur by a different mechanism than other influenza viruses. As of January 2017, these two subtypes appear to be unique to the bat population but have been shown to infect and replicate in other mammalian cells (such as canine cell lines).

There is only one H and one N in each viral subtype as shown in Figure 2.

- H1N1 subtype has an H1 antigen and an N1 antigen.
- H5N1 subtype has an H5 antigen and an N1 antigen.
- H3N2 subtype has an H3 antigen and an N2 antigen.

Combinations of the 16 HAs and 9 NAs found in birds can result in up to 144 different unique subtypes.

The vast majority of these subtypes occur only in wild birds.

Human illness historically has been caused by H1, H2, and H3 subtypes.

Several other avian subtypes, including H5 (e.g., H5N1, H5N6), H7 (e.g., H7N7, H7N9), and H9 (e.g., H9N2) have also caused sporadic illness in humans. Other avian subtypes such as H6 (H6N1) and H10 (H10N7, H10N8) avian subtypes also caused infections in humans.

Each influenza virus is named on the basis of the following features:
- Type of influenza strain
- Host of origin (if other than human)
- Geographic origin
- Laboratory number
- Year of isolation

Figure 2: Viral Structures
AVIAN INFLUENZA IN HUMANS: INDIVIDUAL STUDY GUIDE

EPIDEMIOLOGY, CLINICAL FEATURES AND TREATMENT

- HA and NA subtypes

Examples include the following:

HUMAN STRAIN

**A/Brisbane/59/2007/H1N1**

This strain was originally isolated from a human in Brisbane, Australia, in 2007 and was used as a source for the 2009-10 seasonal influenza vaccine.

**A/Vietnam/1203/2004/H5N1**

This strain was isolated in 2004 from a patient in Vietnam with H5N1 influenza.

AVIAN STRAIN

**A/bar-headed goose/Qinghai/1A/2005/H5N1**

This strain was isolated in 2005 in Qinghai province, China, from a bar-headed goose. A mass die-off of wild migratory birds occurred at Qinghai Lake during that year.

AVIAN STRAIN

**A/chicken/Chile/4977/2002/H7N3**

This strain caused an outbreak of highly pathogenic avian influenza (HPAI) in Chile in 2002.

SWINE STRAIN

**A/Swine/Minnesota/00395/2004/H3N1**

This strain was isolated in Minnesota in 2004 and is an example of a triple-reassortant swine influenza virus (i.e., a strain that contains genes from viruses of human, avian, and swine origin).
AVIAN INFLUENZA IN BIRDS

The term "avian influenza" is used to describe influenza A subtypes that primarily affect chickens, turkeys, guinea fowls, migratory waterfowl, and other avian species. Rarely, humans can be infected with avian influenza viruses. "Avian influenza" is an ecological classification that does not correspond exactly to other classification.

AVIAN INFLUENZA CLASSIFICATION

Outbreaks of AI have been recognized in domestic poultry (chickens, turkeys, and ducks) for many years.

AI strains in domestic chickens and turkeys are classified according to disease severity, with two recognized forms: highly pathogenic avian influenza (HPAI), also known as fowl plague, and low-pathogenic avian influenza (LPAI).

HPAI

AI viruses that cause HPAI are highly virulent, and mortality rates in infected flocks often approach 100%. All HPAI strains identified to date have involved H5 and H7 subtypes.

LPAI

LPAI occurs more frequently than HPAI. LPAI viruses are of much lower virulence, but these viruses can serve as progenitors to HPAI viruses. Evidence that HPAI strains arise from LPAI strains has led the World Organization for Animal Health (OIE) to classify all H5 or H7 strains as notifiable.

H5 Subtypes

- H5 subtypes can be found in birds throughout the world and include both LPAI and HPAI strains.
- H5N1 is responsible for the current panzootic among domestic poultry and other birds in Asia, the Middle East, Europe, and Africa.
- Other HPAI H5 subtypes such as H5N8, H5N9 and H5N6 recently have emerged in Asia and Europe and an H5N2 subtype has cased disease outbreaks in poultry in North America.

H7 and H9 Subtypes

- H7 includes HPAI and LPAI strains.
- H9 is known to include only LPAI strains. H9N2 viruses have been isolated in multiple avian species throughout Asia, the Middle East, Europe, and Africa.
ENVIRONMENTAL SURVIVAL OF AVIAN INFLUENZA VIRUSES

The viruses appear to be able to survive in water or moist environments for extended periods at cool temperatures and for much shorter periods on dry surfaces.

- **Nonporous environmental surfaces**: Viruses can remain infectious for 24 to 48 hours. (Example: a truck tire.)
- **Porous surfaces**: Viruses remain infectious less than 12 hours. (Example: clothing.)
- **Water**: Influenza A viruses can persist for extended periods in water.
  - One study of subtype H3N6 found that virus resuspended in Mississippi River water was detected for up to 32 days at 4°C and was undetectable after 4 days at 22°C.
  - Another study found that several avian influenza viruses persisted in distilled water for 207 days at 17°C and 102 days at 28°C.
  - Data from studies of H5N1 in domestic ducks have shown that H5N1 can survive in the environment for 6 days at 37°C.

Inactivation of the virus occurs under the following conditions:

- Temperatures of 56°C for 3 hours or 60°C or more for 30 minutes
- Acidic conditions
- Presence of oxidizing agents such as sodium dodecyl sulfate, lipid solvents, and B-propiolactone
- Exposure to disinfectants: formalin, iodine compounds
In this lesson we will cover:

- History of the H5N1 Outbreak
- HPAI in Birds 2014-2015

HISTORY OF H5N1 OUTBREAK

Highly pathogenic H5N1 virus was first detected in an isolate from a farmed goose in Guangdong Province, China, in 1996. In 1997, outbreaks of highly pathogenic H5N1 were reported in poultry at farms and live animal markets in Hong Kong. The first human infections with avian influenza H5N1 were also reported in Hong Kong that year.

Then in the fall of 2003, an outbreak of HPAI caused by an H5N1 strain started in Asia and spread in domestic poultry farms at an historically unprecedented rate. The outbreak tapered off in spring 2004 but in summer re-emerged in several countries in Asia (including Cambodia, China, Lao PDR, Thailand, and Vietnam).

In the summer of 2005, H5N1 began expanding its geographic range beyond Asia, creating a panzootic, and the virus has continued to spread to date. The wider geographic spread of the H5N1 viruses increases the opportunities for the virus to infect humans as well as reassort with other influenza viruses.

Since 2003, 54 countries or territories have experienced outbreaks of H5N1 HPAI in poultry.

- Although the number of countries reporting outbreaks has gradually decreased since its peak in 2006, the number of affected countries between January and August of 2010 surpassed that of 2009. 451 H5N1 HPAI outbreaks were reported in this time frame, compared with 297 in all of 2009.
- According to FAO, (the Food and Agriculture Organization of the United Nations), between 2008 and 2011, the overall number of outbreaks had continued to show an increasing trend, particularly in Asia and Egypt (even though the overall number countries experiencing outbreaks has decreased since its peak in 2006). This trend has decreased somewhat since then.

HPAI IN BIRDS 2014-16

From January 2014 through early February January 2017, OIE received multiple reports of multiple subtypes of HPAI in both wild birds and poultry:
H5N8
Austria
Canada
China
Chinese Taipei
Croatia
Czech Republic
Denmark
Egypt
Finland
France
Germany
Greece
Hungary
India
Ireland
Iran
Israel
Italy
Japan
Kazakhstan
Korea
Macedonia
Netherlands
Nigeria
Poland
Romania
Russia
Serbia
Slovakia
Slovenia
Spain
South Korea
Sweden
Switzerland
Tunisia
Ukraine
United Kingdom
United States

H5N2
Canada
China
Chinese Taipei
France
United States
H5N3
China
Chinese Taipei

H5N6
China
Hong Kong
Japan
Laos
South Korea
Vietnam

H5N1
Bangladesh
Bhutan
Burkina Faso
Bulgaria
Cambodia
Cameroon
Canada
China
Côte d’Ivoire
France
Ghana
India
Iran
Iraq
Israel
Korea
Laos
Lebanon
Libya
Myanmar
Nepal
Niger
Nigeria
Palestine
Romania
Russia
Togo
Turkey
United States
Vietnam
AVIAN INFLUENZA IN HUMANS:
EPIDEMIOLOGY, CLINICAL FEATURES AND TREATMENT

H5N9
France

H5N5
Netherlands
Montenegro

H5
Bulgaria
Kazakhstan
Palestine
Russia
Slovakia
Ukraine
Vietnam

H7N1
Algeria

H7N7
Italy
Germany
United Kingdom

H7N3
Mexico

H7N8
United States
LESSON 3: OCCURRENCE OF AVIAN INFLUENZA IN HUMANS

In this lesson we will cover:

- Illustrative Examples
- Novel Strains of AI that Emerged in Humans in 2013-16
- Serologic Surveys

ILLUSTRATIVE EXAMPLES OF HUMAN AVIAN INFLUENZA CASES

The following table provides examples of occurrences of human disease caused by avian influenza virus subtypes.

<p>| 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. |</p>
<table>
<thead>
<tr>
<th>Year</th>
<th>Avian Influenza Strain</th>
<th>Cases</th>
<th>Country</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>H7N7</td>
<td>89 (1 death)</td>
<td>The Netherlands</td>
<td>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 complained of influenza-like illness. The death occurred in a 57-year-old veterinarian. Subsequent serologic testing demonstrated that additional case-patients had asymptomatic infection.</td>
</tr>
<tr>
<td>2004</td>
<td>H10N7</td>
<td>2 (infants)</td>
<td>Egypt</td>
<td>One child's father was a poultry merchant.</td>
</tr>
<tr>
<td>2006</td>
<td>H7N3</td>
<td>1</td>
<td>United Kingdom</td>
<td>Although a number of exposed persons had symptoms of conjunctivitis or influenza-like illness, only one poultry worker had a laboratory-confirmed infection.</td>
</tr>
<tr>
<td>2007</td>
<td>H7N2</td>
<td>4</td>
<td>United Kingdom</td>
<td>Case-patients were associated with a poultry outbreak of H7N2 in Wales. The case-patients had conjunctivitis and influenza-like illness.</td>
</tr>
<tr>
<td>2008</td>
<td>H9N2</td>
<td>1 (infant)</td>
<td>China</td>
<td>The source of infection is unknown.</td>
</tr>
<tr>
<td>2009</td>
<td>H9N2</td>
<td>1 (47 year old)</td>
<td>Hong Kong SAR</td>
<td>Reported travel history to mainland China; Patient had mild disease and recovered.</td>
</tr>
<tr>
<td>2012</td>
<td>H7N3</td>
<td>2</td>
<td>Jalisco, Mexico</td>
<td>Two poultry workers developed conjunctivitis caused by H7N3 in association with an outbreak in poultry.</td>
</tr>
<tr>
<td>2013-17</td>
<td>H7N9</td>
<td>1000</td>
<td>China</td>
<td>As of January 2017 there have been at least 360 deaths associated with the H7N9 virus, which manifests as LPAI in poultry.</td>
</tr>
<tr>
<td>2014-17</td>
<td>H5N6</td>
<td>16</td>
<td>China</td>
<td>According to WHO, 16 cases and 6 deaths had occurred through January 2017.</td>
</tr>
</tbody>
</table>

**NOVEL AVIAN INFLUENZA STRAINS THAT EMERGED IN HUMANS IN 2013–16**

From 2013 through 2016 several strains of AI that had never been seen in humans were identified as the cause of illnesses and deaths.

**H7N9**
In the spring of 2013, a novel H7N9 virus emerged in humans in China. The initial wave occurred in the spring of 2013; a second wave occurred during the winter of 2013-14 and third and fourth waves occurred during the winter winters of 2014-15 and 2015-16, demonstrating a seasonal pattern. According to FAO, as of late January 2017, over 1000 human cases and at least 360 deaths due to H7N9 influenza had been reported.

H6N1

In May 2013, a woman in Taiwan became ill with an H6N1 strain of AI. She recovered from the illness, and no further cases of H6N1 were reported.

H10N8

Three cases of a novel H10N8 AI virus have been reported in the province of Jiangxi, China. The first case, which was fatal, was reported in December 2013. Two more cases were reported in January and February 2014. One of those patients also died.

H5N6

Two cases of an H5N6 AI strain occurred in two different provinces in China in 2014. Both cases had exposure to poultry. Outbreaks of HPAI H5N6 were also reported in 2014 in poultry in China, Lao People’s Democratic Republic, and Vietnam. According to WHO, as of January 2017, a total of 16 cases of H5N6 have occurred in China since 2014, including 6 deaths.

SEROLOGIC SURVEYS FOR AVIAN INFLUENZA ANTIBODIES IN HUMANS

People can be infected with a virus and not show any clinical illness. Here are several examples of serologic studies that examine subclinical AI infections among humans who interact with animals in professional and/or recreational settings.

- A serologic survey of 39 duck hunters and 68 wildlife professionals in Iowa conducted by Gill et al in late 2004 and early 2005 found that one duck hunter and two wildlife workers had serologic evidence of past infection with AI virus H11N9. All three had extensive exposure to wild ducks and geese.

- In a 2007 study of 42 veterinarians, Myers et al showed that the veterinarians were significantly more likely to have antibodies to AI subtypes H5, H6, and H7 (indicating past infection with these viruses) compared with a group of 66 healthy nonveterinarian control subjects. Furthermore, veterinarians who had examined birds had a higher likelihood of having increased antibodies to the three avian subtypes compared with veterinarians who did not have exposure to birds.

- In a 2002 study, Bridges et al found a 10% seroprevalence for H5 antibodies among 1,525 poultry workers in Hong Kong who were sampled within a year of an
extensive H5N1 poultry outbreak that coincided with several sporadic human H5N1 cases. Seroprevalence among employees increased with the number of poultry-related work tasks.

- A 2010 study by Kayali et al found that 21 backyard turkey growers in the U.S. had significantly higher mean antibody titers against AI subtypes H4, H5, H6, H8, H9, and H10 compared with those of 78 unexposed controls; no differences were found for subtypes H7 and H11. Seroprevalence of antibodies to AI subtypes among backyard turkey growers in this study ranged from 0% (H7) to 30% (H5) and from 0% (H7) to 4% (H11) among controls.
LESSON 4: OCCURRENCE OF H5N1 IN HUMANS

In this lesson we will cover:

- Timeline of H5N1 Avian Influenza in Humans
- Characteristics of Cases
- Routes of Transmission

TIMELINE OF H5N1 AVIAN INFLUENZA IN HUMANS

Up through January 2017, the World Health Organization (WHO) has officially recognized more than 850 human cases of H5N1 influenza, with more than 450 deaths and a case-fatality rate (CFR) of 53%. Cases have been reported from Azerbaijan, Bangladesh, Cambodia, Canada, China, Djibouti, Egypt, Indonesia, Iraq, Lao PDR, Myanmar, Nigeria, Pakistan, Thailand, Turkey, and Vietnam.

As of January 2017, case fatality rates were 84% for Indonesia, 60% for China, and 33% for Egypt where the highest total number of cases have occurred at 356.

These human cases are associated with an ongoing extensive panzootic of avian influenza in poultry.

<table>
<thead>
<tr>
<th>Year</th>
<th>Deaths/Cases</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>China 1/1&lt;br&gt;Vietnam 3/3&lt;br&gt;Total: 4/4</td>
<td>China: This fatal case of H5N1 was retrospectively confirmed in August 2006 after initial misdiagnosis as SARS in 2003. Vietnam: First reported human cases in Vietnam. The 3 cases occurred in the same family; human-to-human transmission could not be ruled out.</td>
</tr>
<tr>
<td>2006</td>
<td>Azerbaijan 5/8&lt;br&gt;Cambodia 2/2&lt;br&gt;China 8/13&lt;br&gt;Djibouti 0/1&lt;br&gt;Egypt 10/18</td>
<td>Azerbaijan: First reported human cases in Azerbaijan. Djibouti: First reported case in Djibouti occurs in a 2-year-old girl. Egypt: First reported human cases in Egypt.</td>
</tr>
</tbody>
</table>
### Indicators

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Confirmed Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>Cambodia</td>
<td>1/1</td>
</tr>
<tr>
<td></td>
<td>China</td>
<td>3/5</td>
</tr>
<tr>
<td></td>
<td>Egypt</td>
<td>9/25</td>
</tr>
<tr>
<td></td>
<td>Indonesia</td>
<td>37/42</td>
</tr>
<tr>
<td></td>
<td>Lao PDR</td>
<td>2/2</td>
</tr>
<tr>
<td></td>
<td>Myanmar</td>
<td>0/1</td>
</tr>
<tr>
<td></td>
<td>Nigeria</td>
<td>1/1</td>
</tr>
<tr>
<td></td>
<td>Pakistan</td>
<td>1/3</td>
</tr>
<tr>
<td></td>
<td>Vietnam</td>
<td>5/6</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>59/88</td>
</tr>
<tr>
<td>2008</td>
<td>Bangladesh</td>
<td>0/1</td>
</tr>
<tr>
<td></td>
<td>Cambodia</td>
<td>0/1</td>
</tr>
<tr>
<td></td>
<td>China</td>
<td>4/4</td>
</tr>
<tr>
<td></td>
<td>Egypt</td>
<td>4/8</td>
</tr>
<tr>
<td></td>
<td>Indonesia</td>
<td>20/24</td>
</tr>
<tr>
<td></td>
<td>Nigeria</td>
<td>0/1</td>
</tr>
<tr>
<td></td>
<td>Vietnam</td>
<td>5/6</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>33/44</td>
</tr>
<tr>
<td>2009</td>
<td>Cambodia</td>
<td>0/1</td>
</tr>
<tr>
<td></td>
<td>China</td>
<td>4/7</td>
</tr>
<tr>
<td></td>
<td>Egypt</td>
<td>4/39</td>
</tr>
<tr>
<td></td>
<td>Indonesia</td>
<td>19/21</td>
</tr>
<tr>
<td></td>
<td>Vietnam</td>
<td>5/5</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>32/73</td>
</tr>
<tr>
<td>2010</td>
<td>Cambodia</td>
<td>1/1</td>
</tr>
<tr>
<td></td>
<td>China</td>
<td>1/2</td>
</tr>
<tr>
<td></td>
<td>Egypt</td>
<td>13/29</td>
</tr>
<tr>
<td></td>
<td>Indonesia</td>
<td>7/9</td>
</tr>
<tr>
<td></td>
<td>Vietnam</td>
<td>2/7</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>24/48</td>
</tr>
<tr>
<td>2011</td>
<td>Bangladesh</td>
<td>0/2</td>
</tr>
<tr>
<td></td>
<td>Cambodia</td>
<td>8/8</td>
</tr>
<tr>
<td></td>
<td>China</td>
<td>1/1</td>
</tr>
<tr>
<td></td>
<td>Egypt</td>
<td>15/39</td>
</tr>
<tr>
<td></td>
<td>Indonesia</td>
<td>10/12</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>34/62</td>
</tr>
<tr>
<td>2012</td>
<td>Bangladesh</td>
<td>0/3</td>
</tr>
<tr>
<td></td>
<td>Cambodia</td>
<td>3/3</td>
</tr>
<tr>
<td></td>
<td>China</td>
<td>1/2</td>
</tr>
<tr>
<td></td>
<td>Egypt</td>
<td>5/11</td>
</tr>
<tr>
<td></td>
<td>Indonesia</td>
<td>9/9</td>
</tr>
<tr>
<td></td>
<td>Vietnam</td>
<td>2/4</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>20/32</td>
</tr>
<tr>
<td>2013</td>
<td>Bangladesh</td>
<td>1/1</td>
</tr>
<tr>
<td></td>
<td>Cambodia</td>
<td>14/26</td>
</tr>
<tr>
<td></td>
<td>Canada</td>
<td>1/1</td>
</tr>
<tr>
<td></td>
<td>China</td>
<td>2/2</td>
</tr>
<tr>
<td></td>
<td>Egypt</td>
<td>3/4</td>
</tr>
</tbody>
</table>

**Indonesia:** Indonesia reports the largest family cluster of cases to date, with 7 confirmed cases from 4 households within the same district. Disease did not spread beyond the extended family.

**Iraq:** First reported human cases in Iraq.

**Turkey:** First reported human cases in Turkey.

**2007 Indonesia:** Study shows that 76% of 54 human cases were associated with poultry contact; 24% of infections had no identified source.

**Lao PDR:** First reported human cases in Lao PDR.

**Myanmar:** First reported human case in Myanmar.

**Nigeria:** First reported human case in Nigeria.

**Pakistan:** First reported human cases in a family in Pakistan; limited human-to-human transmission appears likely.

**2008 Bangladesh:** First reported human case in Bangladesh. This case in a 16-month-old boy was retrospectively identified as part of seasonal influenza surveillance activities.

**Cambodia:** First nonfatal case of human H5N1 infection in Cambodia.

**2009 Cambodia:** First nonfatal case of human H5N1 infection in Cambodia.
CHARACTERISTICS OF CASES

A review of case data published in 2016 demonstrated the following epidemiologic characteristics of H5N1 influenza in humans from 1997-2015:

- Male-to-female ratio: 1:1.2
- Median age of 19 years, with 41.2% of cases in children younger than 15 and 80.3% of cases in persons younger than 35
- 67.2% of cases reported between December and March
- Overall case fatality of 53.5%, with a decrease from 70.7% 2003-08 to 43.4% from 2009-15; CFR was higher in Asia (69.4%) than Africa at (32.1%).
- 70% - 95% reported exposure to poultry
- Time from onset of illness to hospitalization was a median of 4 days

ROUTES OF TRANSMISSION

The main route of transmission of H5N1 from poultry to humans is most likely by way of the respiratory tract, but the eye (via the conjunctival mucosa) and the gastrointestinal (GI) tract are other probable routes. Infection through the GI tract could occur, for example, by using contaminated fingers to prepare or handle food or swallowing water contaminated by poultry-infected feces.

- A study published in 2010 demonstrated that the human GI tract expresses abundant avian H5N1 receptors, is readily infected ex-vivo by the H5N1 virus, and produces infectious viral particles in organ culture. These results provide some of the first evidence that H5N1 can directly target human GI tissue.

DIRECT CONTACT WITH DOMESTIC BIRDS

Most cases of H5N1 in humans have involved direct contact with poultry. Types of exposures that have been identified to date include:
• Slaughtering, plucking, and preparing diseased birds
• Handling fighting cocks or ducks that appear to be well
• Playing with or holding diseased or dead poultry
• Consuming raw or undercooked poultry or poultry products (such as duck blood); this mode of transmission is considered to be rare

ENVIRONMENTAL EXPOSURE

In approximately 25% of cases, the source of exposure remains unclear and environment-to-human transmission is considered a possibility (such as through contact with virus-contaminated fomites).

WILD BIRD TRANSMISSION

The first report of H5N1 disease in humans contracted through exposure to wild birds occurred in the spring of 2006. The discovery was made during investigation of a cluster of human H5N1 cases in Azerbaijan; family members denied any contact with ill domestic poultry, but many wild swans had died in the area and were thought to have played a role.

PERSON-TO-PERSON TRANSMISSION

To date, sustained person-to-person transmission has not been recognized, although probable person-to-person spread was identified in Thailand involving transmission from an ill child to her mother and aunt. Several other familial clusters have been recognized.

In May 2006, WHO reported an H5N1 influenza cluster in Indonesia involving seven cases of person-to-person transmission; one of the cases involved two generations of transmission. An Indonesian official recently put the number of clusters in that country at 10, all involving cases in blood relatives.

Inefficient transmission of current H5N1 strains may be related to lack of appropriate avian virus cell receptors in the upper respiratory tracts of humans and the inability of H5N1 strains to recognize human cell receptors.

A mutation allowing H5N1 AI virus to recognize human cell receptors could enhance person-to-person transmission owing to the potential for greater viral replication in the upper respiratory tract. Therefore, the potential exists for mutation of the H5N1 virus that would confer higher transmissibility and result in rapid spread throughout the human population, leading to a pandemic.
LESSON 5: H5N1 IN HUMANS: CLINICAL FEATURES

In this lesson we will cover:

- Incubation Period
- Signs and Symptoms
- Pathogenicity

INCUBATION PERIOD
The incubation period for most patients with H5N1 influenza is 2 to 5 days; however, the range appears to be as long as 8 or 9 days. A recent report from China that assessed incubation periods for 24 patients with H5N1 AI found that the median incubation period for patients exposed to a “wet” poultry market (which sells live birds) was significantly longer than for patients exposed to sick or dead poultry (7 days [range 3.5–9 days] vs 4.3 days [range 2–9 days]).

SIGNS AND SYMPTOMS
H5N1 influenza generally presents as a severe pneumonia that often progresses to acute respiratory distress syndrome (ARDS).

- In a 2008 review by the WHO, the majority of patients reported a mild prodromal phase characterized by fever, cough, and runny nose.
- The prodromal symptoms are typically followed by increasing dyspnea. Other symptoms include myalgia, headache, vomiting, diarrhea, nausea, epigastric pain, convulsion, and constipation.
- Physical signs may include fever, tachypnea, dyspnea, tachycardia, normal to low blood pressure, and crepitations on inspiration. Signs of pleural effusion may be present.
- As patients clinically deteriorate, the degree of respiratory failure worsens and ARDS develops. Patients usually die of progressive respiratory failure. Death can ensue between 6 and 16 days of illness.

PATHOGENICITY
HIGH CASE-FATALITY RATE

H5N1 strains exhibit high CFRs in humans. CFRs by clade are outlined below:

- Clade 1 (Cambodia, Thailand, and Vietnam): 54% (66/123)
- Clade 2.1 (Indonesia): 79% (76/96)
- Clade 2.2 (Azerbaijan, Djibouti, Egypt, Iraq, Nigeria, and Turkey): 44% (26/59)
• Clade 2.3 (China, Lao PDR): 65% (17/26)

The high CFR suggests that the pathogenicity of H5N1 may be similar to (or more severe than) the 1918 H1N1 pandemic strain. Researchers have hypothesized that cytokine storm (ie, overproduction of cytokines) may have played an important role in the pathogenesis of the 1918 pandemic strain and that this process may also be important in the pathogenesis of H5N1.

• A laboratory-based study involving H5N1 strains taken from ill humans in Asia (during 1997 and 2004) and a current seasonal H1N1 strain (circulating in Asia in 1998) found that all the H5N1 viruses caused human alveolar cells and bronchial epithelial cells to secrete significantly higher levels of various cytokines and chemokines than did the seasonal virus.

• A recent report also suggests that avian H5N1 influenza leads to substantial cell death in mammalian airway epithelial cells due to the induction of apoptosis.

GASTROINTESTINAL PRESENTATION

Some patients have presented with primarily GI symptoms. The case report of a 4-year-old Vietnamese boy with H5N1 AI who presented in 2004 with GI symptoms and encephalitis demonstrated the following features:

• The child had a 2-day history of fever, headache, vomiting, and severe diarrhea (approximately 10 episodes per day). His stools were watery without blood or mucus.
• Laboratory tests on admission were unremarkable, and chest x-ray was normal.
• On the third day following initial presentation, the child had a generalized convulsion and became comatose. Respiratory failure developed, and he died on the fifth day after initial presentation. Acute encephalitis of unknown origin was reported as the cause of death; no autopsy was performed.
• H5N1 influenza A virus was isolated from cerebrospinal fluid, fecal, throat, and serum specimens.
• The patient's 9-year-old sister had died 2 weeks earlier from a similar clinical syndrome.

ASYMPTOMATIC OR MILD ILLNESS

In general, asymptomatic or mild infections appear to be uncommon for H5N1, based on available seroepidemiologic data. Exceptions are noted below.
• Asymptomatic seroconversions were detected among some poultry workers and healthcare workers in the 1997 outbreak in Hong Kong, but that strain was different from later strains.

• In response to H5N1 outbreaks in poultry in South Korea in 2004, follow-up serologic testing of more than 2,000 poultry workers found 9 workers over time with serologic evidence of infection but no history of clinical illness. However, the South Korean strain was genetically distinct from Thai and Vietnamese strains and was found to have a low level of pathogenicity in mice.

• Relatively mild illness was noted in three of eight cases detected as part of three case clusters in Indonesia. All of the mild cases were in children.
LESSON 6: H5N1 IN HUMANS: TREATMENT

In this lesson we will cover:

- Available Agents
- Antiviral Resistance
- Current Recommendations for Treatment

AVAILABLE AGENTS

Two groups of antiviral agents are available for treatment and prophylaxis of influenza: M2 ion-channel inhibitors (the adamantanes [amantadine and rimantadine]) and the neuraminidase inhibitors (NIs) (oseltamivir [Tamiflu] and zanamivir [Relenza]).

EFFECTIVENESS AGAINST H5N1

Most H5N1 viruses that have caused human illness and death appear to be resistant to both adamantanes, amantadine and rimantadine.

Of the NIs, oseltamivir has been shown to improve clinical outcomes, particularly when treatment is started early in the course of illness.

- In an analysis of 63 cases of H5N1 avian influenza in Egypt between 2006 and 2009, Kandeel et al found that patients who began treatment with oseltamivir within 0 to 2 days of illness onset had a CFR of only 4% compared with 92% for those who began treatment 7 or more days after illness onset.
- The WHO reported a significant overall survival benefit with oseltamivir treatment (47%) as compared with no treatment (12%) in a multination case series of 244 H5N1 avian influenza patients between 2004 and 2007.

The value of zanamivir (the other commonly used NI, which is inhaled) in treating H5N1 influenza has not been studied to date, although suboptimal delivery to sites of infection in patients with pneumonic or extrapulmonary disease is a concern.

ANTIVIRAL RESISTANCE

The NIs are considered essential drugs for the treatment of A(H5N1) infected patients; however, concerns about resistance exist. Predicting the probability of resistant variants selected under NI pressure is essential.

Available data on antiviral resistance as of early 2011 are outlined below.
RESISTANCE TO ADAMANTANES: For influenza strains in general, transmissible amantadine-resistant organisms are shed by about 30% of patients after 2 to 5 days of treatment.

- Viral resistance to adamantanes can emerge rapidly, because a single point mutation can confer resistance to both amantadine and rimantadine.
- Clade 1 H5N1 viruses and most clade 2 H5N1 viruses from Indonesia are fully resistant to adamantanes, whereas clade 2 viruses from other lineages in Eurasia and Africa remain susceptible.

RESISTANCE TO OSELTAMIVIR: Until recently, levels of resistance to oseltamivir have remained relatively low.

- Oseltamivir-resistant H5N1 strains have been isolated from several patients in Vietnam. One was a Vietnamese child who received prophylactic treatment with the drug; another report involved two additional patients, both of whom died of H5N1 influenza.
- Clade 1 H5N1 viruses appear to be 15 to 30 times more sensitive to oseltamivir than clade 2 H5N1 isolates from Indonesia and Turkey.
- Genetic markers for reduced susceptibility to oseltamivir were noted in H5N1 isolates from two Egyptian patients who became ill and died in December 2006; both patients had been treated with oseltamivir for 2 days before the isolates were obtained.

RESISTANCE TO ZANAMIVIR: No resistance has been detected in previously healthy patients with H5N1 influenza who have been treated with zanamivir.

- An in vivo ferret model was recently used to investigate the development of resistance to oseltamivir and zanamivir in A (H5N1) viruses by treating the ferrets with the usual dose for human treatment or a variety of suboptimal drug concentrations.
- Analysis of viruses shed by the N1-treated ferrets detected one zanamivir-resistant isolate. This is the first report of this mutation being related to N1 susceptibility and one of the few that confer zanamivir resistance.

CURRENT RECOMMENDATIONS FOR TREATMENT

In May 2006, the WHO released guidelines on use of antiviral agents for H5N1 influenza treatment and prophylaxis. Treatment guidelines were updated in August 2007. The updated recommendations on treatment are outlined below.

- Oseltamivir remains the primary recommended antiviral treatment. Evidence that the H5N1 virus continues to replicate for a prolonged period indicates that treatment with oseltamivir also is warranted when the patient presents to clinical care at a later stage of illness.
- Modified regimens of oseltamivir treatment, including twofold higher dosage (i.e., 150 mg twice daily for adults), longer duration, and possibly combination therapy with amantadine or rimantadine (in countries where H5N1 viruses are likely to be
susceptible to adamantanes) may be considered on a case-by-case basis, especially for patients with pneumonia or progressive disease.

- Preclinical studies have shown that combinations of oseltamivir and adamantanes have enhanced antiviral activity and reduced resistance emergence.
- Combination therapy should only be considered when the locally circulating H5N1 viruses (clade 2.2 and 2.3) are likely to be susceptible to adamantanes and, whenever possible, with collection of serial respiratory samples for serial virological monitoring.

- Corticosteroids should not be used routinely but may be considered for septic shock with suspected adrenal insufficiency requiring vasopressors. Prolonged or high-dose corticosteroids can result in serious adverse events in H5N1-infected patients, including opportunistic infection.
- Antibiotic chemoprophylaxis should not be used. When pneumonia is present, however, antibiotic treatment is appropriate initially for community-acquired pneumonia, according to published evidence-based guidelines. When available, the results of microbiologic studies should be used to guide antibiotic usage for suspected bacterial co-infection in patients with H5N1 virus infection.
- Monitoring of oxygen saturation (e.g., pulse oximetry, arterial blood gases) should be performed whenever possible at presentation and routinely during subsequent care, and supplemental oxygen should be provided to correct hypoxemia.
- Therapy for H5N1-associated ARDS should be based on published evidence-based guidelines for sepsis-associated ARDS, specifically including lung-protective mechanical ventilation strategies.
LESSON 7: H7N9 Avian Influenza

In this lesson we will cover:

- The Emergence of H7N9
- H7N9 in Birds
- Timeline of Disease Occurrence in Humans
- Epidemiologic Characteristics of H7N9 AI in Humans
- Clinical Features of H7N9 in Humans
- Treatment of H7N9 in Humans
- Comparison of Clinical and Epidemiologic Features of H5N1 and H7N9 Influenza in Humans

THE EMERGENCE OF H7N9

In March 2013, a novel reassortant avian-origin influenza A virus was isolated from three hospitalized patients in China. The virus was identified as an H7N9 AI subtype. Of the three reported case-patients, two were residents of the city of Shanghai and one was a resident of Anhui province. All three developed severe respiratory disease and died. According to FAO, as of January 2017, more than 1000 cases and over 360 deaths have been reported throughout China. Cases have also been reported in Canada, Taiwan, Hong Kong, and Malaysia but these patients had traveled to outbreak areas in mainland China prior to becoming ill.

In the past, human infections with H7 viruses of avian origin have been rare and generally have caused mild illnesses such as conjunctivitis. Until the emergence of this strain, investigators had not identified the N9 subtype in humans.

Cases of H7N9 were originally recognized in in the first half of 2013. Since then a seasonal pattern has emerged with the majority of cases occurring in winter months or early spring. The beginning of the 2016-17 flu season showed a sudden spike in cases compared to the last 2 seasons.

H7N9 AI IN BIRDS

Investigations of H7N9 cases demonstrate that over 75% of infected individuals had recent exposure to poultry (mostly in live-bird markets). Viruses isolated from poultry markets that were epidemiologically linked to human cases have demonstrated high levels of homology with the viruses isolated from humans.
Unlike HPAI viruses, such as H5N1, which cause severe disease and death in poultry, the H7N9 virus appears to be an LPAI strain in poultry, causing mild or no clinical signs in birds. This makes surveillance for and detection of the virus in birds more difficult.

**H7N9 HUMAN CASES BY PROVINCE OVER TIME**

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*had visited Guangdong province prior to illness onset

(Data from FluTrackers as of 1/31/17).
EPIDEMIOLOGIC CHARACTERISTICS OF H7N9 AI IN HUMANS

- **AGE:** The median age of infected individuals is 61 years (range, 2 to 91 years).
- **GENDER:** Males are more likely to be infected than females (2.4:1 male-to-female ratio).
- **CFR:** The overall CFR is 34%.
  - Among fatalities, the average duration of illness from onset to death is 21 days; the average age at death is 63 years.
- **POULTRY EXPOSURE** Many of the cases (82%) reported recent exposure to animals including chickens (82%) and ducks (22%). These exposures occurred at live-bird markets or through occupational exposure. People who visited live-bird markets 10 or more times within 2 weeks before illness onset were much more likely to contract infection.
  - A serologic survey conducted in one of the Chinese provinces with a high incidence of H7N9 infections found that > 6% of workers in the live-bird markets had evidence of H7N9 infection, while members of the general population had no evidence of infection. These findings provide further evidence that the source of the virus is poultry.
- **TRANSMISSION:** Studies in ferrets have shown that the H7N9 virus replicates efficiently in the animals' respiratory tract and can be transmitted from ferret to ferret by direct contact, but it is not transmitted well via respiratory droplets.
  - Human-to-human spread appears to be uncommon, but this possibility has not been ruled out because several clusters of patients have been epidemiologically linked and the source of exposure has remained unclear.
  - In one instance, a relative of one of the patients became infected with the virus after caring for her sick father; the caretaker had no known poultry exposure. Both patients died from the infection.
- The epidemiologic information primarily reflects cases from the first wave of disease, which occurred in the spring of 2013.
CLINICAL FEATURES OF H7N9 IN HUMANS

- The incubation period for confirmed cases is 3.1 days.
- Similar to H5N1 infection, H7N9 may present as a severe pneumonia that can progress to ARDS.
- Clinical findings in patients with confirmed H7N9 infection at hospital admission include:
  - High fever and non-productive or productive cough are the most common presenting symptoms
  - Shortness of breath and hypoxia
  - Evidence of lower respiratory tract disease with opacities, consolidation, and infiltrates on chest x-ray
  - Lymphocytopenia, thrombocytopenia
- The degree of severity varies and tends to be higher in patients 50 years and older. Individuals 50 years of age or older also tend to have more complications from infection (in part because of the higher prevalence of chronic disease in that age-group). The presence of a co-existing medical condition has been noted as a risk factor for the development of ARDS.
- The presence of antibodies in the serologic survey of poultry workers demonstrates that asymptomatic infections (or mild illnesses) also can occur with H7N9.

TREATMENT OF H7N9 IN HUMANS

- The CDC recommends that all confirmed, probable, and H7N9 cases under investigation be treated with a NAI as soon as possible.
  - Treatment is most effective within 48 hours of illness onset but should be initiated even if that window has passed.
  - NIs include oseltamivir and zanamivir. H7N9 viruses are resistant to adamantanes (amantadine and rimantadine) in laboratory tests.
  - Treatment should not be delayed until laboratory confirmation of H7N9 infection.

Treatment duration should be 5 days for uncomplicated cases and 10 days for more severe disease or in immunocompromised individuals.

COMPARISON OF CLINICAL AND EPIDEMIOLOGIC FEATURES OF H5N1 AND H7N9 INFLUENZA IN HUMANS

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<th>H5N1</th>
<th>H7N9</th>
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<tr>
<td>CFR</td>
<td>~60%</td>
<td>~30%</td>
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<tr>
<td>Median age</td>
<td>26 years</td>
<td>61 years</td>
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Gender

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<th>Urban areas: 75% males; 25% females</th>
<th>Rural areas: 33% males; 67% females</th>
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<tr>
<td>Gender</td>
<td>75% males; 25% females</td>
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Incubation period

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Chronic/preexisting disease as a risk factor

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History of poultry exposure

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Disease in poultry

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Human-to-human transmission

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Pandemic potential

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Although there are similarities between H5N1 and H7N9 avian influenza viruses, there are also important differences (based on available data from the first wave of H7N9 disease, which occurred in the spring of 2013). Unlike H5N1 influenza, H7N9 affects a population similar to that affected by human influenza viruses (older age, those with pre-existing medical conditions). H7N9 has a lower CFR than H5N1. Although a history of poultry exposure is similar for the occurrence of both viruses, the fact that H7N9 manifests as LPAI in poultry makes surveillance for the disease in animals more difficult. This may also affect the implementation of control measures such as the use of personal protective equipment when handling infected birds. Both viruses have the potential to result in global pandemics if they develop the ability to be efficiently transmitted from human to human and effective vaccines are not readily available.
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.
RESOURCES


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All glossary definitions are found at one or more of the following sources (or are adapted from those sources):

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