Avian Influenza (Including Asian H7N9): Resources at Your Fingertips

Original Publication: June 1, 2017
Updated October 6, 2017

This document provides healthcare system and public health preparedness professionals, emergency managers, and other stakeholders with resources and information to consider when improving their readiness for potential human infections with avian influenza A viruses.

Significant concern exists about some avian influenza A viruses, including Asian lineage A(H5N1) and A(H7N9) viruses, that have caused sporadic human infections with high mortality, but no confirmed sustained human-to-human spread. These situations highlight possible issues for providers and planners, including:

- Sporadic cases in the US among travelers returning from affected areas;
- The possibility of an influenza pandemic resulting from a change in one of these viruses that would allow it to infect and transmit efficiently among people.

NOTE: This document and its hyperlinks and guidance references are current as of October 6, 2017; content will be updated as the situation evolves. Information on human infections with avian influenza A viruses is constantly evolving; therefore, if you are a clinician treating a patient or you are making response decisions and need current information during an outbreak, please check the Centers for Disease Control and Prevention (CDC) avian influenza site for the most current information and clinical guidance.

Appendix A contains resources from the U.S. Department of Health and Human Services (HHS) Office of the Assistant Secretary for Preparedness and Response (ASPR) and relevant contact links. **Appendix B** includes citations with annotations for additional relevant resources and avian influenza guidance. Finally, individuals can review ASPR TRACIE (Technical Resources, Assistance Center, and Information Exchange) Topic Collections, which provide a wide array of materials and resources for further research.

Quick Links

What is Avian Influenza?

Avian influenza refers to the disease caused by infection with avian influenza Type A viruses. These viruses occur naturally among wild aquatic birds worldwide and can infect domestic poultry and other bird and animal species. Avian influenza A viruses do not normally infect humans. However, sporadic human infections with avian influenza A viruses have occurred. Avian influenza A viruses are designated as highly pathogenic avian influenza (HPAI) or low pathogenicity avian influenza (LPAI) based on molecular characteristics of the virus and the ability of the virus to cause disease and mortality in chickens in a laboratory setting. Wild waterfowl are the natural hosts for avian influenza A viruses; most infections of wild birds are with LPAI viruses and result in asymptomatic infection in birds.

What Terminology is used to Categorize Influenza A Viruses?

Influenza A viruses are divided into subtypes on the basis of two proteins on the surface of the virus: hemagglutinin (HA) and neuraminidase (NA). There are 18 known HA subtypes and 11 known NA subtypes. Many different combinations of HA and NA proteins are possible. Avian influenza viruses have evolved into distinct genetic lineages in different geographic locations. For example, Asian lineage H7N9 and North American lineage H7N9 viruses are the same subtype, but they are genetically different. Although only H5 and H7 virus subtypes have been identified as HPAI viruses, most H5 and H7 viruses circulating among birds are LPAI viruses.

What Terminology is used to Describe the Characteristics of Avian Influenza A Viruses?

A number of terms are used to describe the characteristics of avian influenza A viruses. These terms include infectivity, pathogenicity, virulence, and transmissibility.

- Infectivity is the ability of a virus to cause infection and replicate in a host.
- Pathogenicity is the ability of a virus to cause disease once it infects a host.
- Virulence is the ability of a pathogenic virus – one that causes disease – to cause severe disease.
- Transmissibility is the ability of the virus to be passed from an infected animal or human to an uninfected animal or human.

Differences in infectivity, pathogenicity, virulence, and transmissibility of specific avian influenza A viruses, as well as existing immunity to the virus among humans, all affect the assessment of the public health risk these viruses pose. The effects of avian influenza A virus infection on birds do not necessarily reflect what the effects of infection in humans may be, as evidenced by the lack of symptoms in birds infected with Asian lineage LPAI H7N9 viruses in contrast with the serious illness and deaths seen in humans infected with similar viruses. The opposite has also been seen – some HPAI virus infections that have been lethal in birds have only caused mild illness (conjunctivitis and/or influenza-like illness) or had no effect on infected humans.

Why is Avian Influenza a Healthcare System and Public Health Concern?

Although avian influenza A viruses usually do not infect people, rare cases of human infection with these viruses have been reported. Most infections in people have occurred after close and prolonged contact with infected birds or the excretions/secretions of infected birds (e.g., droppings, oral fluids) to infect the human respiratory tract. Risk is dependent on exposure. People with close or prolonged unprotected contact with infected birds or contaminated environments are at greater risk of infection. Limited, non-sustained transmission from person-to-person has occurred among close contacts like family and caregivers, including unprotected healthcare personnel. More worrisome, changes in the virus may allow for sustained human-to human-transmission. In part because humans have little or no immunity to avian influenza A viruses, those who become infected may become seriously ill or die.

Scientists and animal and public health officials closely monitor avian influenza A virus outbreaks for indications that the virus can infect humans or spread from person to person. If a novel avian influenza A virus acquires the ability to spread from person to person in a sustained manner, it could trigger a pandemic. Through close monitoring, scientists can detect subtle changes in the virus that may make it more dangerous to humans. Detecting such changes supports preparedness and response activities, such as culling poultry flocks, shutting down live bird markets, advising against contact with birds or contaminated environments, setting travel or trade advisories or restrictions, and developing targeted vaccines for pandemic preparedness.

Which Avian Influenza A Viruses Are of Particular Interest to Health Officials and Clinicians and Why?

A novel influenza A virus is one that has caused human infection, but is different from current seasonal human influenza A viruses spreading among people. Novel influenza A viruses can be viruses that originate in animals that gain the ability to infect humans or human viruses that change significantly so as to be different from current human seasonal influenza A viruses. Some novel influenza A viruses are of extra concern because of the potential impact they could have on public health if they gained the ability to spread from person-to-person easily, triggering a pandemic. Some examples of avian influenza A viruses of concern include:

Asian lineage A(H7N9): There have been nearly 1,600 laboratory-confirmed human infections with Asian lineage A(H7N9) virus reported by China since the first human infection was identified in 2013; (Updated October 6, 2017) the current case fatality rate is approximately 40%.[1] Since October 1, 2016, there has been a substantial increase in the number of human infections with Asian lineage A (H7N9) virus reported in China. While most human infections continue to be associated with exposure to poultry and there is no sustained person-to-person spread of this virus, there have been some changes in recent Asian lineage A(H7N9) viruses identified that are of public health concern. During this fifth epidemic (wave), reports indicate that human cases of Asian lineage A(H7N9) virus infection are more geographically spread throughout China than in previous epidemics, and the number of human cases during the current fifth epidemic is greater than reported during previous epidemics. (Updated October 6, 2017) The increased number of human infections – and associated illnesses and deaths – and the detection of highly pathogenic Asian lineage A(H7N9) viruses in birds (and in some human cases) are being closely monitored. Figure 1 shows the reported numbers of confirmed human infections and deaths from Asian lineage A(H7N9) virus in China over time. Serological studies in both the general population and poultry workers in China have shown low or no human immunity against H7 viruses.

[1] The number of confirmed human infections and case fatality rate reference current information from WHO, FAO, and CDC. Due to the evolving nature of the situation and varying reporting timeframes, these figures may differ from other publicly-reported data.

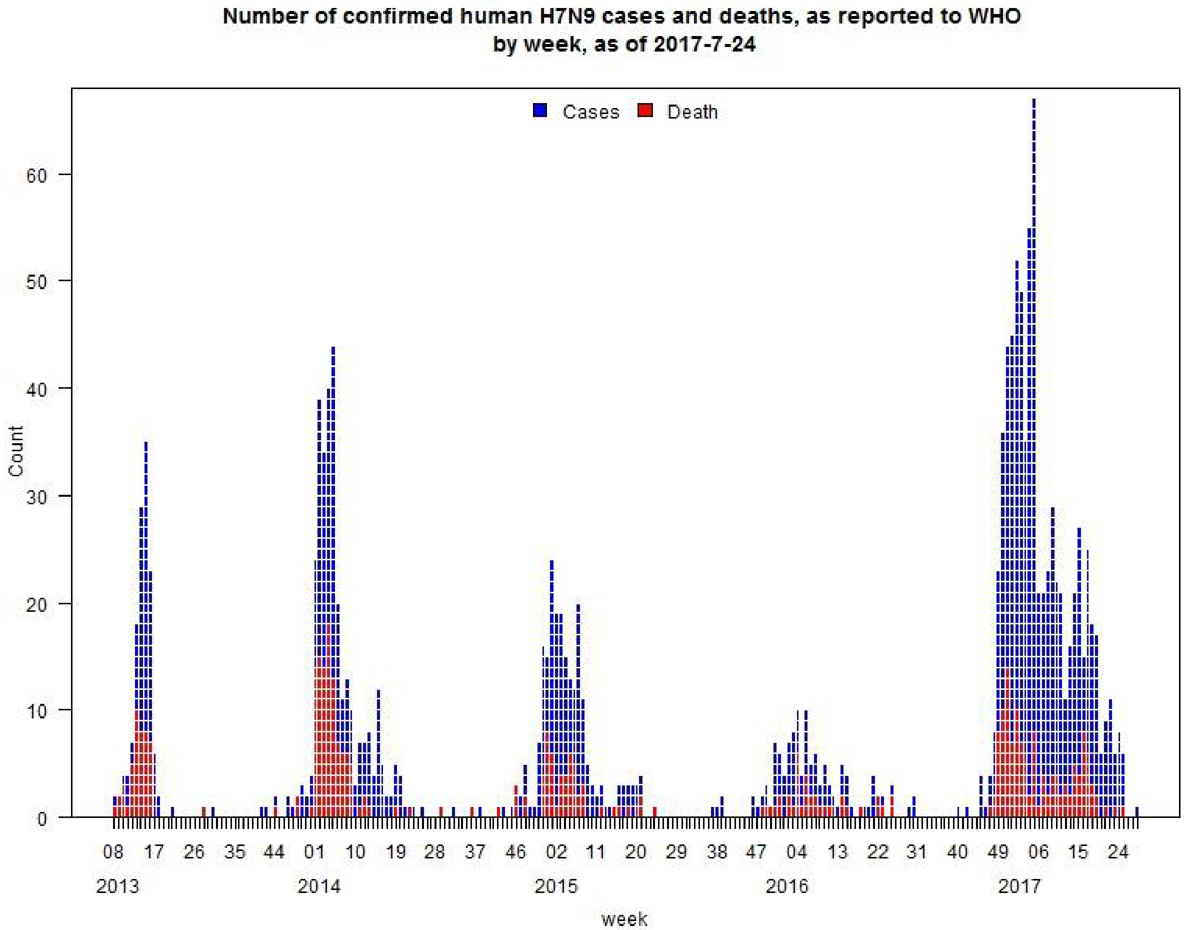

Figure 1. Confirmed Human Asian Lineage A(H7N9) Cases and Deaths. Current as of October 6, 2017.

One of the main concerns regarding Asian lineage A(H7N9) viruses is their ability to bind to receptors in the upper respiratory tract of humans, unlike the Asian lineage A(H5N1) HPAI viruses that bind primarily to receptors in the lower respiratory tract. This suggests that Asian lineage A(H7N9) is better adapted to cause infection in humans than some other avian influenza viruses. High fever, cough, shortness of breath, severe pneumonia, acute respiratory distress syndrome, septic shock, and multi-organ failure have been reported among human cases. Pregnant women, older individuals, and those with chronic health conditions can experience severe illness or death. Limited, non-sustained human to human transmission of Asian lineage A(H7N9) viruses has been reported in hospitals in China. Therefore, patients with relevant travel history, exposure history, and severe respiratory disease should be immediately isolated if infection with Asian lineage A(H7N9) virus is suspected. Providers should consult with the state health department and test for influenza A and B virus, including testing for H7 and other influenza A virus subtypes, as indicated. High suspicion should be maintained at facilities that frequently have patients referred for refractory hypoxemic respiratory failure and screening for travel/exposure should be undertaken prior to the patient's arrival at the referring hospital. Of the known novel influenza A viruses that have been evaluated by CDC, Asian lineage A(H7N9) virus is considered to have the greatest potential to cause a pandemic.

Genetic sequencing of virus samples from a human case and live poultry markets suggests that some Asian lineage A(H7N9) viruses have mutated from LPAI to HPAI; however, LPAI A(H7N9) viruses predominate. While there is no evidence that the increasing numbers of Asian lineage A(H7N9) virus detections and pathogenicity in birds is affecting transmissibility or pathogenicity in humans, this change does raise concerns. Furthermore, genetic sequences from Asian lineage HPAI A(H7N9) viruses recovered from several patients treated with antivirals showed genetic markers previously associated with resistance to neuraminidase inhibitor antiviral medications. This suggests that antiviral resistance to neuraminidase inhibitor (NAI) drugs developed during treatment. Such changes, if they were to become commonplace, would have major implications for clinicians as NAIs are the only available antiviral drugs recommended for treatment of influenza A virus infections, including Asian lineage A(H7N9) virus infection. Figure 2 shows where Asian lineage A(H7N9) virus-infected human cases and detections in animals have occurred.

Figure 2. Human cases and positive findings in birds or the environment during the Asian H7N9 fifth wave (epidemic). Current as of October 6, 2017.

Asian lineage (A/goose/Guangdong/1/96) HPAI H5: Asian lineage A(H5N1) viruses have been the most prominent HPAI virus of concern in recent years, infecting 859 humans (with 453 deaths) reported in 16 countries since 2003. Asian lineage HPAI A(H5N1) was first detected in humans in 1997 during a poultry outbreak in Hong Kong and has since been detected in poultry and wild birds in more than 50 countries in Africa, Asia, Europe, and the Middle East. The virus causes severe illness in humans, and approximately 53% of cases have been fatal. Figure 3 shows the reported number of confirmed human infections with Asian lineage A(H5N1) virus infection by location and time of onset dating from 2003.

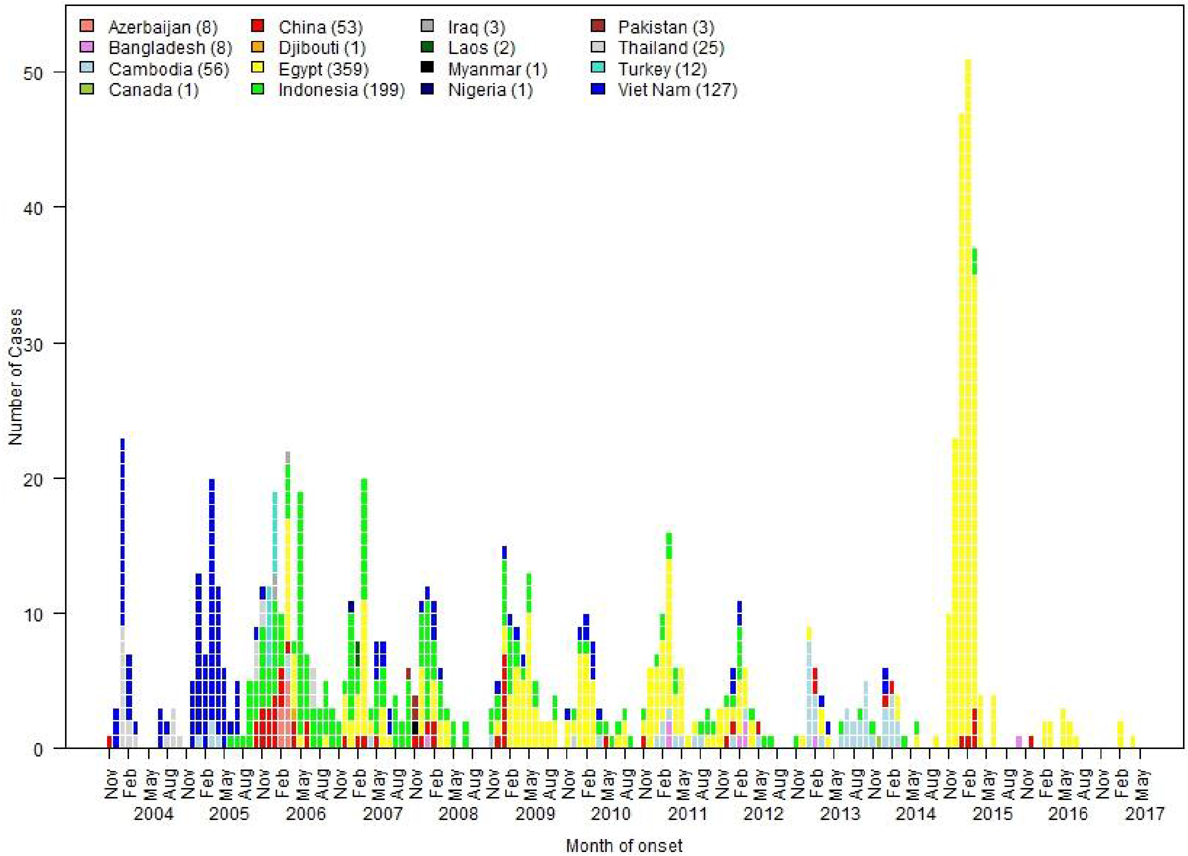

Figure 3. Number of confirmed human cases of Asian A(H5N1) worldwide reported to WHO since 2003. Current as of September 29, 2017.

Recently, Asian lineage HPAI A(H5N1) clade 2.3.4.4 viruses have reassorted with other avian influenza A viruses, generating other subtypes such as H5N2, H5N5, H5N6, and H5N8. Asian lineage A(H5N6) viruses have shown similar epidemiological characteristics and severity in infected humans as Asian lineage HPAI A(H5N1) virus. To date, there have been 17 human infections and 12 deaths with Asian lineage HPAI A(H5N6) virus infection reported in China since 2014. Asian lineage HPAI A(H5N8) viruses have spread intercontinentally in wild birds, but have not caused any human infections to date. Overall, there is no evidence to suggest that Asian lineage HPAI A(H5) viruses have increased in their ability to transmit from birds to humans or from human-to-human. However, the wide and ongoing circulation of Asian lineage HPAI A(H5) viruses in birds increases the potential for human exposures and the opportunity for the virus to mix with human and or swine influenza A viruses.

Where is Avian Influenza Found?

Migratory aquatic birds worldwide are the natural hosts for all avian influenza A viruses. Between January 2014 and November 2016, 13 strains of H5 and H7 viruses in domestic birds and HPAI in wild birds were reported to the World Animal Health Organisation (OIE) from 77 countries. Figure 4 shows the locations of HPAI outbreaks in poultry and wild birds (12 month period up to June 2017).

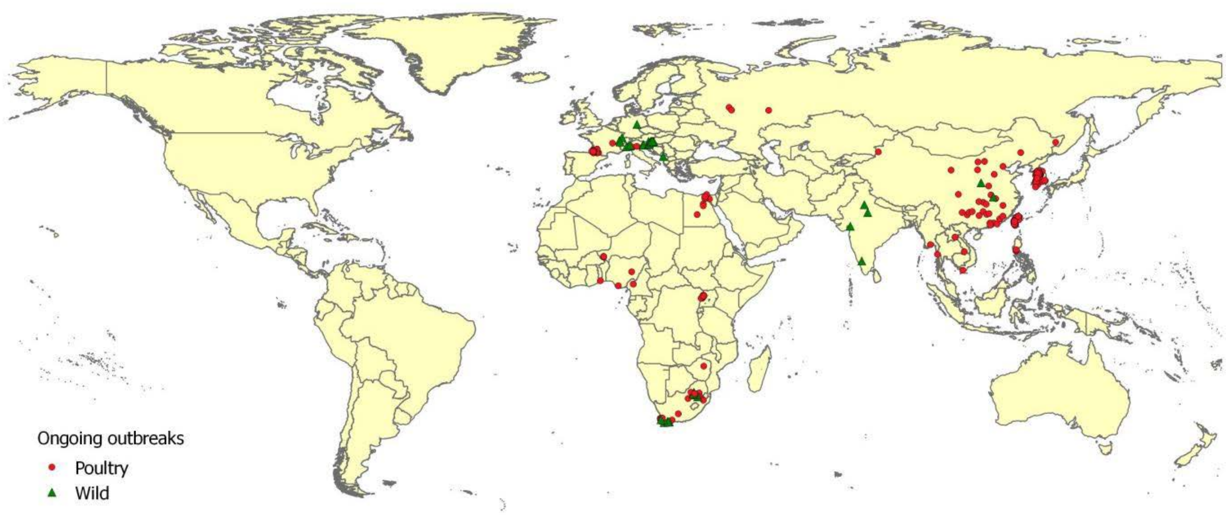

Figure 4. Global map of HPAI outbreaks in poultry and wild birds (12 month period up to September 2017). Current as of October 6, 2017.

LPAI in the US: In the United States, LPAI North American lineage H5 and H7 virus outbreaks in poultry have been reported sporadically, including an H7N2 outbreak that infected a human in Virginia in 2002 and a human infection of unknown origin in New York in 2003. In December 2016, an A(H7N2) virus caused an outbreak among cats in New York City animal shelters, which resulted in one human infection in a person who was working closely with sick, infected cats. In most of these human infections with H7 viruses, clinical signs were mild and the infected individuals made full recoveries. In early 2017, LPAI North American lineage H7 virus was detected in poultry in Georgia, Alabama, Kentucky, and Tennessee, with no associated human infections.

HPAI in the US: Outbreaks of HPAI among poultry have also been reported in recent years in the United States. On March 4, 2017, the U.S. Department of Agriculture Animal and Plant Health Inspection Service (APHIS) confirmed HPAI A(H7N9) virus in a chicken flock in Tennessee; the Tennessee Department of Agriculture quarantined the facility and the 74,000-chicken flock was depopulated and buried onsite. On March 6, 2017 the full subtype was confirmed to be North American lineage (AM) A(H7N9) virus through genome sequencing. This is not the same virus and is genetically distinct from the Asian lineage A(H7N9) viruses circulating in birds and infecting humans in China. A second case of HPAI AM A(H7N9) was found within a 10-kilometer radius of the first infected flock in Tennessee and 55,000 chickens were depopulated. APHIS and the Tennessee Department of Agriculture conducted surveillance of commercial and backyard poultry in the vicinity, all of which tested negative for HPAI. The last quarantine for this outbreak and the LPAI H7 outbreak was released in June 2017. (Updated October 6, 2017)

Other HPAI outbreaks in U.S. poultry were reported in Texas in 2004 (AM H5N2), 21 states in 2014-2015 (Asian lineage H5), and Indiana in 2016 (AM H7N8). The December 2014 to June 2015 outbreaks of HPAI H5 of Asian lineage (H5N8, and a reassortant Asian-AM H5N2) resulted in the deaths or culling of 7.4 million turkeys and 43 million egg-layer and pullet chickens, and represents the most costly animal health event in U.S. history to date. No human infections were identified in association with these HPAI outbreaks.

Can Avian Influenza A Virus be Transmitted Person to Person?

Rarely. Limited, non-sustained human-to-human transmission of some avian influenza A viruses has been reported. None of the avian influenza A viruses circulating among poultry in 2017 appear to have acquired the ability to do so easily or in a sustained manner. Most human infections result from direct human contact with infected animals or contaminated environments. The rare clusters of human cases with avian influenza A virus infections that have been reported are most frequently attributed to common source poultry exposures. Even rarer clusters of limited, non-sustained human to human transmission have occurred among unprotected close family contacts and healthcare workers. The WHO's Disease Outbreak News provides transmission details on human cases as they become available.

How and When Do Clinicians Detect Avian Influenza A Virus Infection in Patients?

Most individuals, including returned travelers, are much more likely to have seasonal influenza A virus infection than avian influenza A virus infection. Clinicians should consider seasonal influenza virus infection first; however, clinicians should investigate for Asian lineage H5N1 or H7N9 avian influenza A virus infection in patients who recently traveled to areas where avian influenza A viruses are known to be circulating in poultry and had unprotected exposure to poultry at a live poultry market or farm or to backyard poultry, had close contact with someone known or suspected to be infected with avian influenza A virus, or experienced unprotected exposure to live avian influenza A viruses in a laboratory. Additionally, clinicians should consider infection with avian influenza A viruses with the potential to cause severe disease in patients with influenza-like illness and acute respiratory infection, including pneumonia who have had contact with domestic poultry or other birds, especially birds that are suspected of being infected or diseased.

Clinicians cannot make a diagnosis of avian influenza A virus infection clinically or by commercially-available influenza laboratory tests. A nasopharyngeal swab, nasal aspirate or wash, or two swabs (nasal and throat) combined into one viral transport media vial should be collected as soon as possible following onset of illness. A lower respiratory tract specimen may be preferable for patients with lower respiratory tract illness. State public health laboratories have the capability to detect influenza A virus infection, including unsubtypeable influenza A virus infection by RT-PCR assays. The state health department should notify the CDC of any unsubtypeable influenza A positive test results and ship the specimens to the CDC for confirmatory testing.

How is Human Infection with Avian Influenza A Viruses Treated?

CDC currently recommends treatment with a neuraminidase inhibitor for human infection with avian influenza A viruses. Analyses of available avian influenza A viruses circulating worldwide suggest that most viruses are susceptible to oseltamivir, peramivir, and zanamivir. However, some evidence of antiviral resistance has been reported in HPAI Asian lineage avian influenza A(H5N1) viruses and Asian lineage avian influenza A (H7N9) viruses. Monitoring for antiviral resistance among avian influenza A viruses is crucial and ongoing. Antivirals can reduce the severity of the illness due to seasonal influenza viruses, particularly when started early, preferably within 48 hours of illness onset. Antiviral treatment should not be delayed to await laboratory results. However, antiviral therapy may still provide clinical benefit if started later. In some rare cases, patients may contract secondary bacterial lung infection, which requires treatment with antibiotics.

What Infection Control Actions Should Healthcare Providers Take to Prevent Transmission in Healthcare Settings?

CDC interim guidance recommends a higher level of infection control measures when managing suspected or confirmed human cases of avian influenza A virus infection than for seasonal influenza. These interim recommendations are based upon current available information and the following considerations:

- Lack of a widely available safe and effective vaccine
- A suspected high rate of morbidity and mortality among infected patients
- Few or no confirmed cases in the United States

Recommended infection prevention and control procedures include adhering to infection control practices: hand hygiene, use of appropriate personal protective equipment (gloves, gowns, use of a fit-tested N95 respirator or equivalent protection, eye protection), patient placement in an airborne infection isolation room (AIIR), caution when performing aerosol-generating procedures, minimizing exposures, implementing engineering controls, training personnel, implementing environmental infection controls, managing visitor access and movement, monitoring severe respiratory infection activity, and monitoring ill and exposed healthcare workers. Seasonal influenza vaccination of healthcare workers who may treat patients with suspected avian influenza A virus infection decreases the opportunity for influenza A viral coinfections and potential for reassortment.

What Makes Avian Influenza A Virus Infections Different From Seasonal Influenza A and B Viruses?

Human seasonal influenza Type A (subtypes H1 and H3) and B viruses circulate year-round among people worldwide and cause epidemics every year, often peaking between December and February in the United States. With ongoing virus circulation, most individuals have some immunity from exposures to seasonal influenza A and B viruses from previous years or from seasonal influenza vaccination. However, some populations – including children younger than 5 years old, people 65 years and older, pregnant women, and those with certain chronic health conditions – are at increased risk for serious illness, possibly leading to hospitalization or death.

In contrast, avian influenza A virus infection in humans is rare. Even healthy individuals could be at risk for serious illness, depending on the avian influenza A virus and underlying health conditions. While groups at-risk for seasonal influenza complications and death may also be at higher risk of severe illness from infection with avian influenza A viruses, the specific characteristics of the virus and its effects on the immune system may result in disproportionate effects on specific patient groups. Seasonal influenza vaccines protect against selected human seasonal influenza viruses and are not intended to prevent infection with avian influenza A viruses. The CDC, WHO, and other health agencies develop candidate vaccine viruses for avian influenza A viruses of public health concern that may be used by manufacturers to produce pre-pandemic vaccines and are an essential component of pandemic preparedness. Should an avian influenza A virus acquire the transmissibility and pathogenicity characteristics required for causing a pandemic, health systems and other institutions could become strained if not overwhelmed if a pandemic occurs.

Is Influenza in Animals Other than Birds a Concern for Humans?

A variety of animals – including pigs, cats, whales, horses, and seals – can become infected with avian influenza A viruses. Zoonotic pathogens are those that can be transmitted between animals and humans, including avian and swine influenza A viruses. Canine and bat influenza A viruses have been found in dogs and bats respectively, but are not known to have infected humans.

Three influenza A virus subtypes currently circulate in pigs. These viruses do not normally infect humans; however, sporadic human infections with influenza A viruses that normally infect swine have occurred. When this happens, these viruses are called "variant viruses." Pigs are of particular interest because of their susceptibility to their endemic influenza A viruses as well as human seasonal and avian influenza A viruses, and they potentially may be infected with influenza A viruses from different species (e.g., ducks and humans) at the same time. If this happens, it is possible for the genes of these viruses to mix and create a new virus. This type of major change in the influenza A viruses that results in human infection is known as antigenic shift. If this new virus causes illness in people and can be transmitted easily from person-to-person, an influenza pandemic can occur. The U.S. Department of Agriculture runs a voluntary surveillance program that tests samples from sick pigs or pigs that may be associated with human infections to detect changes in influenza A viruses.

Per CDC, a total of 20 variant virus infections have been reported in the United States during 2017. Eighteen of these were H3N2v viruses (Texas [1], North Dakota [1], Pennsylvania [1], and Ohio [15]) and two were H1N2v viruses (Ohio [2]). Two of the 20 infected persons were hospitalized as a result of their illness. No deaths have occurred. All variant virus infections have been associated with swine exposure in fair settings and no human-to-human transmission has been identified. (Updated October 6, 2017)

How is the Risk of an Influenza Pandemic Assessed?

The Influenza Risk Assessment Tool (IRAT) is an evaluation tool developed by CDC and external influenza experts that assesses the potential pandemic risk posed by influenza A viruses that currently circulate in animals but not in humans. The IRAT assesses potential pandemic risk based on two different scenarios: “emergence” and “public health impact.” “Emergence” refers to the risk of a novel (i.e., new in humans) influenza virus acquiring the ability to spread easily and efficiently in people. “Public health impact” refers to the potential severity of human disease caused by the virus (e.g., deaths and hospitalizations) as well as the burden on society (e.g., missed workdays, strain on hospital capacity and resources, and interruption of basic public services) if a novel influenza virus were to begin spreading efficiently and sustainably among people. The IRAT used 10 scientific criteria to measure the potential pandemic risk associated with each of these scenarios. These 10 criteria can be grouped into three overarching categories: “properties of the virus,” “attributes of the population,” and “ecology and epidemiology of the virus.” Fourteen novel influenza A viruses have been assessed and classified according to low, moderate, and high risk. The IRAT is intended to assess the pandemic potential of an influenza A virus; it cannot predict an influenza pandemic. (Updated October 6, 2017)

What are the Psychological Aspects of Avian Influenza and How Can They be Addressed?

While there is no ongoing community spread of avian influenza among humans anywhere in the world, the reporting of sporadic human cases or speculation on the possible emergence of an influenza pandemic may cause concern among the public. Community members often experience heightened anxiety and concern for their health and safety when they see or hear reports of an outbreak on television, online, or on the radio. Healthcare workers also experience higher levels of stress during outbreaks and, as caregivers, may be at greater risk of infection without proper infection prevention and control practices. In past outbreaks, this has resulted in increased absenteeism and, in some cases, stigma toward those who are in contact with patients and loved ones who are ill. In addition, grief and loss reactions of survivors of those who perish during an outbreak or pandemic may require intervention. Because a significant stress component exists during any infectious disease outbreak, planners should integrate psychological support and education into their preparedness efforts and in all aspects of a response – should a pandemic emerge – to prevent or manage adverse psychological effects.

Key Points for Consideration and Resources by Profession

Clinicians/Healthcare Providers

Preparedness

- Maintain awareness of avian influenza A virus infections in humans by signing up for public health alerts from local health department and CDC.
- Be prepared to institute additional outpatient and emergency department-based screening if larger outbreaks occur or human-to-human transmission chains are identified.
- Resources:
  - Avian Influenza: Information for Health Professionals and Laboratorians. [CDC]
  - Protect Yourself: Avian Flu Quick Card for Healthcare Workers. [OSHA]

Patient Evaluation

- Ask symptomatic patients about recent travel to areas where avian influenza A outbreaks are occurring and assess for domestic occupational exposure.
- Immediately place a simple mask on patients with suspected exposure and symptoms.
- Consider placing patients suspected of being infected with an avian influenza A virus that has caused or is related to viruses that have caused severe human illness in an airborne infection isolation room (AIIR), if available.
- Rapidly involve infectious disease and infection control personnel at your facility for a suspect case.
- Resources:
  - Interim Guidance on Case Definitions for Investigations of Human Infection with Avian Influenza A (H7N9) Virus in the United States. [CDC]
  - Interim Guidance on Case Definitions for Investigations of Human Infection with Highly Pathogenic Avian Influenza A (H5N1) Virus in the United States. [CDC]

- Interim Guidance on Case Definitions for Investigations of Human Infection with Highly Pathogenic Avian Influenza A H5 Viruses in the United States. [CDC]
- Brief Summary for Clinicians: Evaluating and Managing Patients Exposed to Birds Infected with Avian Influenza Viruses of Public Health Concern. [CDC] (Updated October 6, 2017)

Patient Testing and Diagnosis

- Test symptomatic patients who have possible exposure to avian influenza A viruses when they have traveled to an area with an ongoing outbreak or through domestic occupational exposure.
- Ensure proper sample collection and specimen submission to the jurisdictional public health laboratory.
- Resources:
  - Diagnostics for Detecting H7N9 Using rRT-PCR. [CDC]
  - Interim Guidance for Specimen Collection, Processing, and Testing for Patients with Suspected Infection with Novel Influenza A Viruses Associated with Severe Disease in Humans. [CDC] (Note: This guidance applies to Asian lineage A(H5N1) and A(H7N9) HPAI viruses that have caused severe illness in humans in other countries.)
  - Interim Guidance for Specimen Collection, Processing, and Testing for Patients with Suspected Infection with Novel Influenza A Viruses with the Potential to Cause Severe Disease in Humans. [CDC] (Note: This guidance applies to A(H5) HPAI viruses that have been found in birds in the US.)
  - Influenza Specimen Collection Desk Reference Guide. [CDC] (Updated July 14, 2017)
  - Interim Risk Assessment and Biosafety Level Recommendations for Working with Influenza A(H7N9) Viruses. [CDC]
  - Laboratory Biorisk Management for Laboratories Handling Human Specimens Suspected or Confirmed to Contain Avian Influenza A(H7N9) Virus Causing Human Disease: Interim Recommendations. [WHO]

Patient Treatment and Response

- Treat symptomatic patients with a history of exposure to avian influenza A virus with neuraminidase inhibitor antivirals as soon as possible; do not delay while waiting for confirmatory laboratory results.
- Treat symptoms and provide supportive care.
- Follow recommended infection prevention and control procedures for suspected or confirmed avian influenza A virus infection including appropriate use of respirators (e.g., fit-tested N95 respirators).

- Rapidly involve infectious disease and infection control personnel at your facility for a suspect case.
- Resources:
  - 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. [CDC]
  - Interim Guidance on the Use of Antiviral Medications for Treatment of Human Infections with Novel Influenza A Viruses Associated with Severe Human Disease. [CDC]
  - Interim Guidance on Follow-up of Close Contacts of Persons Infected with Novel Influenza A Viruses Associated with Severe Human Disease and on the Use of Antiviral Medications for Chemoprophylaxis. [CDC]
  - Influenza Antiviral Medications: Summary for Clinicians. [CDC]
  - Interim Guidance on Influenza Antiviral Chemoprophylaxis of Persons Exposed to Birds with Avian Influenza A Viruses Associated with Severe Human Disease or with the Potential to Cause Severe Human Disease. [CDC]
  - Avian Influenza A(H7N9) Virus: Post-exposure Antiviral Chemoprophylaxis of Close Contacts of a Patient with Confirmed H7N9 Virus Infection and/or High Risk Poultry/Environmental Exposures. [WHO]

Emergency Management/ Public Health Preparedness/ Healthcare System Emergency Management Professionals

Current Cases

- No human cases of Asian lineage A(H7N9) or A(H5) virus infection have been detected in the United States.

General Preparedness and Response

- Review and revise existing pandemic influenza plans, or develop plans, if needed.
- Ensure clinicians are provided up to date information on testing criteria and evaluation of suspected human cases and treatment of avian influenza A virus infection.
- Coordinate planning across healthcare coalitions to improve regional information sharing, surveillance, and reporting and to develop consistent healthcare facility infection control and laboratory specimen submission information and, if an outbreak occurs, to develop common visitation rules, access to medical countermeasures, and institute measures such as crisis standards of care, if warranted.
- Resources:
  - Epidemic/Pandemic Flu Topic Collection. [ASPR TRACIE]
  - Top 10 Influenza Pandemic Response Planning Tips for H7N9 Virus. [CDC]
  - Influenza Risk Assessment Tool. [CDC]

- Tool for Influenza Pandemic Risk Assessment. [WHO]
- Genetic Evolution of H7N9 Virus in China, 2013. [CDC]
- Factsheet on A(H5N1). [ECDPC] (Updated October 6, 2017)
- Factsheet on A(H7N9). [ECDPC] (Updated October 6, 2017)
- Community Mitigation Guidelines to Prevent Pandemic Influenza – United States, 2017. [CDC]
- Analysis of Gaps and Needs for the PIP PC Implementation. [WHO]
- Avian Influenza: USDA Has Taken Actions to Reduce Risks but Needs a Plan to Evaluate Its Efforts. [GAO]

Risk Communication

- Communicate protective information to populations at risk of exposure to avian influenza A viruses.
- *Individuals with Occupational or Recreational Exposure to Birds:*
  - Maintain awareness of avian influenza A virus outbreaks in poultry or wild birds.
  - Avoid direct contact with potentially infected birds or contaminated surfaces.
  - Know the signs of avian influenza in birds.
  - Wear appropriate personal protective equipment.
  - Report suspected avian influenza A infections in wild birds, poultry, humans, or other animals.
- *Travelers to Areas of Potential Risk:*
  - Monitor the CDC Travelers' Health webpage for changes in travel guidance. As of March 7, the CDC's current alert level for Asian lineage H7N9 virus in China is Watch – Level 1, which means that travelers should practice usual precautions.
  - Avoid contact with birds or areas they may have contaminated.
  - Properly handle and cook poultry products.
- Resources:
  - Avian Flu Fact Sheet. [OSHA]
  - Summary of Key Information Practical to Countries Experiencing Outbreaks of A(H5N1) and Other Subtypes of Avian Influenza. [WHO]
  - Ensuring the Protection of Employees Involved in Highly Pathogenic Avian Influenza Control and Eradication Activities. [APHIS]
  - Avian Influenza Protecting Poultry Workers at Risk. [OSHA]
  - CDC Interim Guidance for Landfill Workers in the United States Disposing of Poultry Carcasses During Outbreaks of Highly Pathogenic Avian Influenza. [CDC]
  - Guidance for Protecting Employees Against Avian Flu. [OSHA]
  - FY2016 HPAI Response: Initial Recommendations on PPE for Selected Activities. [USDA]
  - How Infected Backyard Poultry Could Spread Bird Flu to People. [CDC]

- Guidance for Hunters – Protect Yourself and Your Birds from Avian Influenza. [APHIS]
- Protect Your Birds from Avian Influenza. [APHIS]
- Biosecurity for Birds. [APHIS] (Updated July 14, 2017)
- Influenza in Cats. [CDC]
- 2016 H5 HPAI around the World. [USDA]
- Avian Flu (H7N9) in China. [CDC]

Behavioral Health

- Integrate psychological support and education into all elements of preparedness and response.
- Maintain awareness of media reporting and social media rumors that may raise concerns among the public.
  - Building Workforce Resilience Through the Practice of Psychological First Aid. [ASPR]
  - Coping with Stress During Infectious Disease Outbreaks. [SAMHSA]
  - Talking with Children: Tips for Caregivers, Parents, and Teachers During Infectious Disease Outbreaks. [SAMHSA]
  - Taking Care of Your Behavioral Health: Tips for Social Distancing, Quarantine, and Isolation During an Infectious Disease Outbreak. [SAMHSA]
  - How to Cope with Sheltering in Place. [SAMHSA]

Administrative Preparedness

- Review emergency authorities and statutes to understand what relief resources may be available in the event of an emergency.
- Understand isolation and quarantine powers in your state relevant to animals and humans and the role emergency management may have in such situations. Federal isolation and quarantine are also authorized for influenza viruses that can cause a pandemic.
- Resources:
  - Regulations and Laws That May Apply During a Pandemic. [CDC]
  - 42 USC 264-272-Quarantine and Inspection. [GPO]
  - 42 CFR Parts 70 and 71-Control of Communicable Diseases. [Federal Register]

Recovery

- Use the HHS Response and Recovery Resources Compendium to search the repository of HHS products, services, and capabilities available to state, tribal, territorial, and local agencies before, during, and after public health and medical incidents.

National and International Plans and Resources

- Pandemic Influenza Plan: 2017 Update. (Updated July 14, 2017)
- National Strategy for Pandemic Influenza.

- North American Plan for Animal and Pandemic Influenza.
- WHO Pandemic Influenza Preparedness and Response Guidance Document.
- International Health Regulations.
- APHIS Highly Pathogenic Avian Influenza Response Plan – The Red Book.

Contributors and reviewers of this document include ***Joseph Annelli,*** *DVM, MS, USDA APHIS;* ***Erin Burns,*** *MA, Centers for Disease Control and Prevention;* ***Guillermo Aviles-Mendoza,*** *JD, ASPR Office of Emergency Management;* ***Elena Behnke,*** *DVM, USDA APHIS;* ***Denise Brinson,*** *DVM, MAM, USDA APHIS;* ***Lyndsay Cole,*** *USDA APHIS;* ***Patricia Fox,*** *DVM, MPH, USDA APHIS;* ***John Hick,*** *MD, ASPR and Hennepin County Medical Center;* ***Dan Hanfling,*** *MD, ASPR, Johns Hopkins Center for Health Security, George Washington University, and George Mason University School of Public Policy;* ***Rick Hunt,*** *MD, ASPR National Healthcare Preparedness Programs;* ***Rachel Kaul,*** *LCSW, CTS, ASPR Office of Policy and Planning;* ***Terri Postma,*** *MD, Centers for Medicare and Medicaid Services;* ***Connie Price,*** *MD, Denver Health and Hospital;* ***Lewis Rubinson,*** *MD, PhD, University of Maryland School of Medicine and University of Maryland Medical Center/R Adams Cowley Shock Trauma Center;* ***Mary Russell,*** *EdD, MSN, Boca Raton Regional Hospital;* ***Jerome Tokars,*** *MD, MPH, Centers for Disease Control and Prevention; and* ***Mia Kim Torchetti,*** *DVM, MS, PhD, USDA APHIS.*

Appendix A: ASPR Resources

PHE.Gov serves as the key one-stop website for all federal public health and medical information sources and assets. The site is searchable for multiple resources. http://www.phe.gov

The Technical Resources, Assistance Center, and Information Exchange (TRACIE) is a healthcare emergency information gateway that provides timely access to resources and promising practices, identifies and remedies knowledge gaps, and connects users with responses to a range of requests for technical assistance. https://asprtracie.hhs.gov/

The HHS Response and Recovery Resources Compendium is an easy to navigate, comprehensive, web-based repository of HHS resources and capabilities available to federal, state, local, territorial and tribal stakeholders before, during, and after public health and medical incidents.
http://www.phe.gov/emergency/hhscapabilities/Pages/default.aspx

Appendix B: Full References with Annotations

Animal and Plant Health Inspection Service. (n.d.). Highly Pathogenic Avian Influenza Webpage.

This webpage maintained by the U.S. Department of Agriculture's Animal and Plant Health Inspection Service features numerous avian influenza resources, including APHIS's response plan and goals, reference guides and standard operating procedures, and an HPAI web mapping tool showing locations of poultry farms, flyways, and other planning information. The page also includes response and policy information on topics including initial response; finance and administration; surveillance and diagnostics; quarantine, movement control, and continuity of business; disposal and cleaning/disinfection; recovery and restocking; and health and safety.

Centers for Disease Control and Prevention. (n.d.). Information on Avian Influenza.

This webpage collects information on current and historic avian flu situations, specific information on infections in birds and humans, and healthcare and laboratory guidance. The CDC continues to update content as more is learned about H7N9.

de Vries, R., Peng, W., Grant, O., et al. (2017). Three Mutations Switch H7N9 Influenza to Human-Type Receptor Specificity. PLOS Pathogens. 13(6):e1006390. (Included July 14, 2017)

The authors conducted mutation analyses to determine whether H7N9 is capable of acquiring human-type receptor specificity, which could enable effective transmission of the virus from human to human. They found that three amino acid mutations were needed to change specificity to human-type receptors.

European Centre for Disease Prevention and Control. (2017). Rapid Risk Assessment: Genetic Evolution of Influenza A(H7N9) Virus in China – Implications for Public Health, Sixth Update, 9 March 2017.

This document summarizes epidemiological and virological information on animal and human infections with H7N9 viruses and updates the risk assessment of the virus to public health.

Food and Agriculture Organization of the United Nations. (2017). H7N9 Situation Update.

The webpage, updated on a weekly basis, provides an overview of the current H7N9 situation, including updates on cases and deaths in humans and other animals and maps and graphs depicting the epidemiological situation and geographic reach.

Food and Agriculture Organization of the United Nations. (2008). Biosecurity for Highly Pathogenic Avian Influenza – Issues and Options.

This paper examines the state of knowledge of biosecurity in relation to highly pathogenic avian influenza H5N1 and presents issues and options for the domestic poultry and captive bird sectors.

Fournie, G., Hog, E., Barnett, T., et al. (2017). A Systematic Review and Meta-Analysis of Practices Exposing Humans to Avian Influenza Viruses, Their Prevalence, and Rationale. The American Journal of Tropical Medicine and Hygiene. (Included July 14, 2017)

The authors conducted a systematic literature review to identify practices associated with human infections of avian influenza, their prevalence, and rationale. They found that both direct and indirect exposure to poultry were associated with infection with all virus subtypes and all settings and that association with infection was stronger in markets than households, for sick and dead than healthy poultry, and for H7N9 than H5N1.

Huo, X., Chen, L., Qi, X., et al. (2017). Significantly Elevated Number of Human Infections with H7N9 Virus in Jiangsu in Eastern China, October 2016 to January 2017. Eurosurveillance. 22(13).

The authors conducted statistical analysis of human and environmental surveillance data, meteorological factors, and phylogenetic analysis on human cases of H7N9 virus infection between October 2016 and January 2017 in Jiangsu, China. Jiangsu is one of the most affected of the seven Chinese provinces that have seen human cases, and the number of human cases in Jiangsu during the ongoing fifth wave of the outbreak exceeds the combined total cases from the first four seasons. Despite greater treatment experience and a shorter interval between illness onset and use of antivirals, the authors observed an acceleration in disease progression with median time interval from onset of disease to intensive care unit admission dropping from 10 days in the first wave and 9 days in the second wave to 7 days in the last three waves and a median time interval from onset of disease to death in the fifth wave dropping to 13.5 days in comparison to a range of 15 to 28 days in previous waves. The number of human cases increased in December. The authors noted that the number of days in December with high risk ambient temperatures was also elevated, suggesting the need for further research. The environmental H7N9 detection rate was also elevated in December and the authors suggested that closures of live poultry markets may have contributed to a drop in cases in January. Other patient characteristics, exposure history to poultry or live poultry markets, and proportion of severe infections and deaths were similar in the fifth wave to previous waves.

Infectious Diseases Society of America. (2017). Animal Influenza Viruses of Zoonotic Concern. The Journal of Infectious Diseases. 216(suppl_4). (Abstracts only.) Included October 6, 2017.

The supplement contains a number of articles on avian and other animal influenza viruses of concern to humans.

Iuliano, A., Jang, Y., Jones, J., et al. (2017). Increase in Human Infections with Avian Influenza A(H7N9) Virus During the Fifth Epidemic – China, October 2016-February 2017. Morbidity and Mortality Weekly Report. 66(9):254-255.

This report notes an increase in human infections during the current season, though clinical characteristics and risk factors do not appear to have changed. The two distinct genetic lineages of the virus are showing indications of differences in cross-reactivity with existing candidate vaccine viruses and antiviral medications.

Jiang, H., Wu, P., Uyeki, T., et al. (2017). Preliminary Epidemiologic Assessment of Human Infections with Highly Pathogenic Avian Influenza A(H5N6) Virus, China. Clinical Infectious Diseases.

The authors analyzed data on laboratory-confirmed Asian lineage HPAI H5N1, H5N6, and H7N9 and found that epidemiologic characteristics and severity of infections of A(H5N6) were similar to those of A(H5N1) and more severe than A(H7N9).

Kile, J., Ren, R., Liu, L., et al. (2017). Update: Increase in Human Infections with Novel Asian Lineage Avian Influenza A(H7N9) Viruses During the Fifth Epidemic – China, October 1, 2016-August 7, 2017. Morbidity and Mortality Weekly Report. 66(35):928-932. (Included October 6, 2017)

This updated report reinforces previous findings of an increase in human infections of Asian lineage A(H7N9) during the fifth season, noting that human infections were reported in more Chinese provinces, regions, and municipalities than in the four previous seasons combined. The authors discuss the emergence of an HPAI mutation, the development of candidate vaccine viruses, and the isolation of two distinct lineages:

the Pearl River Delta lineage and the Yangtze River Delta lineage, with the Yangtze River Delta lineage predominating.

Lai, S., Qin, Y., Cowling, B., et al. (2016). Global Epidemiology of Avian Influenza A H5N1 Virus Infection in Humans, 1997-2015: A Systematic Review of Individual Case Data. The Lancet Infectious Diseases. 16(7):e108-e118. (abstract only)

This study examined 907 human cases of avian influenza A H5N1 from May 1997 to April 2015 to describe changes in global epidemiology. The authors describe an expansion in the number of affected countries from east and southeast Asia west through Asia to Africa. The authors noted a recent increase in cases in Egypt, but found no significant differences in comparison to earlier cases in epidemiological factors such as fatality risk, history of patient contact or exposure to poultry, and time from illness onset to hospital admission.

The Center for Food Security and Public Health and Institute for International Cooperation in Animal Biologics, Iowa State University. (2015). Avian Influenza.

This technical disease card provides detailed information on avian flu, including its etiology, species affected, geographic distribution, infection information in animals and humans, and extensive references.

World Health Organization. (2017). Analysis of Recent Scientific Information on Avian Influenza A (H7N9) Virus.

This analysis from February 10 provides currently known information on H7N9 geographic distribution in animals, cases of human infection, population immunity, disease severity, virology, antiviral susceptibility, and transmission models.

World Health Organization. (2017). Antigenic and Genetic Characteristics of Zoonotic Influenza Viruses and Development of Candidate Vaccine Viruses for Pandemic Preparedness.

This report summarizes antigenic and genetic characteristics of circulating zoonotic influenza viruses and their relevance to current candidate vaccine viruses.

World Organisation for Animal Health. (n.d.). Avian Influenza Portal.

This web page provides the latest updates on avian influenza and its possible effects on humans.

Xiang, N., Li, X., Ren, R., et al. (2016). Assessing Change in Avian Influenza A(H7N9) Virus Infections During the Fourth Epidemic – China, September 2015-August 2016. Morbidity and Mortality Weekly Report. 65(49):1390-1394.

The authors compared epidemiology and virology data from the fourth wave of human cases of avian influenza A H7N9 in China to the preceding waves. The fourth wave had a longer duration, greater geographic spread, a higher proportion of cases in rural areas, and higher percentage patients requiring admission to intensive care. However, the case fatality rate remained at approximately 40% and the authors found no evidence of sustained human to human transmission or increased transmissibility to humans from poultry or environmental exposures.

Zhou, L., Tan, Y., Kang, M., et al. (2017). Preliminary Epidemiology of Human Infections with Highly Pathogenic Avian Influenza A(H7N9) Virus, China, 2017. Emerging Infectious Diseases. 23(8):1355-1359. (Included October 6, 2017)

The authors compared characteristics of eight human infections of highly pathogenic Asian lineage A(H7N9) first identified in 2017 with human infections of low pathogenic Asian lineage A(H7N9) that have been occurring since 2013. They found the HPAI A(H7N9) patients significantly more likely to be hospitalized earlier, live in rural areas, and have exposure to sick or dead poultry. Statistical power to detect other differences in epidemiological characteristics or disease severity was limited by the small sample of HPAI A(H7N9) patients.

Zhu, W., Zhou, J., Li, Z., et al. (2017). Biological Characterisation of the Emerged Highly Pathogenic Avian Influenza (HPAI) A(H7N9) Viruses in Humans, in Mainland China, 2016 to 2017. Eurosurveillance. 22(19).

The authors examined the genetic sequence of highly pathogenic Asian lineage A(H7N9) sampled from infected humans in comparison with low pathogenic Asian lineage A(H7N9) virus samples. The HPAI virus showed a slightly increased binding preference for receptors in both the upper and lower human airways. The authors also found that the HPAI virus did not react strongly with the antisera of the vaccine strain recommended for LPAI A(H7N9) and that HPAI A(H7N9) with the 292K amino acid substitution in the NA protein, which could be acquired two days following administration of antiviral drugs, exhibited multi-drug resistance.