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Commentary

Highly pathogenic avian influenza: considerations for healthcare settings

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Abstract

In this manuscript, we discuss a systematic approach that healthcare facilities can adopt to prepare to identify, confirm, and safely manage highly pathogenic avian influenza in the healthcare setting.

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Current knowledge and background

Influenza A H5N1 also known as Highly Pathogenic Avian Influenza (HPAI), was first detected over 60 years ago among bird populations in Scotland.[1,2] In 2021, the H5N1 Clade 2.3.4.4b virus was found in birds in North America[1] and caused devastating losses to the poultry industry due to its rapid spread and lethality in birds.[3] A multistate outbreak of HPAI in dairy cows was first reported in the United States on March 25, 2024; since then, H5N1 has spread rapidly among cattle and other farm and wild mammals.[4] It is postulated that new mutations in the virus have enabled spread in mammalian species.[5] In cattle, the virus appears to concentrate in the mammary tissue with much lower concentrations in other organs; unpasteurized milk samples in North America reveal high levels of the virus though the risk of drinking these products remains unknown.[6]

Prior to 2024, sporadic human cases of HPAI were reported in 23 countries with a case fatality of > 50%[7] which may well be due to the ascertainment bias associated with testing only the sickest people; transmission of HPAI was primarily through contact with infected poultry. In 2024, most human cases of HPAI were reported among US farm workers with direct exposure to animals presumed or known to have been infected.[8] Infections were mild and, at the time of this writing, human-to-human transmission was not detected.[1] While there is evidence that HPAI has been transmitted to other animals through infected cow's milk, consumption of pasteurized milk products does not appear to be a mode of transmission to humans.[6,9]

In this manuscript, we discuss a systematic approach that healthcare facilities can adopt to prepare to identify, confirm, and safely manage HPAI in the healthcare setting.

Surveillance of H5N1 among people and animals

Human influenza surveillance

A key element of preparedness for healthcare facilities is staying abreast of the HPAI epidemiologic landscape. The Centers for Disease Control and Prevention (CDC) uses a variety of data sources to track influenza activity and severity, determine what strains of the virus are circulating, and detect the emergence of human cases of HPAI or other novel strains. Healthcare facilities can access this information, including data specific to their geographic region, on FluView[10] and FluView Interactive.[11]

CDC publicly reports U.S. influenza surveillance[12] in humans (Table 1):

- **Virologic Surveillance:** Since 2007, human infection with a novel influenza A virus has been a nationally notifiable condition in the United States. Hundreds of public health and clinical laboratories across the United States, Puerto Rico, and Guam participate in influenza surveillance through the U.S. World Health Organization Collaborating Laboratories System or The National Respiratory and Enteric Virus Surveillance System. Clinical and public health laboratories report each week to CDC the number of respiratory specimens tested for influenza and the number positive for influenza viruses.
- **Outpatient illness surveillance:** The United States Outpatient influenza-like Illness Surveillance Network (ILINet) monitors outpatient visits for respiratory symptoms (e.g. fever with cough and/or sore throat) across >3000 participating providers throughout the United States. In the absence of another explanation, an increase in influenza-like illness, particularly outside of the usual influenza season, could raise concerns for an emerging respiratory virus including HPAI.
- **Influenza hospitalizations:** The Influenza Hospitalization Surveillance Network (FluSurv-NET)[13] consists of population-based surveillance for laboratory-confirmed influenza-associated hospitalizations in 14 states, representing 9% of the United States population. A rapid rise or unseasonal spike in severe disease leading to hospitalization could indicate an emerging novel influenza virus. As of November 1, 2024, The Centers for Medicare and Medicaid Services requires all acute care hospitals to report admissions for respiratory infection to the National Healthcare Safety Network.

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Table 1. U.S. influenza surveillance

Human Influenza Surveillance[1]	
Virologic Surveillance	Public health laboratories submit a subset of specimens to CDC biweekly for genetic (next-generation sequencing) and antigenic (hemagglutination inhibition and neutralization assays) characterization as well as antiviral susceptibility.
Outpatient Illness Surveillance (ILINet)	Outpatient visits for respiratory symptoms (e.g. fever with cough and/or sore throat) across 3400 participating providers throughout the United States.
Inpatient Surveillance (FluSurv-NET)	Population-based surveillance for laboratory-confirmed influenza-associated hospitalizations in 14 states representing 9% of the United States population. Information regarding hospital and intensive care unit admissions for influenza is also reported to the National Healthcare Safety Network (NHSN).
Influenza Deaths	Data on mortality due to pneumonia, influenza and/or COVID-19 from death certificates obtained from state vital statistics offices.
Wastewater surveillance	To bolster monitoring for HPAI, wastewater surveillance is now being tested for the presence of influenza A.
State and Local Surveillance	Networks of healthcare facilities may work together to report rates locally and at the state level.
Animal Influenza Surveillance	
Virologic Surveillance	The US Department of Agriculture (USDA) routinely tests samples from wild birds for avian influenza viruses and provides information about where avian influenza has been detected. A national requirement issued by the USDA requires states to test lactating dairy cows for avian influenza before they are shipped across state lines only.

[1]Information summarized from CDC website: U.S. Influenza Surveillance: Purpose and Methods | CDC.

- **Influenza deaths**: The National Center for Health Statistics collects data on mortality due to pneumonia, influenza, and/or COVID-19 from death certificates obtained from state vital statistics offices.[14] Though it is a lagging indicator, an increase in influenza related deaths would warrant investigation into whether a new influenza strain has emerged in humans or an existing one has become more lethal.
- **Wastewater surveillance:** To bolster monitoring for HPAI, wastewater surveillance is now being tested for the presence of influenza A.[15] While current wastewater monitoring methods can distinguish influenza A viruses from influenza B, wastewater testing cannot determine the subtype or the source of influenza A. If wastewater levels indicate abnormally high levels of influenza, particularly outside of traditional influenza season, further investigation could be conducted regionally.
- **Animal influenza surveillance:** The US Department of Agriculture (USDA) routinely tests samples from wild birds for avian influenza viruses, and shares information regarding counties and jurisdictions where avian influenza has been detected in poultry and mammals.[16] Currently, the USDA only requires farms to test lactating dairy cows when they are moved across state lines.[17] There is little additional active surveillance of cattle or other mammals and scant publicly available information about animal testing compared to reporting of human surveillance for influenza.

Healthcare facilities should use the publicly available information to establish systems to monitor national, regional, and local influenza rates. However, there are several limitations to consider: (1) surveillance of hospitalization data reported by FluSurv-NET is limited to a small number of US hospitals, and (2) inherent delays in public reporting of national, state and county health department data. In order to fill these gaps, local and state health departments should facilitate the timely collection and sharing of influenza admission data among regional healthcare facilities. Dashboards or weekly reports indicating local number of positive tests for influenza, subtyping if available, and test positivity can help provide visibility regarding changing trends that might warrant closer attention and action. Rising rates of influenza-like illness, especially outside the usual influenza season, and/or increasing severity of illness (hospitalization and/or death) could indicate the emergence or spread of a novel strain including HPAI. This knowledge should be used by healthcare facilities to adjust screening, testing, and containment strategies.

Respiratory hygiene, screening, and testing for HPAI in healthcare settings

Standard Precautions include strategies that aim to minimize transmission of pathogens, including respiratory viruses, in healthcare facilities and should be in place and regularly emphasized regardless of the season and local influenza epidemiology.[18] Healthcare facilities should use messaging and/or signage (in a variety of languages or using pictograms) educating patients and visitors regarding basic strategies to minimize transmission of respiratory viruses, such as wearing a facemask when appropriate, performing hand hygiene, and covering mouth and nose with a tissue when coughing. Healthcare facilities can consider symptom screening at registration, especially at points of entry with individuals seeking care for acute illness (such as emergency departments and primary care clinics), with instructions on masking and physical distancing for those with respiratory disease manifestations, and should encourage the use of appropriate personal protective equipment (PPE) (i.e., N95 respirator or equivalent, gown, gloves and eye protection) by healthcare personnel (HCP) when caring for such patients.

To date, subtyping of influenza A to confirm HPAI is performed exclusively through state and regional public health laboratories or CDC, though some platforms cleared by the US Food and Drug Administration (FDA) that are used by clinical laboratories can distinguish between influenza A and B viruses as well as determine seasonal influenza A virus subtypes.[19] A heightened concern for HPAI should exist when a test has been identified by a clinical laboratory as influenza A and (1) does not match seasonal subtypes using a platform designed to detect seasonal subtypes (e.g. Biofire®) or (2) is identified as influenza A(H1) rather than A(H1) pdm09 (the seasonal H1 strain).[20]

Because resources for HPAI testing and isolation of suspected patients are finite, healthcare facilities must balance the risk of HPAI based on local epidemiology and patient characteristics with determining the need for further subtyping. A history of animal exposure, particularly dairy cattle and commercial poultry, and compatible symptoms for influenza should be considered a risk

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factor for HPAI anywhere in the United States during times when the virus is circulating on farms. However, at this time, it is not resource-efficient to universally screen every patient with respiratory symptoms for this exposure. Instead, healthcare facilities that serve a large number of farm workers, particularly in states with active outbreaks, should screen all patients with respiratory symptoms (e.g. conjunctivitis, upper or lower respiratory tract symptoms) for animal, farm, or animal product (e.g. unpasteurized milk) exposure. Clinicians such as those in the ED and primary care offices, but also including ophthalmologists, who do not typically evaluate patients for influenza, should be alerted that HPAI can present with conjunctivitis alone. In areas without known cases or active HPAI outbreaks, HCP should preferentially screen for these exposures among patients who have tested positive for influenza A (or non-typeable or untyped influenza) during times of low levels of circulating influenza or if wastewater surveillance suggests unexpected presence of influenza virus outside of the normal influenza season.

It is important to recognize that not every patient with a high-risk exposure for HPAI will have HPAI, nor will it always be possible to subtype every positive influenza A specimen for HPAI. Positive influenza A specimens obtained from patients with compatible animal or animal product exposure should be subtyped. In addition, HPAI testing of influenza A positive specimens should be performed in specific clinical settings, which include: (1) patients with non-farm animal exposure (e.g. hunting, backyard chickens, live animal market, etc), (2) patients who are part of unusual clusters of severe disease, (3) patients from communities with multiple cases of HPAI or documented human-to-human spread, and (4) patients who may have been in contact with a known human infection.

Even in the absence of a substantial number of human HPAI cases, if all positive influenza A specimens from symptomatic patients with epidemiologic risk factors were sent to reference laboratories for subtyping, a busy influenza season in a region heavily populated with farm workers could quickly overwhelm the capability of these reference laboratories to provide timely results, which could lead to prolonged periods of unnecessary isolation of patients who are suspected to have HPAI in private hospital rooms, in turn overwhelming the capacity of healthcare facilities. Therefore, it is critical that federal authorities and test manufacturers work together now to facilitate commercialization of testing, in order to increase availability and reduce turnaround time. We have learned from the COVID-19 pandemic that, depending on the clinical scenario, there is a role for both laboratory-based and rapid point-of-care testing modalities for respiratory viruses. The May 2024 FDA decision to provide greater oversight of laboratory developed tests has the potential to impede hospitals' ability to develop in-house testing capacity quickly during a pandemic.[21]

HPAI transmission and approaches to isolation

There are several important considerations for healthcare facilities in determining the best approach to isolation of hospitalized patients with suspected or confirmed HPAI. As we learned during the COVID-19 pandemic, the approach used to prevent disease transmission depends on the overall goals: containment requires aggressive strategies that are intended to prevent all transmission while less aggressive mitigation strategies may be utilized when disease transmission outpaces containment or when countermeasures such as effective vaccines and therapies are widely available.[22]

While the risk of HPAI human-to-human transmission is low today, a containment strategy is appropriate given the theoretical potential for mutation of the virus to one that is more transmissible, and the devastating consequences to society should that occur. With little to no population immunity, morbidity and mortality could be high depending on the virulence of a new variant. Personal protective equipment shortages were a widespread problem during the early months of the COVID-19 pandemic, and healthcare facilities may need to resume the use of supply dashboards and conservation measures if the HPAI outbreak grows larger. Healthcare facilities should clearly communicate goals and rationale for containment vs. mitigation strategies with HCP, patients, and visitors, and also prepare for strategies to evolve as more information becomes available and the epidemiology is better understood. To illustrate, CDC currently recommends placement of a patient with suspected HPAI in a single-patient airborne infection isolation room (AIIR) and rapid implementation of Airborne (use of an N95 respirator or equivalent) and Contact (use of gowns and gloves) Precautions with the additional use of eye protection, in addition to Standard Precautions.[23] CDC recommends that HCP who are potentially exposed to patients with HPAI be excluded from work until 10 days after their last exposure while monitoring for signs and symptoms of respiratory illness.[23] In contrast, for non-HPAI influenza, CDC recommends placing the patient in a private room with Droplet Precautions and does not make any specific recommendations for exposed asymptomatic HCP.[24] It is likely that, over time, the strategies for prevention of HPAI transmission could change to more closely resemble those used for non-HPAI influenza. Further, if the number of patients with suspected HPAI exceeds the number of available AIIRs in a healthcare facility, it is entirely reasonable to adapt healthcare facility-specific policies to allow placement of those patients in neutral pressure rooms with the door closed. Healthcare facilities should communicate those potential changes and the rationale in advance to engender trust among HCP and patients and prevent the fear that is inherently associated with de-escalation of mitigation measures.

Prevention

Clinicians should counsel patients about how to avoid HPAI exposure in the community. CDC recommends that people refrain from unprotected exposure to sick or dead animals including wild birds, chickens, and other wild or domesticated animals, as well as to animal feces, litter, or materials contaminated by birds or other animals with suspected or confirmed HPAI virus infection.[25] Communication channels developed during the COVID-19 pandemic should be leveraged to disseminate messages to the public.

Lessons from the COVID-19 pandemic have also shown that rapid scale-up of large vaccination centers, including those based in some healthcare facilities, is a critical public health strategy.[26] While there is no HPAI vaccine currently available, early preparation for influenza vaccination sites will minimize the time required to vaccinate people if it becomes necessary.

For individuals who have been exposed (without proper PPE) to a known case of HPAI in the community or a healthcare setting, post-exposure prophylaxis with oseltamivir is recommended. Because of the potential for severe disease, CDC recommends the use of treatment dosing (twice daily for 5 days) to avoid subtherapeutic levels of antiviral that might lead to the emergence of drug-resistant strains. Barring the emergence of new mutations

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Table 2. Highly Pathogenic Avian Influenza (HPAI) summary: key considerations for healthcare facilities

HPAI epidemiologic landscape
• CDC uses a variety of data sources to track influenza activity and severity, determine what strains of the virus are circulating, and detect the emergence of human cases of HPAI or other strains new to humans. Healthcare facilities can access this information, including data specific to their geographic region, on FluView and FluView Interactive. • Healthcare facilities should use the publicly available information to establish systems to monitor national, regional, and local influenza rates.
Respiratory Hygiene, Screening and Testing
• Healthcare facilities should make use of messaging and/or signage educating patients and visitors regarding basic strategies to minimize transmission of respiratory viruses. • To date, subtyping of influenza A to confirm HPAI is performed exclusively through state and regional public health laboratories or CDC, which may impede turnaround time. • At this time, it is not resource-efficient to universally screen every patient with respiratory symptoms about a relevant exposure. • Positive influenza A specimens obtained from patients with compatible animal or animal product exposure should be subtyped.
HPAI Transmission and Approaches to Isolation
• Given the potential for genetic mutation conferring enhanced human-to-human transmission, it is reasonable to aim for containment of HPAI as opposed to mitigation in healthcare settings. • Healthcare facilities should clearly communicate goals and rationale for containment vs. mitigation strategies with healthcare personnel, patients, and visitors, and also prepare for strategies to evolve as more information becomes available and the epidemiology is better understood.
Prevention
• Clinicians should counsel patients about how to avoid HPAI exposure in the community. • Exposed individuals should receive prophylaxis with oseltamivir. • Early preparation for influenza vaccination sites will minimize the time required to vaccinate people if it becomes necessary.
Communication
• Healthcare epidemiologists and infection preventionists, who serve as trusted sources of information, should play a prominent role in the healthcare facility's response to HPAI. • The rationale for specific policies and procedures should be clearly conveyed, along with changes that are anticipated as more information becomes available and the outbreak evolves. • Effective communication should carefully balance the need to inform the public while minimizing the risk of causing alarm or panic.

that confer resistance, clinical[27] and phenotypic evidence[28] suggest that oseltamivir will be effective for both treatment and prophylaxis of HPAI. In the event of a larger outbreak, rapid scale-up of trials of therapeutics for treatment and prevention should be prioritized. Head-to-head studies of existing antivirals should be conducted. Funding should be directed to development of new compounds such as monoclonal antibodies.

Conclusions and recommendations for healthcare facilities (summarized in Table 2)

The current risk of transmission of HPAI among the general public is low, though individuals with direct exposure to infected birds or cattle are at higher risk for infection.[8] However, even people who report high-risk exposures may not develop HPAI, as indicated by the extensive negative testing of contacts and high-risk individuals.[8]

Healthcare facilities should consider the possibility of an increase in HPAI cases and human-to-human transmission while also balancing resource allocation appropriately given available information about disease transmission and severity. While there is extensive human influenza surveillance publicly available, we recognize the lack of information regarding HPAI prevalence among cattle makes it difficult to know the true prevalence of HPAI in a region. Healthcare facilities should stay abreast of national, regional, and local epidemiology as it relates to HPAI.

If the number of human cases rises, access to timely, effective tests will be essential. However, currently, clinical laboratories cannot subtype influenza virus to confirm HPAI. Therefore, healthcare facilities in regions where HPAI has been confirmed should focus on screening appropriate patients with influenza-like symptoms for possible farm or animal exposure and determining the need to send positive influenza A specimens for subtype confirmation. In accordance with CDC recommendations, we agree that testing for HPAI should only be conducted among patients with compatible symptoms and high-risk exposures. As we learned during the COVID-19 pandemic, stewardship of viral diagnostic tests in healthcare facilities is prudent and helps to maintain supplies, control costs, and avoid unnecessary isolation and delays in care.[29] Considering that, to date, nearly all HPAI have been detected among persons with exposures to farm animals in certain states, implementing the blanket use of screening questions regarding animal exposure among patients presenting to hospitals located in urban areas may not be worthwhile given the resources such screening would require (e.g. intensive education, auditing of practice, and changes to the point-of-entry registration process). Additionally, healthcare facilities should prepare for large-scale vaccination sites that provide a convenient location to quickly vaccinate people if necessary.

An important lesson from the COVID-19 pandemic is that transparency is vital for building public trust. Healthcare epidemiologists and infection preventionists, who serve as trusted sources of information, should play a prominent role in the healthcare facility's response to HPAI. The rationale for specific policies and procedures should be clearly conveyed, along with changes that are anticipated as more information becomes available and the outbreak evolves. Effective communication should carefully balance the need to inform the public while minimizing the risk of causing alarm or panic. Balancing public safety with protecting personal freedoms is crucial and any strategies used to prevent the spread of HPAI should strive to maintain that equilibrium.

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