Background

Wild birds are the natural reservoir for influenza A viruses. These viruses are well adapted to the bird hosts and therefore are called avian influenza (AI) viruses, in contrast to human-adapted influenza A viruses that cause seasonal flu. \(^1\) AI viruses can be of many genotypes based on their surface antigens—hemagglutinin (H) and neuraminidase (N)—and are frequently found in both wild birds and domestic poultry. Those that cause little or no apparent illness are referred to as low pathogenic avian influenza (LPAI). \(^2\) On occasion, some of these viruses will acquire a mutation that makes them highly pathogenic to poultry and other birds with near 100% mortality, collectively referred to as highly pathogenic avian influenza (HPAI). LPAI viruses are often implicated in outbreaks in poultry and pig farms in the US and globally. \(^3\)

HPAI of the H5N1 genotype was first discovered in the late 1990s in China. In 2002, an outbreak in Hong Kong caused the first recognized human outbreak. \(^4\) Since then, a total of 882 human cases have been detected across 23 countries with a 50% case fatality ratio. \(^5\) Globally, human HPAI H5N1 cases peaked during the 2015 Egypt outbreak, and since then there have been very few human cases detected. \(^6\) However, since 2022, a new panzootic of H5N1 has circulated in birds that has also caused outbreaks among several types of mammals, often with high mortality, increasing the possibility of spillover events and human H5N1 outbreaks. \(^7\)

The range of symptoms experienced by humans infected with novel influenza A viruses varies and can be difficult to predict. Human disease can vary from no symptoms to mild illness such as conjunctivitis, fever, and cough, to severe conditions like rapid-onset pneumonia, or acute respiratory distress syndrome. Novel influenza A viruses are of significant public health concern due to the lack of existing immunity in the human population, and the potential for them to be highly transmittable and cause a wide range of disease in humans. \(^8\)
**Current Situation**

On March 25, 2024, the US Department of Agriculture’s Animal and Plant Health Inspection Service reported that samples from sick cattle collected from 2 dairy farms in Kansas and 2 in Texas tested positive for highly pathogenic avian influenza (HPAI). Further testing in the local areas confirmed AI in flocks of deceased birds, leading investigators to conclude that the cases in cows may be due to infection from the wild bird population. These cases represent the first recorded instances of bovine H5N1 infection. Among infected herds, an estimated 10% of cattle are infected. Since the first detection, a total of 34 farms across 9 states have identified outbreaks in dairy herds.

Several days following confirmed bovine cases at a Texas farm, an individual working closely with the cattle reported developing conjunctivitis and was presumed to be infected with H5N1. Respiratory and conjunctival specimens were collected, and initial influenza A and subtype testing at Texas Tech University determined specimens were presumptive positive for H5N1. Subsequent RT-PCR testing by the Centers for Disease Control and Prevention (CDC) confirmed high pathogenicity avian influenza (HPAI) A(H5N1) virus clade 2.3.4.4b. The affected individual experienced only conjunctivitis and recovered at home. Both the case and their close contacts were offered oseltamivir (Tamiflu), a standard flu treatment, and contacts did not report symptoms. This individual is only the second human case of H5N1 recorded in the United States; the first was identified in Colorado in 2022 in a person involved in culling birds at commercial poultry factory.

Genetic analysis of the specimen collected from the Texas case revealed only minor changes in the genetic sequence. One of the genetic mutations (PB2 E627K) is known to be associated with viral adaptation for replication within mammalian hosts. The mutation has been detected before in people and other mammals infected with HPAI A(H5N1) virus, as well as other avian influenza subtypes (e.g., H7N9) involved in previous outbreaks. However, there were no specific mutations detected that were associated with adaptation for human-to-human transmission.
Human Infection Prevention and Control

Poultry farmers and workers, backyard bird flock owners, livestock farmers and workers, veterinarians and veterinary staff, and other workers and responders may be at increased risk for potential exposure to H5N1. According to CDC recommendations, farmers, workers, and responders should avoid unprotected direct physical contact or close exposure with sick or dead animals or animal materials. This includes carcasses, feces, milk, or litter. When in direct contact with these materials, farmers, workers, and responders should wear recommended personal protective equipment (PPE) such as an N95 filtering facepiece respirator, eye protection, and gloves, and perform thorough hand washing after contact.15

In healthcare settings, clinicians should consider the possibility of HPAI A(H5N1) virus infection in persons showing signs or symptoms of acute respiratory illness who have relevant exposure history. For health care professionals treating patients with suspected or confirmed novel influenza A infection, assuming no or few confirmed cases of H5N1 in the US, current CDC guidance recommends contact and airborne precautions in addition to standard precautions.16,17 A list of case definitions for novel influenza A virus are available on the CDC website.18

Laboratory Testing and Diagnosis

The same tests used for seasonal flu would most likely detect H5N1 viral infections because both viruses are influenza A; however, these standard tests cannot determine if the strain is H5N1. For patients presenting with flu-like symptoms and exposure to animals affected with H5N1, dairy farms, or unpasteurized dairy products, providers should consider ruling out H5N1 by collecting an additional specimen to test for influenza A H1N1 or H3N2.19 Most healthcare facilities have the capacity to complete H1N1 and H3N2 testing, as these subtypes commonly circulate among humans. If a test is positive for influenza A and negative for H1N1 and H3N2, this may indicate H5N1 infection, and specimens should be sent to the state health department for H5N1 testing. There are a total of 99 public health laboratories across the US that are equipped with the subtyping assays to detect novel H5N1. The CDC is also fully equipped to complete confirmatory testing as needed.5
**Treatment**

CDC’s preliminary analysis of A(H5N1) viruses indicate that the current FDA-approved flu antiviral medications are likely effective against this virus.¹ Interim CDC guidance states that all patients with possible H5N1 infection be treated with antivirals as soon as possible. Treatment should not be delayed pending test results, even if more than 48 hours have elapsed since symptom onset. For outpatients, oseltamivir (Tamiflu) is the preferred antiviral agent, administered twice daily for a duration of 5 days, regardless of symptom onset timing. For patients hospitalized with severe pneumonia, clinicians should consult the CDC Influenza Division in partnership with their state health department. Healthcare providers should exercise clinical judgement, particularly regarding patients with resolving symptoms, when determining the need for antiviral therapy.²⁰

**Vaccines**

Currently, seasonal flu vaccines do not protect against the novel H5N1 strain. However, human vaccination against H5N1 is not appropriate at this time, as H5N1 continues to be mostly an animal health issue. If vaccination becomes necessary, the Biomedical Advanced Research and Development Authority’s (BARDA) National Pre-pandemic Influenza Vaccine Stockpile (NPIVS), in partnership with CDC, FDA, and NIH, has prepared relevant candidate virus vaccines, appropriate medical stockpiles, and industry contracts to streamline development, clinical trials, scale-up, and deployment of vaccines for the public.²¹,²²

Although US public health and medical agencies are engaged in constant preparedness initiatives to reduce the time necessary to make a vaccine readily available in the event of a human H5N1 outbreak, vaccines would likely not be available for weeks to months, and nonpharmaceutical initiatives such as isolation, quarantine, and masking would likely still be a necessary aspect of the public health response.
References


