KEY POINTS:
First Reported Case of Avian Influenza A (H5N1) Virus Infection in a Human in the Americas

SITUATION SUMMARY

- On January 8, 2014, Canada reported a confirmed case of human infection with a highly pathogenic avian influenza A (H5N1) virus in a patient who died, and CDC received isolates of the H5N1 virus for laboratory testing.
- Laboratory testing in Canada confirmed this virus to be the same as the highly pathogenic avian influenza A (H5N1) viruses that have been reported in poultry in Asia, Africa and Europe and that have resulted in more than 600 reported human infections.
- A manuscript describing additional laboratory findings was published on February 7, 2014, in the journal *Emerging Infectious Diseases*, and is summarized below in the section "Genomic analysis of an H5N1 virus isolated from a fatal case in a Canadian traveler".
- The Canadian patient had recently traveled to Beijing, China, where highly pathogenic avian influenza A H5N1 is endemic (ever-present) among poultry.
- Canadian public health authorities investigated the situation. No additional cases of H5N1 in Canada were detected. Canadian health reported this as an isolated, imported case of H5N1 virus infection.
- This is the first detected case of human infection with highly pathogenic avian influenza A H5N1 virus in North or South America.
- It also is the first case of human infection with highly pathogenic H5N1 ever imported by a traveler into a country where this virus is not present in poultry.
- Highly pathogenic H5N1 viruses have NOT been detected in people or in animals in the United States.
- Rarely, cases of human infection with highly pathogenic H5N1 virus have occurred after exposure to infected poultry or contaminated environments.
- While human infection is rare, it often results in serious illness with very high mortality (60%).
- At this time, highly pathogenic H5N1 viruses do not spread easily from person to person.
- Most of the human cases of infection with this virus in other parts of the world have resulted from direct or close contact with infected poultry (e.g., domesticated chickens, ducks and turkeys) or surfaces contaminated with poultry excretions, or with visiting live poultry markets in countries where these viruses are endemic among poultry.
- Transmission of avian influenza viruses, including highly pathogenic H5N1 viruses, from person-to-person is uncommon, and when it occurs, is not sustained.
- The few cases of person-to-person transmission with highly pathogenic H5N1 that have occurred in other parts of the world are thought to have resulted after prolonged and close unprotected contact with someone who is very sick with H5N1 virus, usually among family members.
- The current health risk posed by detection of one case of H5N1 in Canada is very low.

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- "Novel influenza A infections" such as H5N1, have been nationally notifiable diseases in the United States since 2007.
- Novel influenza A virus infections include all human infections with influenza A viruses that are different from currently circulating human seasonal influenza H1 and H3 viruses. These viruses include those that are subtyped as nonhuman in origin and those that are unsubtypable with standard laboratory methods and reagents.
- Rapid reporting of human infections with novel influenza A viruses facilitates prompt detection and characterization of influenza A viruses and accelerates the implementation of effective public health responses.
- The United States has had enhanced surveillance measures to detect possible cases of H5N1 in place since 2003.
- While the current risk from H5N1 virus is low and CDC believes it very unlikely that cases of H5N1 have occurred in the United States, on January 15, 2014, CDC sent out a reminder to clinicians in this country about when and how to test for H5N1 infection.

Genomic analysis of an H5N1 virus isolated from a fatal case in a Canadian traveler

- On February 7, 2014, an article titled "Full-Genome Analysis of Avian influenza A(H5N1) Virus from a Human, North America, 2013", coauthored by CDC and Canadian public health experts, was published in the peer-reviewed journal *Emerging Infectious Diseases*.
- This article describes results of full-genome sequence analysis of an influenza A (H5N1) virus that was isolated from an infected patient and reported by Canadian health officials on January 8, 2014. Some key laboratory results from the paper are listed below.
- This H5N1 virus isolate is similar to avian influenza A (H5N1) viruses that have been detected in other parts of the world, but is considered a "reassortant virus" because it has one gene derived from a different avian influenza virus subtype.
- "Reassortant" viruses are the outcome of "reassortment." Reassortment typically occurs when a host – animal or human – becomes infected with two or more different influenza viruses at the same time. This allows the influenza viruses to mix and exchange genetic information with each other, which in turn, can result in the emergence of new influenza viruses.
- Seven of the virus's eight genes are closely related to previously recognized H5N1 viruses. The virus's PB2 gene is related to avian influenza A (H9N2) viruses detected in China.
- Over time, H5N1 viruses have evolved into different groups called "clades". The virus isolate's hemagglutinin gene (HA) belongs to Clade 2.3.2.1c. H5N1 Clade 2.3.2.1c viruses have been detected in China and other Asian countries.
- Analysis of the HA protein sequence suggests the H5N1 virus isolate does not have the ability to easily bind to mammalian upper respiratory cells.
- Additional analysis of the other viral protein sequences show that a well-known characteristic of the PB2 gene that is associated with adaptation to mammals is not present in this virus.
- Comparison of the HA gene of this H5N1 virus isolate to the Clade 2.3.2.1c WHO candidate vaccine virus (A/duck/Vietnam/NCVD-1584/2012) shows there are very few amino acid changes. This suggests that a flu vaccine developed from the candidate vaccine virus would likely provide some protection against this H5N1 virus.

- No mutations were detected that are predicted to confer resistance to either class of antiviral medications used to treat influenza (adamantanes, neuraminidase inhibitors).
- The article is available at http://wwwnc.cdc.gov/eid/article/20/5/14-0164_article.htm.

CDC Interim Guidance

- A CDC Health Advisory was distributed via the CDC Health Alert Network on January 15, 2014, and is available at http://emergency.cdc.gov/HAN/han00360.asp.
- CDC recommends that clinicians consider the possibility of avian influenza A (H5N1) virus infection in persons exhibiting symptoms of severe respiratory illness who have appropriate travel or exposure history.
- State health departments are encouraged to investigate potential human cases of avian influenza A (H5N1) virus infection and should notify CDC within 24 hours of identifying a probable or confirmed case of novel influenza A virus infection, including avian influenza A (H5N1) virus infection
- Potential cases of human infection with influenza A (H7N9) virus should also be investigated, using current case definitions and testing recommendations for avian influenza A (H7N9) virus (http://www.cdc.gov/flu/avianflu/healthprofessionals.htm).
- CDC is currently updating several of the H5N1 and general avian influenza interim guidance documents. When finalized, the updated documents will be posted to http://www.cdc.gov/flu/avianflu/healthprofessionals.htm.
- For the most up-to-date recommendations regarding case investigations, testing, infection control, treatment and prophylaxis for avian influenza A (H5N1) virus infection, please see http://www.cdc.gov/flu/avianflu/healthprofessionals.htm.
- Updated case definitions for influenza A (H5N1) and influenza A (H7N9) are now available at http://www.cdc.gov/flu/avianflu/healthprofessionals.htm.
- Please note that until the updated documents are posted, and in instances when only H7N9 guidance is currently available, it is appropriate to use the H7N9 guidance for issues related to all human infection with avian influenza viruses that cause severe illness in people.
- More information about H5N1 is available on the CDC website at http://www.cdc.gov/flu/avianflu/h5n1-virus.htm.
- At this point, there are no special actions that the U.S. public needs to take regarding H5N1 virus.
- More concerning for Americans right now is seasonal flu, which is widespread in much of the country. People who have not gotten their seasonal flu vaccine yet this season should get one now. For many, it's not too late to benefit from vaccination this season. A seasonal vaccine will protect you against seasonal flu viruses.
- For people traveling to China, CDC would have the same recommendations for protecting against H5N1 as we do against H7N9 or other avian influenza A viruses.
- This information is available on the CDC website at http://wwwnc.cdc.gov/travel/diseases/avian-bird-flu.

H5N1 IN CHINA

- As mentioned previously, avian influenza A H5N1 is endemic in poultry in China.
- Since January 1, 2003, 45 cases of human infection with highly pathogenic influenza A H5N1 have been reported in China and 30 (67%) have died (according to the latest WHO cumulative report, published on January 24, 2014).
- Cases have ranged in age from 2 years to 62 years, but the average age is 26 years.
- The most recent cases reported were in February 2013 in Guizhou, a province in central southern China.
- Two cases of H5N1 have been reported in Beijing, one in 2003 and another in 2008.

PANDEMIC THREAT

- The detection of one isolated case of H5N1 virus infection in a returned traveler does not signal the start of a pandemic.
- Two of the main criteria of a pandemic—the appearance of a new influenza virus which causes human illness, and for which people have little or no protection—first occurred more than 10 years ago. However, the third criteria of a pandemic—the easy and repeated spread of the virus from person to person—has not occurred.
- This isolated case does not change the current risk assessment for pandemic potential.
- A pandemic would only result if the H5N1 virus were to gain the ability to spread efficiently from person to person.
- There is no indication that this has occurred.

WHAT CDC AND OTHER HHS AGENCIES ARE DOING

- CDC has been collaborating closely with Canadian public health partners and has provided laboratory and other support as needed.
- CDC has issued a reminder to health care professionals about guidance for testing for H5N1. The Health Advisory is available at http://www.bt.cdc.gov/HAN/han00360.asp.
- CDC provided support to the Public Health Agency of Canada on follow-up with American passengers who may have been exposed to the ill person during their travel.
- After receiving passenger information from the Public Health Agency of Canada, CDC notified state public health officials so that they could contact U.S. residents who were on the same flights with the ill traveler.
- There were 14 U.S. passengers from five states (Alaska, Washington, Illinois, California, and Texas) who shared a flight(s) with the ill Canadian passenger.
- State health officials followed up with these passengers and no cases of H5N1 were identified.
- Although the risk of getting sick from sharing an airplane with someone infected with this type of flu is very low, public health officials were checking to ensure that passengers did not experience any influenza-like-illness symptoms within 10 days of their flight.
- (The longest incubation period ever seen for H5N1 transmission has been 10 days.)

- CDC, NIH and the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR) will continue to monitor this situation closely and work with public health partners to rapidly test specimens and advise local and state authorities regarding control measures.
- CDC will continue to work closely with ASPR's Biomedical Advanced Research and Development Authority (BARDA) and the National Institutes of Health on long-term preparedness measures.
- Long-term preparedness measures against H5N1 include a stockpile of FDA-approved H5N1 vaccine maintained by vaccine manufacturers as well as a stockpile of the components to produce additional H5N1 vaccine quickly. These measures also include a supply of both FDA-approved antiviral drugs (Tamiflu and Relenza) in the Strategic National Stockpile (SNS).
- BARDA continues to support advanced development of new influenza vaccines and antiviral drugs, partnering with manufacturers that have broad experience in producing vaccines and antiviral drugs for novel influenza viruses. With these partners, BARDA has supported development of vaccines for H5N1, as well as the 2009 H1N1 virus, H7N1, H3N2v, and H7N9.

WHAT YOU CAN DO

- No human cases of infection with this H5N1 virus have been identified in the United States to date. At this point, there are no special actions that the U.S. public needs to take regarding H5N1 virus.
- More concerning for Americans right now is seasonal flu, which is widespread in much of the country. People who have not gotten their seasonal flu vaccine yet this season should get one now. For many, it's not too late to benefit from vaccination this season. A seasonal vaccine will protect you against seasonal flu viruses.
- CDC has posted a travel health notice (Level 1, Watch) with recommendations for travelers to prevent H5N1. This information is available on the CDC website at http://wwwnc.cdc.gov/travel/notices/watch/h5n1-avian-flu-imported-case-canada.

BACKGROUND

- H5N1 is a virus that occurs mainly in birds, is highly contagious among birds, and can be deadly to them, especially domestic poultry.
- Since November 2003, highly pathogenic avian influenza A (H5N1) virus infections in birds have been reported in Asia, Africa, the Pacific, Europe and the Near East.
- H5N1 viruses are considered endemic (ever-present) in poultry in at least six countries (alphabetically: Bangladesh, China, Egypt, India, Indonesia and Vietnam) with sporadic detection in wild birds and poultry outbreaks occurring in other countries.
- HPAI H5N1 viruses also are circulating among poultry with periodic outbreaks in other countries in those regions.
- From 2003 through January 24, 2014, 650 laboratory-confirmed human cases with H5N1 virus infection have been officially reported to WHO from 15 countries.
- Of these cases, 386 died (59%).
- Human cases of H5N1 virus infection are rare and sporadic events, occurring mostly in areas where the virus is circulating endemically in poultry and following close contact with infected wild birds or poultry.

- Limited non-sustained person-to-person spread of H5N1 viruses is thought to have occurred in the past.
- This includes "clusters" of cases that have occurred within families.
- Clusters of human H5N1 cases, usually 2 cases but ranging from 2-8 cases per cluster, have been identified in several countries.
- Nearly all of the clusters have occurred among blood-related family members, especially those living in the same household.
- In cases where limited human-to-human transmission of H5N1 virus is thought to have occurred, spread occurred after a very long period of unprotected close contact (hours in length) with a very sick blood-related infected family member (e.g., mother-daughter or brother-brother). There has been one reported case of limited, non-sustained human to human transmission of H5N1 virus from a patient to a non-blood related health care worker. These cases reportedly occurred in a home and in a hospital room.
- So far, however, the spread of H5N1 virus from person-to-person has been very rare, limited, and not sustained.
- At the current time, there is no ongoing transmission of any avian influenza A viruses in humans, including H5N1 viruses.
- However, the H5N1 epizootic poses an important public health threat.
- Influenza viruses evolve and swap genes frequently.
- If H5N1 viruses gain the ability for efficient and sustained transmission among humans, an influenza pandemic could result, with potentially high rates of illness and death worldwide.
- As standard procedure for a virus with pandemic potential, in 2004, BARDA, within the HHS Office of the Assistant Secretary for Preparedness and Response, began working with private industry to develop the essential components of a vaccine.
- Since 2005, BARDA has worked with manufacturers to maintain the domestic pre-pandemic stockpile to produce vaccine quickly should it be needed to protect against H5N1.
- The stockpile includes two H5N1 vaccines licensed in the United States. One is made by Sanofi and was approved by the Food and Drug Administration in 2007. The other, called Q-PAN H5N1, is made by GlaxoSmithKline and was approved by FDA in 2013. This vaccine includes an adjuvant which helps the body mount a better immune response. The adjuvant is an "oil-in-water" adjuvant called AS03. It is a squalene-based adjuvant. Squalene is a natural, organic ingredient found in high concentrations in shark livers, rice bran, wheat germ and olives. The squalene used in this vaccine comes from shark livers.
- The pre-pandemic stockpile also includes a bulk supply of vaccine antigen for four H5N1 virus strains and two vaccine adjuvants. Both stockpiled for the H5N1 vaccine are "oil-in-water" adjuvants, AS03 and MS59. Both are squalene-based adjuvants.
- Adjuvanted vaccine requires less antigen (the part of the vaccine that stimulates an immune response against the H5N1 virus), which means more doses of vaccine can be made available and more people can be protected against H5N1 if the virus spreads from person to person. Because the use of an adjuvant allows for an increased number of available doses, adjuvanted vaccine can help with faster implementation of a vaccination campaign in the event of a pandemic.
- Clinical studies of these H5N1 vaccines show that two doses of either vaccine are needed to produce a protective immune response against H5N1.

- This antigen and adjuvant can be used by vaccine manufacturers to finish manufacturing vaccine quickly. The vaccine can be filled in multi-dose vials by domestic vaccine manufacturers and the new BARDA fill-finish manufacturing network within 4-6 weeks and then distributed for use.
- With this pre-pandemic stockpile, manufacturers could produce 16.5 million doses of vaccine without adjuvant or nearly 400 million doses of vaccine with the adjuvant.
- Antiviral drugs have been shown to be effective against influenza viruses when used to treat people who have become ill from the virus or to prevent illness in people who have been exposed but are not yet sick. HHS maintains a stockpile of 68 million treatment courses of influenza antiviral drugs at the Strategic National Stockpile, managed by CDC. This stockpile includes various formulations of both FDA-approved antiviral drugs, Tamiflu and Relenza.
- BARDA is supporting advanced development of new antiviral drugs that are in the last stages of clinical evaluation for safety and efficacy. In a public health emergency, there are investigational drugs that could be used if authorized for emergency use by FDA. These investigational products include intravenous antiviral drugs for hospitalized patients.
- Because some influenza viruses have been shown to develop resistance to currently approved antiviral drugs, BARDA continues to support the development of new influenza drugs that work differently than traditional antiviral drugs. Some of the new drugs in development target infected cells in the person rather than the virus to decrease the chances of developing resistance.
- The Centers for Disease Control and Prevention (CDC), the HHS Office of the Assistant Secretary for Preparedness and Response, the National Institutes of Health, the World Health Organization (WHO) and Food and Agriculture Organization of the United Nations (FAO) conduct routine surveillance to monitor influenza viruses, including H5N1 viruses, for changes that may have implications for animal and public health.
- More information on H5N1 is available at http://www.cdc.gov/flu/avianflu/h5n1-virus.htm.