

## Key Points: Update on Asian H7N9 Bird Flu in China May 23, 2017

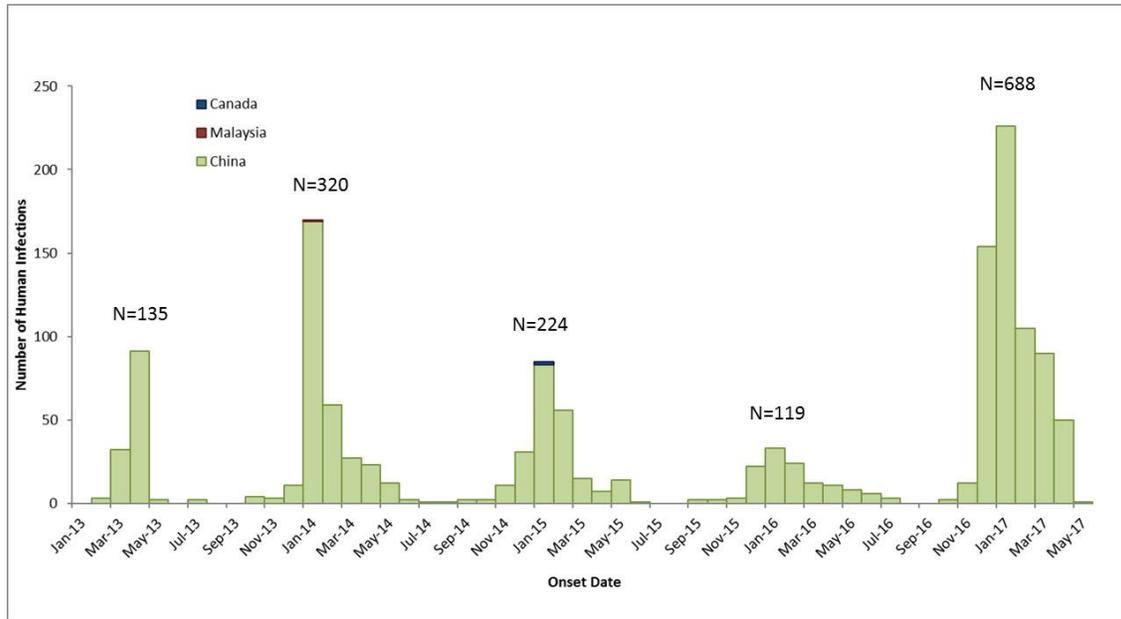
**SUMMARY:** *There has been a substantial increase in the number of human infections with Asian H7N9 reported in China, making the current epidemic the largest and longest to date since this virus emerged to infect people in 2013. While most human infections continue to be associated with exposure to poultry and there is no sustained person-to-person spread of this virus, there have been some changes in recent Asian H7N9 viruses identified that are of public health concern. While the current risk to the public's health from this virus remains low, CDC is watching the situation carefully and is taking routine preparedness measures, including making a candidate vaccine virus (CVV) that is matched to a recently emerged new lineage of H7N9 viruses.*

**Update:** *Today, the World Health Organization reported another 23 human infections with Asian H7N9, bringing the total number of human infections to 688 during the current fifth epidemic and 1,486 cumulatively since 2013. At this time, CDC has completed the new H7N9 CVV and is coordinating shipping to various manufacturers. Information about the availability of the CVV was posted on the WHO on Friday, May 18, 2017 at [http://www.who.int/influenza/vaccines/virus/candidates\\_reagents/a\\_h7n9/en/](http://www.who.int/influenza/vaccines/virus/candidates_reagents/a_h7n9/en/).*

### SITUATION UPDATE:

- Human infections with an avian influenza A(H7N9) virus were first reported in China in March 2013.
- Annual increases in the number of human infections with so-called Asian lineage H7N9 viruses (“Asian H7N9”) in China have occurred each winter since 2013 and are called “epidemics.”
- According to a [Morbidity and Mortality Weekly Report published in mid-December 2016](#), among reported human infections with Asian H7N9 virus during the first four epidemics in China (N=775), 88% of patients developed pneumonia, 68% were admitted to an intensive care unit and 41% died.\*
- During the first four epidemics, most human infections occurred between December and March.
- China is currently experiencing its 5<sup>th</sup> epidemic of human infections with Asian H7N9 viruses.
- On May 23, 2017, the World Health Organization reported an additional 23 cases of human infection with Asian H7N9 viruses, bringing the total number of Asian H7N9 human infections since October 1, 2016 (fifth epidemic) to 688 people.
- Of these fifth epidemic infections, 679 were detected in mainland China, eight were detected elsewhere in people who had traveled to mainland China (Hong Kong: 5, Macao: 2, Taiwan: 1), and one infection was detected in an asymptomatic poultry worker in Macao.
- The 5<sup>th</sup> epidemic of Asian H7N9 virus is by far the largest epidemic of Asian H7N9 to date.
- While new infections continue to be reported, the number of new infections being reported each week has declined since the peak of activity during January of the fifth epidemic.
- The cumulative number of human infections with Asian H7N9 viruses reported by WHO between 2013 and May 23, 2017, was 1,486.
- Below is an epidemic curve showing laboratory-confirmed human infections with Asian H7N9 viruses reported by WHO through May 23, 2017.

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- Previous numbers of reported human infections by epidemic in China are:
  - 1<sup>st</sup> epidemic (2013): 135 infections;
  - 2<sup>nd</sup> epidemic (2013-2014): 320 infections;
  - 3<sup>rd</sup> epidemic (2014-2015): 226 infections;
  - 4<sup>th</sup> epidemic (2015-2016): 119 infections.
- Besides an increase in the number of infections being reported during the current epidemic and an increase in the geographic areas in China where human infections with Asian H7N9 are being reported, the epidemiology of H7N9 virus infections in humans does not appear to have changed.
  - Asian H7N9 viruses continue to circulate among poultry in China.
  - Most human infections with Asian H7N9 virus continue to occur after exposure to poultry.
  - Most patients with Asian H7N9 virus infection during the 5<sup>th</sup> epidemic ([90 percent](#)\*\*\*) have severe respiratory illness (e.g., pneumonia).
  - Estimates of mortality during the 5<sup>th</sup> epidemic are not available since the Asian H7N9 outbreak is still ongoing and some hospitalized patients are still receiving medical treatment.
  - Rare, limited, non-sustained person-to-person spread of this virus continues to be identified, and there still is no evidence of sustained person-to-person spread of Asian H7N9 virus.
  - A few human infections of Asian H7N9 have been reported outside of mainland China but most of these infections have occurred among people who had traveled to China before becoming ill.
  - **These Asian H7N9 viruses have not been detected in people or birds in the United States.** (The North American lineage H7N9 viruses that have been detected in poultry outbreaks in Tennessee, Kentucky, Georgia and Alabama are different from Asian H7N9 viruses. In the past, there have been only a very small number of sporadic human infections with North American H7 viruses identified [fewer than 10 in the last 15 years]; these infections have mostly been associated with mild respiratory illness and/or conjunctivitis.)

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- CDC routinely examines the genetic and antigenic properties of novel influenza viruses.
  - Sequences of Asian H7N9 viruses isolated during the 4<sup>th</sup> epidemic in China during fall 2015 to spring 2016 showed few genetic and/or antigenic changes from viruses from earlier epidemics. (A report in CDC's MMWR published in December 2016 describes H7N9 activity through the 4<sup>th</sup> epidemics and is available at: [https://www.cdc.gov/mmwr/volumes/65/wr/mm6549a2.htm?s\\_cid=mm6549a2\\_w](https://www.cdc.gov/mmwr/volumes/65/wr/mm6549a2.htm?s_cid=mm6549a2_w).)
  - **Genetic and antigenic analysis** of viruses from the 5<sup>th</sup> epidemic is ongoing at CDC, but results to date suggest that genetic and antigenic changes have occurred in some 5<sup>th</sup> epidemic viruses.
  - The [Global Initiative on Sharing Avian Influenza Data](#) (GISAID) database currently contains 134 hemagglutinin (HA) gene sequences from 5<sup>th</sup> epidemic Asian H7N9 viruses.
  - Analysis of Asian H7N9 viruses obtained from recent human and live bird market environmental samples show these viruses have diverged into distinct genetic lineages.
  - One Asian H7N9 virus lineage is called the Pearl River Delta lineage.
  - A new genetically distinct lineage called Yangtze River Delta has been detected in genetic sequences posted from the 5<sup>th</sup> epidemic.
    - 129 of the 134 (96%) available sequences are in the Yangtze River Delta lineage;
    - 5 of the sequences are in the Pearl River Delta lineage.
  - Asian H7N9 viruses belonging to the Pearl River Delta lineage continue to be inhibited by ferret antisera raised to existing H7N9 candidate vaccine viruses (CVVs) as measured using the hemagglutinin-inhibition ([HI](#)) test.
  - This means that at this time the Asian H7N9 viruses from the Pearl River Delta lineage have remained antigenically similar to existing CVVs.
  - However, antigenic analysis of some Asian H7N9 viruses belonging to the Yangtze River Delta lineage has showed reduced cross-reactivity with existing CVVs, suggesting that Yangtze River Delta lineage viruses are antigenically different from Pearl River Delta lineage viruses and existing CVVs.
  - 12 out of 134 viruses (8.9%) from the 5<sup>th</sup> epidemic have markers in the neuraminidase gene indicating [reduced susceptibility \(resistance\)](#) to one or more neuraminidase inhibitor antiviral medications.
  - The neuraminidase inhibitor class of antiviral drugs (oseltamivir, zanamivir and peramivir) are currently recommended for the treatment of H7N9 virus infection.
  - Influenza viruses can become resistant to antiviral drugs spontaneously or resistance can emerge during the course of antiviral treatment.
  - During epidemics 1-4, 4% of viruses analyzed from human infections showed markers associated with reduced susceptibility to the neuraminidase inhibitors.\*
  - Most of the virus samples collected from human infections in China were reportedly collected after antiviral treatment had begun.
  - Additionally, 16 virus samples from the 5<sup>th</sup> epidemic contain amino acid changes in the viruses' HA surface protein (specifically a four amino acid insertion in a host protease cleavage site in the HA protein) that are **characteristic of highly pathogenic avian influenza viruses (HPAI)**.
  - All Asian H7N9 viruses characterized from epidemics one through four were classified as low pathogenic avian influenza viruses (LPAI).

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- Avian influenza viruses are classified into two categories (low pathogenic or highly pathogenic) based on their molecular characteristics and their ability to cause disease and mortality in chickens in a laboratory setting. Both HPAI and LPAI viruses can spread rapidly through poultry flocks.
  - Infection of poultry with LPAI viruses may cause no disease or mild illness (such as ruffled feathers and a drop in egg production) and these virus infections in birds may go undetected as a result.
  - Infection of poultry with HPAI viruses can cause severe disease with high mortality.
- Chinese authorities are investigating and monitoring closely for outbreaks of HPAI among poultry.
- There isn't enough information to know if the new HPAI Asian H7N9 viruses will cause more severe illness in people. It is possible that these genetic changes could allow HPAI viruses to replicate more easily in multiple organs. This can be associated with more disseminated infection with potential fatal immune responses. Evaluation of clinical illness associated with HPAI Asian H7N9 viruses will give more insight into this.
- Experts from World Health Organization (WHO) Global Influenza Surveillance and Response System (GISRS) met in Geneva, Switzerland February 27-March 1, 2017 to review available epidemiologic and virologic data related to influenza A(H7N9) viruses and to evaluate the need to produce additional candidate vaccine viruses to maximize influenza pandemic preparedness.
- Two additional Asian H7N9 CVVs were recommended for development: a new CVV derived from an A/Guangdong/17SF003/2016-like virus (HPAI), which is a highly pathogenic virus from the Yangtze River Delta lineage; and, a new CVV derived from A/Hunan/2650/2016-like virus, which is a low pathogenic virus also from the Yangtze River Delta lineage.
- At this time, CDC is preparing a CVV derived from an A/Hunan/2650/2016-like virus using reverse genetics.
- The report on the World Health Organization (WHO) Global Influenza Surveillance and Response System (GISRS) meeting ([Antigenic and genetic characteristics of zoonotic influenza viruses and development of candidate vaccine viruses for pandemic preparedness](http://www.who.int/influenza/vaccines/virus/201703_zoonotic_vaccinevirusupdate.pdf?ua=1)) is available at [http://www.who.int/influenza/vaccines/virus/201703\\_zoonotic\\_vaccinevirusupdate.pdf?ua=1](http://www.who.int/influenza/vaccines/virus/201703_zoonotic_vaccinevirusupdate.pdf?ua=1)
- An update on the epidemiology and virology of H7N9 during the 5th annual epidemic was released in a Morbidity and Mortality Weekly Report on Friday, March 3, 2017. The report is available at [https://www.cdc.gov/mmwr/volumes/66/wr/mm6609e2.htm?s\\_cid=mm6609e2\\_e](https://www.cdc.gov/mmwr/volumes/66/wr/mm6609e2.htm?s_cid=mm6609e2_e).

### CDC RISK ASSESSMENT:

- While the current risk to the public's health from this virus is low, Asian H7N9 virus is among the non-human influenza viruses that are most concerning to public health officials because of their pandemic potential and ability to cause severe disease in infected humans.
- Among the 12 novel influenza A viruses rated by the [Influenza Risk Assessment Tool \(IRAT\)](#), Asian H7N9 virus is ranked as having the highest potential pandemic risk of all of the viruses evaluated, as well as potentially posing the most risk to severely impacting public health.
- Using the IRAT, the potential risk of Asian H7N9 viruses for sustained person-to-person spread is assessed to be "moderate." If the current Asian H7N9 viruses were to achieve the ability for sustained person-to-person spread, the potential impact risk worldwide is "high-moderate."
- (IRAT summary scores are available at: <https://www.cdc.gov/flu/pandemic-resources/monitoring/irat-virus-summaries.htm>)
- Influenza viruses constantly change, and it is possible that Asian H7N9 viruses could gain the ability to spread easily and sustainably among people, causing a pandemic.

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- However, there is no evidence of sustained human-to-human spread of this virus at this time. Sustained human-to-human spread is necessary for a pandemic to occur.

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### WHAT TO EXPECT:

- It's likely that sporadic human infections with Asian H7N9 virus associated with poultry exposure will continue to occur in China.
- It's also possible that Asian H7N9 virus may spread to poultry in neighboring countries and that human cases associated with poultry exposure may be detected in neighboring countries.
- It's also possible that Asian H7N9 cases may be detected among travelers returning from countries affected by Asian H7N9 outbreaks in poultry, even possibly in the United States.
- However, as long as there is no evidence of ongoing, sustained person-to-person spread of these viruses, the public health risk assessment would not change substantially.

### WHAT CDC IS DOING:

- The U.S. Government supports international surveillance for Asian H7N9 and other influenza A viruses with pandemic potential.
- CDC is collaborating closely with CDC China through the World Health Organization's Global Influenza Surveillance and Response System (GISRS).
- CDC staff in China and globally are following the Asian H7N9 virus situation closely and coordinating with domestic and international partners.
- CDC is working with countries that border China to scale-up surveillance and response activities.
- CDC routinely reviews new data as it becomes available and updates IRAT scores as appropriate.
- The last IRAT scoring of Asian H7N9 virus was conducted in April of 2016. The 2016 IRAT score is being updated at this time based on recent developments.
- CDC had previously developed three Asian H7N9 candidate vaccine viruses (CVVs) to use for vaccine production if needed. These CVVs were antigenically "like" viruses circulating during the 4<sup>th</sup> epidemic.
- CDC has developed a CVV to match H7N9 viruses from the newly emerged Yangtze lineage that are different from existing CVVs.
- Creating a candidate vaccine virus is a multistep process that takes months to complete. (More information about making an avian influenza CVV is available at <https://www.cdc.gov/flu/avianflu/candidate-vaccine-virus.htm>.)
- The CDC CVV was derived from a low pathogenic A/Hunan/2650/2016-like virus and was made using reverse genetics.
- At this time, CDC has completed the new H7N9 CVV and is coordinating shipping to various manufacturers.
- Information about the availability of the CVV was posted on the WHO website on May 18, 2017 at [http://www.who.int/influenza/vaccines/virus/candidates\\_reagents/a\\_h7n9/en/](http://www.who.int/influenza/vaccines/virus/candidates_reagents/a_h7n9/en/).
- CDC will conduct additional genetic and antigenic analysis of 5<sup>th</sup> epidemic Asian H7N9 viruses and will continue to monitor for genetic markers associated with drug resistance to the influenza antiviral drugs classified as neuraminidase inhibitors.
- CDC has received a number of H7N9 virus samples from the 5<sup>th</sup> epidemic and will conduct additional testing on these viruses, including:
  - Studies in animal models to evaluate transmission and disease severity.
  - Serology studies to see 1.) whether vaccination (of people) with existing stockpiled H7N9 vaccine might offer some protection against 5<sup>th</sup> epidemic viruses; and, 3.) once it is available,

Influenza Division, National Center for Immunization and Respiratory Disease (NCIRD)  
Centers for Disease Control and Prevention (CDC)

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whether the CVVs being developed by CDC would be likely to protect against 5<sup>th</sup> epidemic Asian H7N9 viruses.

- Studies using a specific functional assay (the neuraminidase inhibition [NI] assay) to confirm genetic data suggesting antiviral resistance to the antiviral neuraminidase inhibitors.
- CDC has had Asian H7N9 guidance for clinicians and public health authorities in the United States since 2013. This guidance is available at <https://www.cdc.gov/flu/avianflu/healthprofessionals.htm>. CDC is reminding U.S. clinicians and laboratorians to consider H7N9 virus infection in returning travelers, most recently with influenza COCA call and APHL laboratory communications.
- CDC supports all U.S. state health departments with diagnostic test reagents that can detect H7N9 virus and other novel influenza A viruses. CDC also provides these reagents to other countries to assist them with detection.
- On January 28, 2017, CDC posted Information on Asian [H7N9 for travelers to China](#) since large numbers of people typically travel to and from China around the Chinese Lunar New Year. This was a “Watch Level – 1 Practice Usual Precautions” travel notice.
- CDC will provide updated information as it becomes available.

### CDC, China and Influenza, Background

- CDC’s Influenza Division began working with the China National Influenza Center (CNIC), part of the China CDC, in the late 1980s.
- CDC helped China to establish the Chinese National Influenza Surveillance Network and laboratory capability in order to capture more of the influenza viruses circulating in China.
- Since 2004, CDC and China CDC have participated in a series of cooperative agreements that have further improved and sustained China’s surveillance network and supported genetic, antigenic and drug resistance surveillance (in part to inform vaccine recommendations), and also strengthened influenza response capacity at all levels.
- In October 2010, CNIC was designated as a World Health Organization Collaborating Center for Reference and Research on Influenza.
- CNIC is one of a handful of WHO Collaborating Centers for Reference and Research on Influenza in the world (U.S. CDC in Atlanta, Georgia, also is a WHO Collaborating Center).
- Among other things, as a Collaborating Center CNIC regularly provides information from China’s recently enhanced surveillance system to help inform decisions about the composition of the seasonal flu vaccine.
- Collaborating Centers also train researchers in specialized techniques, collect epidemiological information on influenza disease prevalence in China and surrounding countries, and assist in developing pandemic preparedness plans. They also receive, characterize, and preserve representative vaccine viruses sent from laboratories around the world, then share that information with other researchers.
- U.S. CDC has an office with an influenza program in China.

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### REPORTS AND LINKS:

- \*Xiang N, Li X, Ren R, et al. [Assessing Change in Avian Influenza A\(H7N9\) Virus Infections During the Fourth Epidemic — China, September 2015–August 2016](#). MMWR Morb Mortal Wkly Rep 2016;65:1390–1394. DOI: <http://dx.doi.org/10.15585/mmwr.mm6549a2>.
- \*\*Zhou L, Ren R, Yang L, et al. [Sudden increase in human infection with avian influenza A\(H7N9\) virus in China](#), September–December 2016. WPSAR 2017;8(1). <http://ojs.wpro.who.int/ojs/index.php/wpsar/article/view/521/733>
- \*\*\*[Antigenic and genetic characteristics of zoonotic influenza viruses and development of candidate vaccine viruses for pandemic preparedness](#)) is available at [http://www.who.int/influenza/vaccines/virus/201703\\_zoonotic\\_vaccinevirusupdate.pdf?ua=1](http://www.who.int/influenza/vaccines/virus/201703_zoonotic_vaccinevirusupdate.pdf?ua=1)
- [CDC Avian Influenza A \(H7N9\) Virus website](#): <https://www.cdc.gov/flu/avianflu/h7n9-virus.htm>