**Situation Summary**

- New reports of human infections with avian influenza A (H7N9) have decreased since the month of April, when multiple cases were being reported each day.
- One additional human case of H7N9 infection and one death have been reported to the World Health Organization as of May 29, 2013. This brings the total number of human cases to 132, with 37 deaths.
- The decline in newly reported cases may be a result of control measures implemented in China — including closure of live bird markets — or it may be a result of a seasonal pattern previously seen with other avian influenza viruses. (For more information, see "H7N9 Situation and CDC Response Update" at [http://www.cdc.gov/flu/spotlights/h7n9-cdc-response.htm](http://www.cdc.gov/flu/spotlights/h7n9-cdc-response.htm).)
- The first cases were internationally reported by WHO on April 1, 2013.
- No cases of H7N9 have been detected in the United States or anywhere outside of China at this time.
- Most of the reported cases of human infection with H7N9 have had very serious illness. There also are reports of some milder illness and asymptomatic illness.
- The H7N9 situation is of international public health concern because of the potential for this virus to change and trigger a pandemic, which could be severe based on the epidemiological information currently available.
- An ongoing investigation suggests that most people have been infected with the virus after having contact with infected poultry or contaminated environments. (See "Avian Influenza Background" for information on how this type of transmission might occur.)
- Follow-up investigations among more than 2,000 close contacts of people infected with H7N9 by Chinese health officials indicate that there is no sustained (ongoing) spread of this virus from person to person at this time; however a few small clusters of human infection have occurred where the possibility of limited human-to-human spread cannot be excluded.
• Based on previous experience with other avian influenza viruses, it would not be surprising to see some limited human-to-human spread of this H7N9 virus.

• Most important, however, is the fact that there is no evidence of efficient and sustained (ongoing) spread in the community, which is what is needed to trigger a pandemic.

What May Happen

• It would NOT be surprising to see limited human-to-human transmission during the current H7N9 situation in China.

• It’s also possible that H7N9 cases may at some point be detected in the United States (for example, in a traveler returning from China).

• This would not signal an increase in the potential risk to the public’s health unless the transmission pattern of the virus was to change.

• If a person in the United States has H7N9 flu, they will be isolated (separated from other people who are well) and cared for.

• While there is no vaccine against this virus at this time, influenza antiviral drugs can be used for treatment and prevention of influenza infection.

• In addition, a contact investigation will be done with people who may have been exposed to the sick person.

• Contact investigations are one of the ways CDC works with partners in the United States and other countries to protect the health of people exposed to an illness. This process involves finding, interviewing, and, in some cases, testing or treating the people who came into contact with the sick person.

• The purpose of a contact investigation for a traveler with H7N9 flu returning from China is to:
  o provide information to exposed passengers and crew so they can get preventive antiviral treatment if needed, recognize any symptoms of disease, isolate themselves if needed, and receive care.
  o refer passengers or crew with influenza-like illness for medical evaluation, testing, and antiviral treatment, if needed.
  o determine whether spread of H7N9 flu may have occurred on the flight and which passengers were at greatest risk.

• All of this can reassure us that the virus is not spreading further in the United States.

Public Health Concern

• The concern right now is that this H7N9 virus might either mutate or adapt to allow efficient transmission during the infection of mammals, or reassort its gene segments with human influenza viruses during the co-infection of a single host, which would result in a new virus that might be transmissible from person to person.
• Such events are believed to have preceded the influenza pandemics of 1918, 1957, 1968 and 2009.

• Because H7N9 viruses do not commonly infect humans, there is probably little or no immune protection against them in the human population. (CDC is conducting serologic studies to confirm this.)

• If sustained, ongoing human-to-human transmission of H7N9 viruses begins, many more people will become ill, some severely, and unfortunately more deaths will occur.

• CDC is preparing for various scenarios – including sustained human-to-human transmission – to ensure that the agency will be in the best position to help protect the public from this virus.

• It is important to note, however, that efficient and sustained human-to-human transmission would be needed to trigger a pandemic. There is no indication that such transmission is happening.

• The investigation is ongoing and CDC will provide more information as it becomes available at http://www.cdc.gov/flu/avianflu/h7n9-virus.htm.

**What CDC Is Doing**

• CDC is following this situation closely and coordinating with domestic and international partners, including China CDC and the World Health Organization.

• CDC is taking routine preparedness measures, including the following:
  
  o Developing candidate vaccine viruses that could be used to make vaccine if it becomes necessary.

  • So far, CDC has completed development of one H7N9 candidate vaccine virus (CVV) that has been designated “A/Shanghai/2/2013(H7N9)-PR8-IDCDC-RG32A.”

  • On May 23, WHO issued a statement that the IDCDC-RG32A CVV has passed all relevant safety testing and two-way hemagglutination inhibition (HI) test. (Read more at http://www.who.int/influenza/vaccines/virus/candidates_reagents/summary_a_h7n9_cvv_20130523.pdf.)

  • This CVV was generated by reverse genetics using synthetic hemagglutinin (HA) and neuraminidase (NA) genes.

  • CDC used plasmid-based reverse genetics to recover a reassortant virus with the hemagglutinin (HA) and neuraminidase (NA) genes of A/Shanghai/2/2013(H7N9) and the remaining genes from A/Puerto Rico/8/1934(H1N1) in accordance with WHO guidelines for pandemic candidate vaccine virus development.

  • CDC is developing other potential CVVs using plasmid-based reverse genetics.
• No CVVs have been created using conventional reassortment at this time.

• At this time, no decision has been made to mass-produce H7N9 vaccine in the United States.

• In addition, neither the World Health Organization or the U.S. Food and Drug Administration have made any recommendation regarding which H7N9 potential candidate vaccine virus to use for vaccine manufacturing. (See section H7N9 Vaccine Development for more information.)

• CDC also is:
  o Sharing test kits that detect the H7N9 virus that can be used by other public health laboratories. Information about these test kits is available at http://www.cdc.gov/flu/avianflu/h7n9-detecting-diagnostics.htm.
    - CDC began shipping the kits on April 25, 2013. To date, 159 test kits have been shipped domestically (107) and internationally (52). Test kits had been distributed to all 50 states, the District of Columbia and Puerto Rico as of May 28, 2013.
  o Conducting serologic testing to detect antibodies to H7N9 viruses.
    - Studies to see if existing seasonal influenza vaccines may provide any cross reactive* antibodies to H7N9 infection are ongoing.
      *Cross reactivity refers to the ability of antibodies developed against a vaccine virus to recognize and neutralize the H7N9 virus.
    - Recently CDC finished planning for serological studies that will determine if there is any pre-existing cross-reactive immunity against H7N9 in the current U.S. population.
    - CDC has continued looking at already-developed H7 candidate vaccine viruses (H7N1, H7N3, H7N7) to see if any of these elicit cross reactive antibodies to H7N9 infection.
  o Conducting ongoing testing to determine H7N9 susceptibility to the licensed influenza antiviral drugs, oseltamivir (commercially known as Tamiflu®) and zanamivir (Relenza®), as well as to investigational antiviral drugs.
    - It is possible for an influenza virus to develop resistance to an antiviral drug or class of antiviral drugs.
    - Antiviral resistance (or reduced susceptibility) means that a flu virus has changed in such a way that, when tested in the laboratory, the antiviral drug does not effectively block the virus in the laboratory effectively. This may mean that the drug is less effective in treating or preventing illnesses caused by the virus.
    - Resistance can occur spontaneously, or emerge during the course of antiviral treatment or exposure to an antiviral drug in the laboratory setting.
Through antiviral testing, CDC Influenza Laboratory and China CDC have found evidence of reduced susceptibility to some antiviral drugs in a small number of H7N9 viruses.

The H7N9 viruses with reduced susceptibility all have a genetic mutation known as the “R292K substitution.”

This mutation is found in the neuraminidase (NA) gene of the virus and is a known resistance marker that has been associated with reduced susceptibility to the neuraminidase inhibitor (NAI) class of influenza antiviral drugs. (Note: This particular mutation has been observed before in other influenza viruses of subtype N2 and N9.)

CDC will continue antiviral testing to investigate whether the R292K substitution confers antiviral resistance among patients infected with H7N9. (A study by Chinese authors examines the association between adverse clinical outcomes in H7N9 patients and antiviral resistance was published in The Lancet on May 28, 2013. See section “Article: The Lancet” below for more information.)

- Providing recommendations for travelers as needed.
- Together with partners at ports of entry, CDC staff is assessing ill travelers returning from affected areas to determine whether any additional public health action is needed.
- CDC also is gathering more information to make a more thorough public health risk assessment.

**What Clinicians and Public Health Professionals Should Do**

- Patients with illness compatible with influenza (1) who have recently traveled to countries where human cases of novel influenza A (H7N9) virus infection have recently been detected or (2) who have had recent contact with confirmed human cases of infection with novel influenza A (H7N9) virus should be candidates for RT-PCR testing for influenza.

- Clinicians should consider the possibility of H7N9 influenza infection in patients with illness compatible with influenza and an appropriate recent travel or exposure history.

- Because of the potential severity of illness associated with H7N9 virus infection, it is recommended that all confirmed cases, probable cases, and H7N9 cases under investigation receive antiviral treatment with oseltamivir or zanamivir as early as possible. See Interim Guidance on the Use of Antiviral Agents for Treatment of Human Infections with Avian Influenza A (H7N9) in the United States on the CDC website.

- Clinicians also should be aware of appropriate infection control guidelines for patients with suspected novel influenza A viruses.
Because it has been shown to cause severe respiratory illness in cases identified so far, health care personnel (HCP) caring for patients with suspected H7N9 virus infection should adhere to **Standard Precautions plus Contact and Airborne Precautions**, including eye protection, until more is known about the transmission characteristics of the A (H7N9) virus.

- All clusters of respiratory illness in HCP caring for patients with severe acute respiratory illness should be investigated.

- See [Interim Guidance for Infection Control Within Healthcare Settings When Caring for Patients with Confirmed, Probable or Cases Under Investigation of Avian Influenza A(H7N9) Virus](#).

**What the Public Should Do**

- At this time, no cases of human infection with avian influenza A (H7N9) viruses have been detected in the United States and the virus does not seem to be spreading from person to person.

- Other than the advice for travelers or ill persons below, CDC is not making any additional or special recommendations for public action specific to H7N9.

**Travelers**

- Travelers should continue to visit [www.cdc.gov/travel](http://www.cdc.gov/travel) or follow @CDCtravel on Twitter for up-to-date information about CDC’s travel recommendations.

- CDC does not recommend restricting travel to China at this time.

- Travelers to China should practice hand hygiene, follow food safety practices, and avoid contact with animals.
  
  - Travelers should wash their hands often or use hand sanitizer. They should try not to touch their eyes, nose, or mouth, except with very clean hands.
  
  - Travelers should eat meats and poultry products, including eggs, only if they have been cooked thoroughly.
  
  - Travelers should avoid touching animals, alive or dead, and should stay away from farms, poultry markets, or other markets where there are live or dead animals.

- Symptoms of H7N9 flu include fever, cough, and shortness of breath. If travelers get sick after returning from China, they should tell their doctors about their recent travel.

**H7N9 Vaccine Development**

- While there is no evidence of sustained (ongoing) person-to-person spread of the H7N9 virus, the Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), National Institutes of Health (NIH) and the Department of Health and Human Services (HHS) are taking standard pandemic preparedness precautions.
As of today, a decision to produce H7N9 vaccine for a national vaccination response has not been made.

However, given the number and severity of human illnesses from H7N9 in China, HHS and its partners are taking routine steps to develop a H7N9 candidate vaccine virus and are planning for H7N9 vaccine clinical trials.

Influenza vaccine production is complex and can be unpredictable. It has many critical and time-sensitive steps; delay at any point during these steps can result in delays in the availability of influenza vaccine.

It usually takes about six months to produce large quantities of influenza vaccine.

The development of a high-yield candidate vaccine virus is the first step in developing a vaccine.

A candidate vaccine virus is a flu virus that CDC (or one of the other WHO Collaborating Centers) selects and prepares for use by vaccine manufacturers to make a flu vaccine. Candidate vaccine viruses are typically chosen based on their similarity to flu viruses spreading and causing illness in people as well as their ability to grow easily in chicken eggs, which is the method of manufacturing influenza vaccine traditionally used.

Without a high-yield candidate vaccine virus, it can be very difficult to manufacture vaccine to protect against a new influenza virus.

CDC, NIH, FDA, BARDA (Biomedical Advanced Research and Development Authority in the Office of the Assistant Secretary for Preparedness and Response) and vaccine manufacturers are collaborating to develop a high-yield candidate vaccine virus that could be used to begin production of an H7N9 vaccine.

BARDA has existing contracts in place with manufacturers of U.S.-licensed influenza vaccines that use egg-, cell-, and recombinant-based technologies. These contracts can support the development, manufacturing, and clinical evaluation of H7N9 vaccines and adjuvants. These contracts also ensure that the candidate vaccine viruses developed would be shared freely and would support commercial scale manufacturing, if needed.

Once the candidate vaccine virus has been developed, manufacturers can use it to develop a vaccine against the avian influenza A (H7N9) virus.

Once a vaccine manufacturer receives a candidate vaccine virus, the manufacturer then creates what is known as a "seed strain." The seed strain is adapted to make the virus grow better using the manufacturer's technology and production systems. Once the seed strain is prepared, the vaccine manufacturer uses it to grow large quantities of virus for producing flu vaccine.

Influenza vaccine manufacturers need 8 to 11 weeks to make small lots of vaccine and test whether the candidate vaccine virus works well in the manufacturing process.
FDA and other WHO Essential Regulatory Laboratories will make reagents to test the potency of both cell- and egg-based vaccine lots.

- NIH and vaccine manufacturers will sponsor clinical studies of investigational H7N9 vaccines to evaluate the safety and determine the optimal dosing and whether an adjuvant is needed for an adequate immune response. FDA is working closely with NIH and other stakeholders in the design of these clinical trials.
  - The clinical trials will be conducted among people who volunteer to participate in vaccine studies. Information about safety and how people’s immune systems respond to the vaccine will be important for planning vaccine production and a vaccine program, if such a program is needed.

- If it is decided that an H7N9 vaccination program is needed, even if production goes as planned, it would be several months before the first doses of H7N9 influenza vaccines are available.

- Although no decision has been made to initiate a H7N9 vaccination program in the United States, CDC recommends that local authorities and preparedness programs take time to review and update their pandemic influenza vaccine preparedness plans since it could take several months to ready a vaccination program, if one were necessary.

- Keep in mind that CDC and HHS continue to gather information to make a more thorough public health risk assessment. This is an evolving situation and there is still much to learn.

- Information will be shared as available at [http://www.cdc.gov/flu/avianflu/h7n9-virus.htm](http://www.cdc.gov/flu/avianflu/h7n9-virus.htm).

### Avian Influenza Background

- Subtypes of H7 viruses are that have been identified in birds include the following: H7N1, H7N2, H7N3, H7N4, H7N5, H7N6, H7N7, H7N8, and H7N9.

- Most H7 viruses identified worldwide in wild birds and domestic poultry are low pathogenic avian influenza A (LPAI) viruses. LPAI viruses generally cause mild illness in birds, and some birds may not have symptoms.

- H7 virus infection in humans is uncommon, but has been documented in persons who have direct contact with infected birds, especially during outbreaks of H7 virus among poultry. Illness in humans may include conjunctivitis and/or upper respiratory tract symptoms.

- In humans, LPAI (H7N2, H7N3, H7N7) virus infections have caused mild to moderate illness.

- Highly pathogenic avian influenza (HPAI) (H7N3, H7N7) virus infections have caused mild to severe and fatal illness in humans.

- The H7N9 viruses recently reported in China are the first known human cases of H7N9 influenza infection.
• To date, there have been no human infections with H7N9 in the United States or any countries other than China.

• Different avian influenza A (H7N9) viruses have been identified in birds in North America. Wild waterfowl and shore birds may carry the virus during migrations and may introduce it to domestic poultry. The North American lineage of H7N9 is different from the Eurasian lineage of H7N9 viruses that are currently circulating in China.

• The threat to humans from the North American lineage of H7N9 influenza viruses is low.

• Avian flu viruses do not normally infect humans. However, sporadic human infections with avian flu do occasionally occur.

• Most commonly, human cases of avian influenza happen in people with direct exposure to infected poultry.

• Infected birds can shed a lot of flu virus, for example, in their droppings or their mucus. If someone touches an infected bird or an environment contaminated with virus and then touches their eyes, nose or mouth, they may be infected with bird flu virus.

• There is some evidence that infection may also occur if the flu virus becomes airborne, such as when an infected bird flaps it wings. If someone were to breathe in airborne virus, it’s possible they could get infected.

• While most instances of human infection with animal influenza viruses do not result in human-to-human transmission, each case should be fully investigated to be sure that such viruses are not spreading among humans and to limit further exposure of humans to infected animals, if infected animals are identified.

• Poultry, poultry products (eggs) and pork can be safely consumed provided they are properly cooked and properly handled during food preparation.

• Surveillance for avian influenza viruses in North American birds is under the purview of the United States Department of Agriculture (USDA) and the Department of the Interior (DOI). Questions regarding avian influenza infections in U.S. birds should be referred to these agencies.

• International cases of novel influenza A are reportable to the World Health Organization under the International Health Regulations (IHR 2005).

• In 2007, human infection with a novel influenza A virus became a nationally notifiable condition in the United States. Novel influenza A virus infections include all human infections with influenza A viruses that are different from currently circulating human influenza H1 and H3 viruses. Novel viruses include those that are subtyped as non-human in origin and those that are unsubtypable with standard methods and reagents.

• For more information about avian influenza, visit the CDC website at http://www.cdc.gov/flu/avianflu/index.htm.
- Person-to-person spread of other avian influenza viruses is thought to have occurred in the past, most notably with H5N1 viruses.
- In the majority of these instances, spread occurred after prolonged and close contact between the sick person and someone caring for them (most often a family member).
- See “Background on Human Infections with other Avian Influenza Viruses” at http://www.cdc.gov/flu/avianflu/h5n1-human-infections.htm for more information.

**Human-to-Human Spread, Background**

- It’s important to remember that human-to-human transmission ranges along a continuum; from occasional, “dead-end” human-to-human transmission, to efficient and sustained human-to-human transmission.
- “Dead end” transmission usually refers to when a virus from an animal host infects a person and then there is some subsequent transmission that eventually burns out.
- For example, when a host infects one person who then subsequently infects someone else that is called “first generation spread.” If that second person then infects someone else that is called “second generation spread,” and so forth.
- Previously, third generation transmission of H5N1 viruses has been documented in one instance at least (Pakistan). ([WHO, Weekly Epidemiological Record. “Human cases of avian influenza A(H5N1) in North-West Frontier Province, Pakistan, October–November 2007.”](http://www.cdc.gov/flu/avianflu/h5n1-human-infections.htm))
- However, efficient and sustained (ongoing) transmission in the community is needed for an influenza pandemic to begin.

**CDC and China, Background**

- U.S. CDC 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.
  o The office includes 1 U.S. Direct Hire and 3 local employees dedicated to the influenza program.
  o U.S. CDC in China has a total of 54 staff members, including one secunded to WHO.
  o Apart from influenza team staff, other staff with expertise in laboratory, epidemiology and communications have supported the H7N9 response and assisted the Embassy committee in tracking the outbreak.

Article: The Lancet – Investigating the Association Between Clinical Outcomes and Antiviral Resistance

• On Tuesday, May 28, 2013, the journal *Lancet* published a paper titled “Association between clinical outcomes in human disease caused by novel influenza A H7N9 virus and sustained viral shedding and emergence of antiviral resistance”, by Yunwen Hu et al.

• No CDC experts contributed to the paper.

• Fourteen patients with confirmed H7N9 disease were studied. They were all admitted to Shanghai Public Health Clinical Centre between April 4 and April 20, 2013, and were given antiviral treatment (oral oseltamivir) for less than two days before admission.

• The amount of virus present in the throat, stool, serum, and urine was determined for serial specimens during the hospitalization for each patient.

• H7N9 viral RNA from each specimen was sequenced to look for and study mutations associated with resistance to neuraminidase inhibitor drugs.

• Antiviral treatment was associated with a reduction of H7N9 viral load in throat specimens in 11 surviving patients.

• Reduction in H7N9 viral load following antiviral treatment was correlated with an improved outcome (patients who had fewer H7N9 viruses detected in their throat specimens over time tended to get better.)

• All patients developed pneumonia, seven of them required mechanical ventilation, and three of them further deteriorated and became dependent on an external artificial lung.
• Two patients (who had received corticosteroid treatment) showed emergence of the H7N9 292K mutation.

• The authors concluded that the emergence of H7N9 292K virus in two patients led to treatment failure and a poor clinical outcome.

• Further, the emergence of antiviral resistance in H7N9 viruses, especially in patients receiving NAI treatment and corticosteroid therapy, is concerning and needs to be closely monitored.
  - Corticosteroids are immunomodular drugs that suppress the immune system and are not recommended for treatment of influenza virus infections. Observational studies have reported an association of corticosteroid treatment and prolonged influenza viral replication in hospitalized influenza patients and no clinical benefit.

• This article is available at http://www.sciencedirect.com/science/article/pii/S0140673613611253 (link may require institutional permissions to this view this article).

**Links to Additional Information**

**CDC Resources**

• CDC will provide updated information as it becomes available at http://www.cdc.gov/flu/avianflu/h7n9-virus.htm.

• On May 17, 2013, CDC issued a new diagram depicting the origins of the H7N9 virus in China. The diagram shows how the H7N9 virus’s genes are derived from other influenza viruses found in birds. The diagram is available for download from CDC’s H7N9 virus images page http://www.cdc.gov/flu/avianflu/h7n9-images.htm and also via the Public Health Image Library (PHIL): http://phil.cdc.gov/phil/whatsnew.asp (image ID#15798).

• An MMWR “Emergence of Avian Influenza A(H7N9) Virus Causing Severe Human Illness — China, February–April 2013” was published on May 1, 2013 and is available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm62e0501a1.htm?s_cid=mm62e0501a1_w.

• CDC has posted a Questions & Answers document called “H7N9: Frequently Asked Questions” for the general public. This Q&A is available at http://www.cdc.gov/flu/avianflu/h7n9-faq.htm.

• CDC has posted a number of materials for health professionals, laboratorians and clinicians, including:
  - Interim Guidance on the Use of Antiviral Agents for Treatment of Human Infections with Avian Influenza A (H7N9)
  - Interim Guidance for Infection Control Within Healthcare Settings When Caring for Patients with Confirmed, Probable, or Cases Under Investigation of Avian Influenza A(H7N9) Virus Infection
Interim Guidance on Case Definitions to be Used for Novel Influenza A (H7N9) Case Investigations in the United States

The World Health Organization Representative Office in China has published the statement and transcript from a press briefing held after the international H7N9 assessment team completed its mission to China. These materials are available at http://www.wpro.who.int/china/en/.

WHO Resources

WHO updates information related to human cases of H7N9 avian influenza (and other novel viruses) at http://www.who.int/csr/don/en/.


Resources from Other Organizations

The Chinese Center for Disease Control and Prevention has posted a Q&A document related to this situation. It is available at http://www.chinacdc.cn/en/ne/201303/t20130331_79282.html.

The European Centre for Disease Prevention and Control is publishing their latest updates and risk assessments on influenza A(H7N9) at “Avian influenza in humans.” This page is available at http://ecdc.europa.eu/en/healthtopics/avian_influenza/whats_new/Pages/whats_new.aspx.