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WHO Regional Office for Europe update on avian influenza A(H7N9) virus

Situation update 4: 15 May 2013

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CONTENTS

	<i>Page</i>
1) Situation update	2
2) WHO risk assessment as of 10 May 2013	7
3) Recommendations	7
4) Additional information	9
5) References	10

This update summarizes the available information and recommendations made by WHO about human infections with avian influenza A(H7N9) virus in China for Member States of the WHO European Region.

WHO/Europe emphasizes the need for Member States to maintain the capacity to detect any unusual health event, including those that may be associated with a new subtype of influenza A which should be notified to WHO in accordance with the International Health Regulations (2005). Human health and animal health sectors should maintain close and systematic interactions for timely exchange of information and to conduct joint risk assessments for the prevention and control of zoonotic diseases, as necessary. This work should be done under the relevant components of multi-hazard plans for preparedness and response to public health events.

WHO/Europe is coordinating its activities related to this outbreak with the European Commission, the European Centre for Disease Prevention and Control (ECDC), the EuroFlu network (www.euroflu.org) and the Community Network of Reference Laboratories for Human Influenza in Europe (CNRL).

This update is posted every week in English and (with a possible slight delay for translation) in Russian and includes:

- a situation update;
- latest WHO risk assessment (this week as of 10 May 2013);
- recommendations; and
- additional information .

What is new in this update?

- World Organisation for Animal Health mission to China (see page 3 in this update).
- Update of WHO biosafety risk assessment and guidelines for the production and quality control of human influenza vaccines against avian influenza A(H7N9) virus (see page 6 in this update).
- Summary of status of development and availability of avian influenza A(H7N9) candidate vaccine viruses – 10 May 2013 (see page 6 in this update).
- Updated WHO risk assessment on human infections with avian influenza A(H7N9) virus – 10 May 2013 (see page 7 in this update).
- The interim WHO surveillance recommendations for human infection with avian influenza A (H7N9) virus – 10 May 2013 (see page 8 in this update).
- Laboratory biorisk management for laboratories handling human specimens suspected or confirmed to contain avian influenza A(H7N9) virus causing human disease – interim recommendations – 10 May 2013 (see page 8 in this update).

1) Situation update

On 31 March 2013, the health authorities of China notified WHO of three laboratory-confirmed human cases of avian influenza A(H7N9) virus infection. These cases reported from China are the first known cases of human infection with A(H7N9). Since that time China has continued to report new human cases. As of 9 May 2013, 130 laboratory confirmed human cases with A(H7N9) virus including 32 fatalities in China have been reported from

eight provinces (Anhui, Fujian, Henan, Hunan, Jiangsu, Jiangxi, Shandong and Zhejiang) and two municipalities (Beijing and Shanghai). In addition, one case has been reported from Tapei Centers for Disease Control.

WHO expert mission to China

A joint China National Health and Family Planning Commission and WHO team of international and Chinese influenza experts carried out a mission to China on 16–23 April 2013 visiting laboratories, hospitals, clinics, markets and affected areas in Shanghai. It was found that the response by the Chinese government is being carried out with strong leadership and a high level of commitment. The strategies implemented such as health education, communication and closure of live poultry markets were found sound and effective. The mission team came up with a number of recommendations for the prevention and control of A(H7N9), which can be found [here](#).

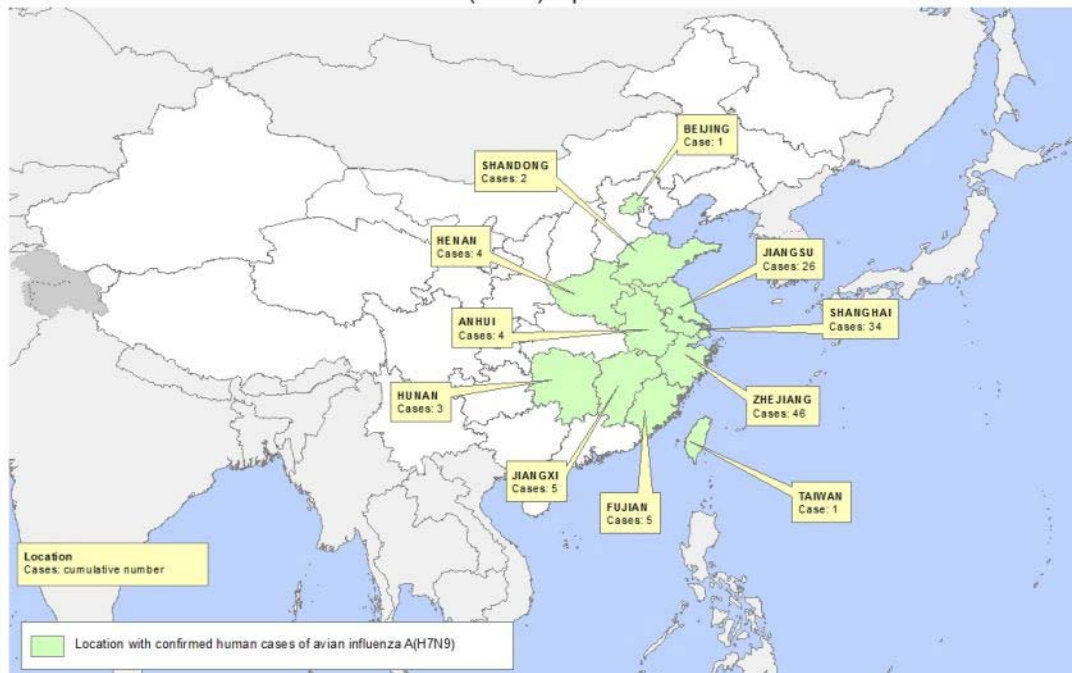
World Organisation for Animal Health mission to China

The World Organisation for Animal Health (OIE) conducted a mission to China in April under the Tripartite framework between the OIE, WHO and the Food and Agriculture Organization (FAO) of the United Nations. The mission experts found that live bird markets may play a key role in human and animal infections with A(H7N9). The mission highlights the importance of collaboration between human health and animal health sectors to improve understanding of transmission of A(H7N9) to humans. A summary of the mission is available [here](#).

The following map, table of confirmed cases and epidemiological curve were published by WHO headquarters in the weekly report *Number of confirmed human cases for avian influenza A(H7N9) reported to WHO* as of 9 May 2013.¹

Geographical location

Confirmed human cases of avian influenza A(H7N9) reported to WHO



Data as of 09 May 2013, 8:00 GMT+1
Source: WHO/GIP

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Cumulative number of confirmed cases of avian influenza A(H7N9) reported to WHO, by month, 2013

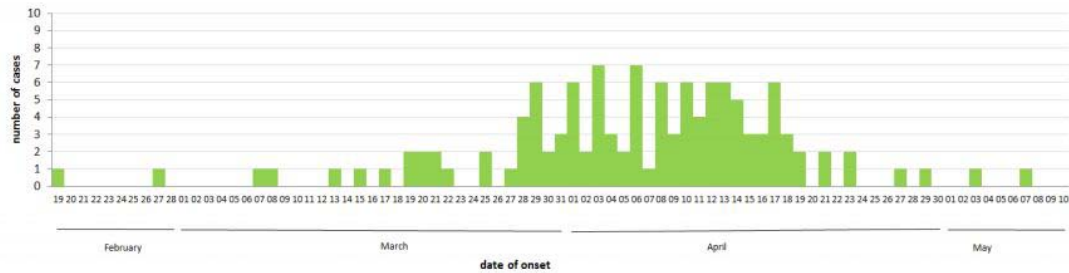
	February		March		April		May		unknown month of onset		Total	
	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths
Total	2	2	30	12	87	7	2	0	10	11	131	32

Total number of cases includes number of deaths
WHO reports only laboratory cases
All dates refer to onset of illness

Data in WHO/HQ as of 09 May 2013, 08:00 GMT+1
Source: WHO/GIP

Epidemiological curve of confirmed cases of avian influenza A(H7N9) reported to WHO, by day, 2013

N = 121 confirmed cases for whom date of onset is known



All dates refer to onset of illness

Data in WHO/HQ as of 09 May 2013, 08:00 GMT+1
Source: WHO/GIP



See also: *Disease Outbreak News*, WHO headquarters, www.who.int/csr/don/en/index.html

Infections with avian influenza A(H7N9) virus and epidemiology

Although these cases reported from China are the first known cases of human infection with an avian influenza A(H7N9) virus, this virus is one subgroup among the larger group of influenza A(H7) viruses which have previously been reported to cause sporadic human infections associated with poultry outbreaks. These infections in humans have mainly resulted in mild disease (e.g. conjunctivitis and mild upper respiratory symptoms). In contrast, many of the reported cases of human infection with avian influenza A(H7N9) virus have resulted in severe disease and deaths.

The source of infection and the mode of transmission for the A(H7N9) virus are currently unknown. Small clusters that may indicate limited human-to-human transmission have been detected, but there is no evidence of sustained, efficient human-to-human transmission. More than 2000 close contacts of confirmed cases and health care workers providing care for patients infected with A(H7N9) have been monitored by public health authorities for infection and have not developed clinical disease.

This virus has now also been isolated from poultry (including ducks and pigeons) in live bird markets in some areas of China. National and international human and animal health authorities are working hard to determine the source of infection. This work is complicated by the fact that so far this virus has not been associated with reports of severe disease in poultry and appears to be a low pathogenicity avian influenza (LPAI) virus.² Investigations are ongoing to determine if any animal reservoir of this virus exists, including other domestic and wild bird species, and mammalian species such as swine.

Clinical presentation

The main clinical feature among most avian influenza A(H7N9) patients has been respiratory disease resulting in severe pneumonia. Symptoms include fever, cough and shortness of breath. Many of the reported patients have required intensive care and mechanical ventilation. Only a few of the cases have reported mild disease.

Investigations are ongoing to determine the full spectrum of disease associated with avian influenza A(H7N9) infection.

Virology

The virus contains a group of avian influenza virus genes from multiple avian influenza viruses. The gene for the haemagglutinin or HA protein belongs to a Eurasian group of H7 avian influenza viruses, but is genetically distinct. The gene for the neuraminidase or NA protein is similar to avian A(H11N9) viruses found in South Korea in 2011, in Hongze, Jiangsu, China in 2010 and in the Czech Republic in 2005. The 6 genes coding for the internal proteins are similar to recent A(H9N2) viruses found in China and South Korea. Influenza A(H9N2) viruses are endemic in birds, including poultry, in Asia and elsewhere. Sequence analyses have shown that the genes of the avian influenza A(H7N9) viruses show signs of adaption to growth in mammalian species. These adaptations include an ability to bind to mammalian cell receptors, and to grow at temperatures close to normal body temperature of mammals (which is lower than that of birds).^{3,4}

Treatment

Laboratory tests have shown that avian influenza A(H7N9) viruses are sensitive to the neuraminidase inhibitors class of influenza drugs (oseltamivir and zanamivir), but resistant to the antiviral drugs amantadine and rimantadine. When antiviral drugs are given early in the course of illness, they have been found to be effective against seasonal influenza virus and influenza A(H5N1) virus infection. Treatment should still be initiated >48hrs after symptom onset if the patient has severe disease or is deteriorating.

Prevention

No vaccine is currently available, but the viruses from the initial cases have been isolated and characterized with the aim to select candidate viruses for the vaccine. WHO and its partners will continue to characterize available viruses to identify the best candidate viruses to be used should a need for global vaccine production arise. On 2 May WHO published the *Vaccine response to the avian influenza A(H7N9) outbreak – step 1: development and distribution of candidate vaccine virus*⁵, which describes the process of selecting candidate vaccine viruses as well as their release. An overview of the potential reassortant candidate vaccine viruses was published on 10 May 2013 and can be viewed on the WHO headquarters web site.⁶ Manufacturers, research institutes and other interested bodies can request the virus by contacting the WHO Collaborating Centres for Influenza and Essential Regulatory Laboratories of the Global Influenza Surveillance and Response System (GISRS)⁷.

On 10 May, WHO published the *Update of WHO biosafety risk assessment and guidelines for the production and quality control of human influenza vaccines against avian influenza A(H7N9) virus*⁸. The document updates WHO guidance to national regulatory authorities and vaccine manufacturers on the safe production and quality control of human influenza vaccines produced in response to a pandemic threat. It details international biosafety expectations for both pilot-scale and large-scale production, and quality control of vaccines against avian influenza A(H7N9) virus now causing human infections in China.

WHO/Europe would like to emphasize that while the source of infection and the mode of transmission have not yet been determined, it is prudent to follow good hygiene practices to prevent infection. For advice on infection prevention, contact with animals and food preparation, see [here](#). Guidance for infection prevention and control in health care settings is available [here](#).

2) WHO risk assessment as of 10 May 2013

There are several critical gaps in information at this stage, including lack of knowledge about the animal reservoir(s) in which this virus is likely circulating, the main exposures and routes of transmission for humans and the current extent of spread of the A(H7N9) virus among animal and human populations. The current WHO risk assessment published on 10 May 2013, can be summarized as follows:

I. Risk of the occurrence of further cases in the affected areas of China and other areas

The understanding of the epidemiology of this outbreak and virus remains limited, including the main reservoirs of infection and the extent of geographic spread among animals. However, it is likely that most human A(H7N9) infections have been associated with contacts with animals or live bird markets. Further human cases should be expected. Other avian influenza viruses such as A(H5N1) have demonstrated a seasonal pattern in which human cases have been less frequent in summer months and more frequent in winter months. It remains to be seen whether A(H7N9) infections will follow the same seasonal pattern (see epidemiological curve above). Most human cases have resulted in clinically severe illness.

II. Risk of human-to-human transmission

There is no evidence of sustained human-to-human transmission. However, the two possible family clusters suggest that limited human-to-human transmission may occur where there is close contact between cases and other people, as occurs in families and potentially in health care settings. Moreover, the genetic changes seen among these viruses that suggest adaptation to mammals is of concern, and further adaptation may occur. Should sustained human-to-human transmission occur with an increased number of clinically severe cases, health systems are likely to be strained.

III. Risk of international spread

There is no indication that international spread has occurred. An infected person, whether symptomatic or not, who travels to another country, could spread the infection. However, as the virus does not appear to cause sustained human-to-human transmission, extensive community spread is unlikely. If transmissibility were to increase, then possibility of spread would likewise increase.⁹

3) Recommendations

WHO/Europe reemphasizes the need for Member States to maintain the capacity to detect any unusual health event, including those that may be associated with a new subtype of influenza A, in accordance with the International Health Regulations (2005). Human health and animal health sectors should maintain close and systematic interactions for timely exchange of information and conduct joint risk assessments for the prevention and control of zoonotic diseases, as necessary. This work should be done under the relevant components of multi-hazard plans for preparedness and response to public health events.

Member States are encouraged to conduct national risk assessment, and update and implement the relevant components of multi-hazard plans for preparedness and response based on available information. A list of relevant information sources is provided at the end of this document.

WHO does not advise the implementation of special screening at points of entry with regard to this event, nor does it recommend that any travel or trade restrictions be applied.

Epidemiological and laboratory surveillance

Interim surveillance recommendations for human infection with avian influenza A (H7N9) virus were published by WHO on 10 May 2013.¹⁰ The investigation of cases should include complete epidemiological and clinical information, for example: clinical signs and symptoms, date of onset of symptoms, underlying clinical conditions, history of influenza vaccination, history of treatment with oseltamivir or zanamivir, contact with animals, and history of travel, among others. The recommendations include case definition and a minimal data set reporting form which should be completed for all confirmed cases and shared with WHO.

In addition to the above, **all specimens that cannot be subtyped for influenza A and those with inconclusive or unexpected subtyping results should be forwarded, immediately, to the WHO Collaborating Centre (WHO CC) for Reference and Research on Influenza, at the National Institute of Medical Research, London, United Kingdom for additional testing.**¹¹

Guidance for establishing real-time RT-PCR assays for the detection of avian influenza A(H7N9) virus by National Influenza Centres (NICs) in the WHO European Region has been developed by WHO Regional Office for Europe in collaboration with ECDC and the Community Network of Reference Laboratories for Human Influenza in Europe (CNRL) and has been distributed to NICs¹². Protocols for real-time RT-PCR were published by WHO on 8 April 2013 on the Global Influenza Programme web site.¹³ NICs could request the avian influenza A(H7N9) virus control material to validate their assays from the WHO CC, following the mechanism described in the Pandemic Influenza Preparedness (PIP) Framework.¹⁴ WHO CC for Surveillance, Epidemiology and Control of Influenza, at the Centers for Disease Control and Prevention, Atlanta, the United States of America has developed a new H7 Real-Time RT-PCR diagnostic kit which is available free of charge to all NICs and can be ordered from the Influenza Reagent Resource¹⁵.

Interim recommendations on laboratory biorisk management for laboratories handling human specimens suspected or confirmed to contain avian influenza A(H7N9) virus causing human disease were published by WHO on 10 May 2013.¹⁶ These recommendations reflect current understanding of avian influenza A(H7N9) virus causing human disease and recommend that all diagnostic laboratory work on clinical specimens taken from patients who are suspected or confirmed to be infected with avian influenza A(H7N9) virus be conducted according to practices and procedures described for basic laboratory — Biosafety Level 2 (BSL2).¹⁷ Virus isolation on clinical specimens from patients who are suspected or confirmed to be infected with avian influenza A(H7N9) virus should be performed only in laboratories capable of meeting the containment requirements for Biosafety Level 3 (BSL3). The document contains:

1. biorisk management checklist for laboratory managers and staff;
2. recommendations addressing essential working conditions associated with specific manipulations in laboratory settings.

Information for the public

Although there is no evidence of ongoing human-to-human transmission, it is important to implement the following measures to prevent transmission of respiratory viruses:

- Washing hands to reduce transmission.
- Use of “respiratory etiquette” to help prevent transmission of the virus.
- Individuals with flu-like symptoms should avoid leaving their homes to go to work or to other public places and seek medical advice if their condition worsens.

Preventive and control measures in the community should be disseminated in multiple languages to reach all population groups.

4) Additional information

WHO/Europe and other international organizations provide information about this event through the web sites listed below. WHO/Europe is working to make key documents available in Russian. As documents become available in Russian, they will be listed in this update. IHR National Focal Points will continue to receive information through the Event Information Site (EIS).

- WHO headquarters
www.who.int/influenza/human_animal_interface/influenza_h7n9/en/index.html
- WHO Regional Office for Europe
[www.euro.who.int/A\(H7N9\)](http://www.euro.who.int/A(H7N9))
- World Organisation for Animal health
<http://www.oie.int/en/animal-health-in-the-world/web-portal-on-avian-influenza/>
- Food and Agriculture Organization of the United Nations
http://www.fao.org/ag/againfo/programmes/en/empres/AH7N9/index_H7N9.html
- European Centre for Disease Prevention and Control
http://ecdc.europa.eu/en/healthtopics/avian_influenza/Pages/index.aspx

5) References

- ¹ Number of confirmed human cases of avian influenza A(H7N9) reported to WHO [web site]. Geneva, World Health Organization, (www.who.int/influenza/human_animal_interface/influenza_h7n9/Data_Reports/en/index.html, accessed 10 May 2013).
- ² Understanding avian influenza: Current state of knowledge on Highly Pathogenic Avian Influenza [web site]. Rome, Italy, Food and Agriculture Organization of the United Nations (FAO) (http://www.fao.org/avianflu/documents/key_ai/key_book_ch2.htm, accessed 22 April 2013).
- ³ Public health relevant virological features of influenza A(H7N9) causing human infection in China [web site]. Copenhagen, Denmark, World Health Organization Regional Office for Europe. (<http://www.euro.who.int/en/what-we-do/health-topics/communicable-diseases/influenza/publications/2013/public-health-relevant-virological-features-of-influenza-ah7n9-causing-human-infection-in-china>, accessed 22 April 2013).
- ⁴ Liu D, Shi W, Shi Y, Wang D, Xiao H, Li W, et al. Origin and diversity of novel avian influenza A H7N9 viruses causing human infection: phylogenetic, structural, and coalescent analyses. In: Lancet. 2013/05/07 ed. Available at: <http://www.sciencedirect.com/science/article/pii/S0140673613609381>.
- ⁵ Vaccine response to the avian influenza A(H7N9) outbreak - step 1: development and distribution of candidate vaccine viruses as of 2 May 2013 [web site]. Geneva, Switzerland, World Health Organization http://www.who.int/influenza/vaccines/virus/CandidateVaccineVirusesH7N9_02May13.pdf
- ⁶ http://www.who.int/influenza/vaccines/virus/candidates_reagents/a_h7n9/en/index.html
- ⁷ WHO Collaborating Centres for influenza and Essential Regulatory Laboratories : http://www.who.int/influenza/gisrs_laboratory/collaborating_centres/list/en/index.html
- ⁸ Update of WHO biosafety risk assessment and guidelines for the production and quality control of human influenza vaccines against avian influenza A(H7N9) virus [web site]. Geneva, World Health Organization. (http://www.who.int/biologicals/areas/vaccines/influenza/biosafety_risk_assessment_10may2013.pdf, accessed 13 May 2013).
- ⁹ WHO risk assessment: Human infections with influenza A(H7N9) virus as of 10 May 2013 [web site]. Geneva, Switzerland, World Health Organization, (http://www.who.int/influenza/human_animal_interface/influenza_h7n9/RiskAssessment_H7N9_10May13.pdf accessed 13 May 2013).
- ¹⁰ Interim WHO surveillance recommendations for human infection with avian influenza A(H7N9) virus as of 10 May 2013 [web site]. Geneva, Switzerland, World Health Organization, (http://www.who.int/influenza/human_animal_interface/influenza_h7n9/InterimSurveillanceRecH7N9_10May13.pdf, accessed 13 May 2013).
- ¹¹ WHO Collaborating Centres for influenza and Essential Regulatory Laboratories [web site]. Geneva, Switzerland, World Health Organization, (www.who.int/influenza/gisrs_laboratory/collaborating_centres/list/en/ (accessed 22 April 2013).
- ¹² Technical Briefing note: Diagnostic preparedness in Europe for detection of avian influenza A(H7N9) viruses [web site]. Stockholm, Sweden, European Centre for Disease Prevention and Control (ECDC). (<http://ecdc.europa.eu/en/publications/publications/avian-influenza-h7n9-microbiology-diagnostic-preparedness-for-detection.pdf>, accessed 25 April 2013).
- ¹³ Real-time RT-PCR Protocol for the Detection of Avian Influenza A(H7N9) Virus [web site]. Geneva, Switzerland, World Health Organization (http://www.who.int/influenza/gisrs_laboratory/a_h7n9/en/, accessed 22 April 2013).

¹⁴ Pandemic Influenza Preparedness (PIP) Framework [web site]. Geneva, World Health Organization, (http://www.who.int/influenza/resources/pip_framework/en/), accessed 08 May 2013).

¹⁵ CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel-Influenza A/H7 (Eurasian Lineage) Assay (EUA) (Catalog No. FluEUA-01), FR-1240. Influenza Reagent Resource, Influenza Division, WHO Collaborating Center for Surveillance, Epidemiology and Control of Influenza, Centers for Disease Control and Prevention, Atlanta, the United States of America (<http://www.influenzareagentresource.org/> accessed 08 May 2013).

¹⁶ Laboratory biorisk management for laboratories handling human specimens suspected or confirmed to contain avian influenza A(H7N9) virus causing human disease - interim recommendations [web site]. Geneva, Switzerland, World Health Organization, (http://www.who.int/influenza/human_animal_interface/influenza_h7n9/InterimRecLaboratoryBioriskManagementH7N9_10May13.pdf), accessed 13 May 2013).

¹⁷ World Health Organization (2004). *Laboratory biosafety manual*. 3 ed. Geneva, Switzerland.