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REGIONAL OFFICE FOR Europe

WHO Regional Office for Europe overview on avian influenza for public health professionals

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This overview summarizes the available information and recommendations made by WHO about human infections with avian influenza viruses 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.

Avian influenza overview

Avian influenza viruses cause infections in wild, domestic and captive birds. They are divided into two groups based on their ability to cause disease in chickens: high pathogenicity (HPAI) that cause severe disease and high death rates or low pathogenicity (LPAI) that are more often associated with subclinical infection **[1]**. Human infections with avian influenza are rare and may be caused by both HPAI and LPAI viruses. When they have occurred, these viruses have not spread easily from person to person. However, because avian and other animal influenza viruses that cross the animal-human divide have the potential to become a pandemic threat if they become easily transmittable between people, an intersectoral approach to control the disease in animals as well as the implementation of public health measures to prevent and manage infections in humans is needed. WHO supports countries' activities in this area together with partners World Organization for Animal Health (OIE) and Food and Agriculture Organization of the United Nations (FAO).

This overview summarizes information on avian influenza viruses currently known to infect humans. Three subtypes of avian influenza A (H5, H7 and H9) are known to infect people; however rare, sporadic infections of humans with other subtypes have been documented (see Table 1 for cases of known AI viruses to have infected humans). Since 2013, several new LPAI viruses (**A(H7N9)**, **A(H6N1)**, **A(H10N8)**) have infected humans and sometimes led to severe or lethal cases. HPAI **A(H5N1)** has been detected in humans since 2003 and regularly causes new fatalities. One novel HPAI **A(H5N6)** virus have been reported to cause human disease for the first time in 2014. In addition, according to reports received by OIE, several outbreaks of avian influenza in poultry as well as infections in wild birds have been reported in Europe and in other WHO regions, including the first detection of HPAI **A(H5N8)** and **A(H5N1)** in birds in the Americas.

Table 1. Human infection with avian influenza viruses

Subtype	Pathogenicity in chickens	Country reporting/year of first report in human	Laboratory confirmed human cases*	Clinical severity	Viruses found in birds
A(H5N1)	HPAI	Azerbaijan/2006 [2], Bangladesh/2008 [3], Cambodia/2005 [4], Canada/2014 [5], China/1997 [6], Djibouti/2006 [7], Egypt/2006 [8], Indonesia/2005 [9], Iraq/2006 [10], Lao People's Democratic Republic/2007 [11], Myanmar/2007 [12] , Nigeria/2007 [13], Pakistan/2007 [14], Thailand/2004 [15], Turkey/2006 [16], Viet Nam/2004 [17].	18 in 1997, 784 since re-emergence in 2003	Severe, high fatality	Enzootic in some countries
A(H5N6)	HPAI	China/2014 [18]	3	Severe	Detected in poultry in multiple locations in China
A(H6N1)	LPAI	China/2013 [19]	1	Moderate	Circulates in bird populations worldwide

A(H7N2)	LPAI	United Kingdom/2007 [20], USA/2003 [21]	5	Mild to moderate	Detected in poultry
A(H7N3)	LPAI/HPAI	Canada/2004 [22], Mexico/2012 [23], United Kingdom/2006 [24].	5	Mild	Circulates in bird populations worldwide
A(H7N7)	LPAI/HPAI	Italy/2013 [25], Netherlands/2003 [26], United Kingdom/1995 [27].	96	Mild	Circulates in bird populations worldwide
A(H7N9)	LPAI	China/2013 [28], Canada/2015 [29], Malaysia/2014 [30].	602	Severe, high fatality	Detected in pigeons and chickens and environments in poultry markets in China
A(H9N2)	LPAI	Bangladesh/2011 [31], China/1998 [32], Egypt/2015 [33].	19	Usually mild	Endemic in poultry in Africa, Asia and the Middle East
A(H10N7)	LPAI	Australia/2010 [34], Egypt/2004 [35].	4	Mild	Circulates in bird populations worldwide
A(H10N8)	LPAI	China/2013 [36]	3	Severe, fatal	Limited information on circulations in bird populations

***** The most current information on confirmed cases can be found in: Disease Outbreak News (DONs), Monthly Risk Assessment Summary.

Human cases of avian influenza due to LPAI A(H9N2), A(H7N9) and A(H10N8)

The **A(H9N2)** virus was first detected in China. Since then, it has become the dominant virus in poultry in China despite vaccination campaigns **[37]**, and is now enzootic in a number of other countries **[38]**. Since 1999, a handful of mild human cases have been detected in Hong Kong Special Administrative Region of China, mainland China, Bangladesh, and most recently Egypt.

Although **A(H9N2)** has so far not been reported to cause severe disease in humans, through genetic reassortment it contributes to the evolution and emergence of new LPAI capable of infecting humans and causing severe disease. Indeed, a constellation of internal genes from **A(H9N2)** has been found in A(H5N1) **[39]**, **A(H7N9) [40]** and **A(H10N8) [41]**, all of which have led to severe disease in humans over the past two years.

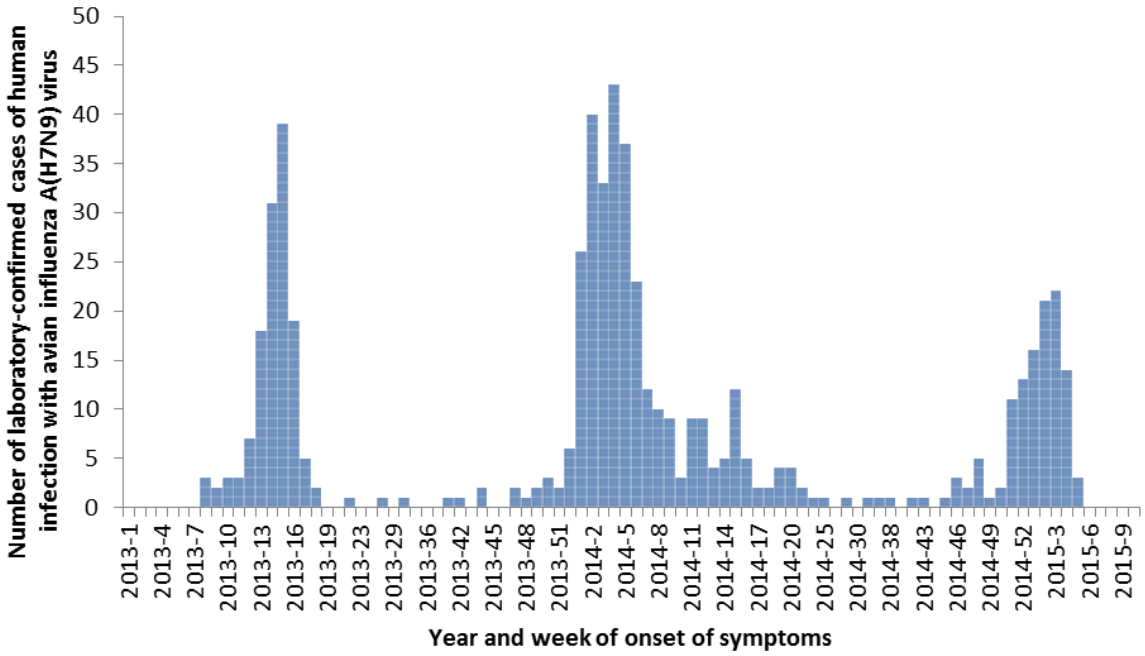
The influenza A(H7) viruses are known to circulate in poultry populations worldwide. Occasionally, human cases of infection with influenza A(H7) viruses have been reported in people with direct exposure to poultry causing usually mild disease. However some infections could lead to severe disease **[21, 24, 27, 42, 43]**. In March 2013, a LPAI A(H7N9) virus have been detected in humans in China associated with the severe respiratory disease. Since then, the **A(H7N9)** virus has caused over 600 human cases and 227 deaths, the majority of which show a seasonal pattern (see Fig 1) and have occurred in persons with median age of 57 years (range 0-91 years). Severe disease is more likely to occur in older patients with underlying chronic conditions such as coronary heart disease, diabetes, and chronic obstructive pulmonary disease [**44**]. The cases have been identified in the eastern part of mainland China, Hong Kong Special Administrative Region of China and Taiwan, but China travel-related cases have been reported in Malaysia and Canada.

A(H7N9) contains six internal genes that originated from **A(H9N2)**, and several recent studies show that poultry farms and live poultry markets are sites of continuing reassortment between various strains of **A(H7N9)** and **A(H9N2) [45,46]**. **A(H7N9)** may more readily infect humans than **A(H9N2)** due, among other factors, to the relative affinity of H7 for human receptors **[47**, **48, 49]**.

The **A(H10N8)** virus was first detected in humans in 2013, the virus has previously been detected in wild and domestic birds China, there have only been three human cases of **A(H10N8)**. The investigation of these cases is ongoing, so far, there is no evidence of human-to-human transmission [**36**].

One of the main causes of concerns regarding LPAI viruses is that they cause subclinical disease in poultry, making it difficult to detect and control them, yet may cause severe disease in humans.

Fig. 1. Laboratory-confirmed cases of human infection with avian influenza A(H7N9) virus by week of onset



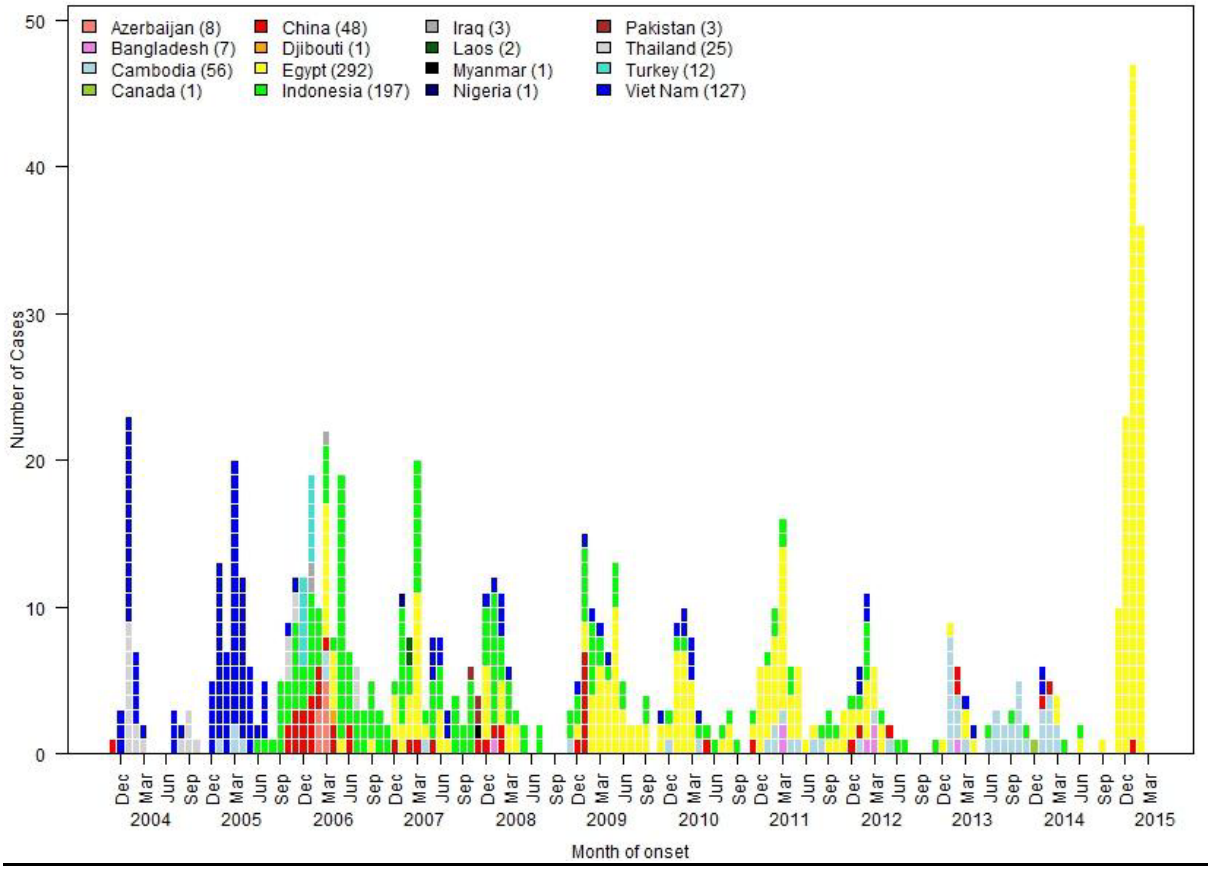
Source: WHO risk assessment of human infection with avian influenza A(H7N9) virus, 23 February 2015.

Human cases of avian influenza due to HPAI A(H5N1) and A(H5N6)

As of March 2015, there have been more than 780 laboratory confirmed human cases of **A(H5N1)**, and over 400 deaths since 2003. Human cases have been reported in 16 countries in all six WHO regions with the majority of cases occurring in south east Asia, China and Egypt. Most recently, Egypt, where the virus was first detected in 2006, has been reporting a high number of cases and the number of laboratory confirmed human cases of avian influenza **A(H5N1)** virus infection reported by Egypt in December 2014, January and February 2015 was the highest reported by any country in a single month (Fig.2). Since the beginning of 2015, another 83 cases were reported by Egypt.

Current epidemiological and virological investigations of the situation are ongoing, and preliminary results point at a mixture of factors including increased circulation of influenza **A(H5N1)** viruses in poultry, lower public health awareness of risks in middle- and upper- Egypt and seasonal factors such as closer proximity to poultry because of cold weather and possible longer survival of the viruses in the environment, rather than at major genetic changes in the virus.

Fig. 2. Laboratory-confirmed cases of human infection with avian influenza A(H5N1) virus by week of onset



Source: WHO Monthly Risk Assessment Summary: Influenza at the Human-Animal Interface, 3 March 2015

Three human cases of **A(H5N6)** were reported in China in recent months (April and December 2014, February 2015). These are the only 3 known human cases of **A(H5N6)**. Genetic studies indicate that these **A(H5N6)** viruses might be reassortants between **A(H5N1)** clade 2.3.4 and **A(H6N6)** viruses **[50]**.

Poultry Outbreaks

Various H5 subtypes have caused outbreaks in the recent months in Europe, North America and Asia without leading to documented human infections: **A(H5N2), A(H5N3)**, and **A(H5N8)**.

The first detections of HPAI **A(H5N8)** and **A(H5N1)** in birds in the Americas were reported in December 2014/January 2015. The North American **A(H5N1)** reassortant is genetically different from the avian influenza **A(H5N1)** viruses reported elsewhere.

Widespread outbreaks of **A(H5N8)** were reported earlier in the Republic of Korea, Japan and China, and the virus reached Europe in late 2014, causing outbreaks in Germany, Israel, Italy, the Netherlands, Russian Federation and the United Kingdom. Most recently, the virus was detected in a duck farm in Hungary in late February and in wild birds in Sweden in March. Investigations of at least some of these outbreaks point at contact with wild species as the most likely source of infection. Some countries in the WHO European Region, Bulgaria, Israel and Romania, reported outbreaks of HPAI **A(H5N1)** in wild birds and poultry in 2015.

Advice to national authorities[1]

Intersectoral approach

Control of the disease in animals is the first step in decreasing risks to humans. Therefore, it is important, both in the animal and human health sector, to undertake prevention and control activities in a coordinated and collaborative manner. Efficient information sharing mechanisms should be established and/or strengthened to facilitate coordinated decision-making.

Surveillance for human infections

People directly or indirectly exposed to infected birds and those individuals participating in the culling and cleaning operations on affected farms are at risk of infection. Appropriate personal protective equipment (PPE) and other protective measures to prevent zoonotic transmission in these operators is strongly recommended.

For early detection of animal-human transmission, surveillance of exposed persons is recommended. It is recommended to monitor for the occurrence of influenza-like-illness (ILI) or severe acute respiratory infection (SARI) in persons who have been exposed to birds (domestic, wild or captive birds) infected with avian influenza viruses.

Clinicians and health care workers should be informed of the possibility of human infection in exposed people and should consider testing patients with ILI or SARI who have had recent contact with birds with HPAI or LPAI, especially in areas where these viruses have been identified.

Laboratory diagnostics

The specific diagnosis of human infection with avian influenza is based on the detection of viral genome by molecular techniques (Polymerase chain reaction – PCR) in swab specimens (oropharyngeal or nasopharyngeal), nasopharyngeal aspirate or bronchoalveolar lavage (only in hospitalized patients), taken within the first seven (7) days (maximum 10) from the onset of symptoms.

The diagnostic algorithm includes an initial screening for Influenza A or B followed by the identification of the specific hemagglutinin protein gene that will define the subtype (H1, H3, H5, H7,

[1] Adapted from 6 February 2015: Epidemiological Alert – Detection and outbreaks of Avian Influenza due to reassortant viruses, public health implications for the Americas , WHO Regional Office for Americas

H9 etc.). All influenza A viruses for which it has not been possible to determine the subtype (unsubtypable) or those that are defined as an avian subtype (H5, H7, etc.) should be immediately sent, under appropriate conditions, to a WHO Collaborating Centre (WHO CC) for a more complete antigenic and molecular characterization.

As part of the WHO Global Influenza Surveillance and Response System (GISRS), all Member States of the WHO European Region with influenza surveillance schemes in place (50) have the capacity for molecular detection of H5 (and some also to subtype H7 and H9). In order to maintain the quality and standards of detection of subtype influenza viruses using PCR, National Influenza Centres (NICs) in the WHO European Region participate in the annual WHO External Quality Assessment Programme for the Detection of Influenza Viruses by PCR. WHO Regional Office for Europe supports the regional influenza laboratory network by providing training, technical guidelines and external quality assurance programmes in cooperation with the WHO Collaborating Centre for Reference and Research on Influenza, at the Medical Research Council National Institute for Medical Research, London, United Kingdom (WHO CC), with the European Centre for Disease Prevention and Control (ECDC) and European Reference Laboratory Network for Human Influenza (ERLI-Net).In addition, established mechanisms are in place for shipment of samples and virus isolates for complete characterization to the WHO Collaborating Centres.

Antiviral treatment

Evidence suggests that some antiviral drugs, notably oseltamivir, can reduce the duration of viral replication and improve the prognosis. In suspected cases, irrespective of severity, oseltamivir should be prescribed as soon as possible (ideally, within 48 hours following symptom onset) to maximize its therapeutic benefits and immediately on admittance to hospital for severe cases. The use of corticosteroids is not recommended.

Related links

- Pan American Health Organization (PAHO), Epidemiological Alert, Detection and outbreaks of Avian Influenza due to reassortant viruses, public health implications for the Americas, 6 February 2015
  http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&Itemid=270&gid=29002&lang=en

- WHO: Influenza at the Human-Animal Interface
  http://www.who.int/influenza/human_animal_interface/en/

- WHO Monthly Risk Assessment Summary at the human-animal interface
  http://www.who.int/influenza/human_animal_interface/Influenza_Summary_IRA_HA_interface_26January2015.pdf?ua=1

- WHO: Warning signals from the volatile world of influenza viruses
  http://www.who.int/influenza/publications/warningsignals201502/en/

- WHO Regional Office for Europe, Zoonotic influenza
  http://www.euro.who.int/en/health-topics/communicable-diseases/influenza/zoonotic-influenza

- World Organization for Animal Health (OIE), Avian influenza portal
  http://www.oie.int/animal-health-in-the-world/web-portal-on-avian-influenza/

- Food and Agriculture Organization of the United Nations (FAO), Avian Influenza A(H7N9)
  http://www.fao.org/ag/againfo/programmes/en/empres/H7N9/index.html

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