



## RAPID RISK ASSESSMENT

# Human infection with avian influenza A(H5N1) virus, Egypt

First update, 13 March 2015

### Main conclusions and options for action

Human cases and fatalities due to influenza A(H5N1) virus continue to increase in Egypt, with cases from the country now accounting for the highest number of human cases reported worldwide.

Continuous increase of virus circulation in backyard poultry and exposure to infected poultry are most probably contributing to the increase in human cases. Whenever avian influenza viruses circulate in poultry, sporadic infections and small clusters of human cases are possible in people exposed to infected poultry or contaminated environments.

Although Egypt has reported an increased number of animal-to-human infections over the past few months, the influenza A(H5) viruses do not appear to transmit easily among people, and no sustained human-to-human transmission has been observed. As such, the risk of these viruses spreading in the community remains low.

Increased human infectivity of the circulating virus and the protection conferred by the poultry vaccines currently in use should be further investigated.

The current assessment remains that there is no risk for the general public in the EU. Travellers from the EU should avoid direct contact with poultry or poultry products when travelling to Egypt.

There is a low but ongoing and continuous risk of the virus being introduced and cases being imported into Europe and therefore both veterinary and public health authorities should maintain preparedness.

## Source and date of request

ECDC internal decision, 9 March 2015

## Public health issue

This document aims to:

- summarise the epidemiological, virological and environmental information about human infections with avian influenza A viruses of subtype A(H5N1) in Egypt;
- assess potential changes in the risk to public health in the EU/EEA and to EU/EEA citizens.

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## Disease background information

Highly pathogenic avian influenza (HPAI) virus type A(H5N1) is very infectious for a number of bird species, including most species of domestic poultry [1–4]. Unlike most other avian influenza viruses, this virus type has also infected mammals, including cats, tigers and pigs, and is potentially infectious for humans [5]. However, the virus remains poorly adapted to humans, and transmission from birds to humans is infrequent [6–10]. Since the first zoonotic transmission of A(H5N1), limited clusters of human cases have been observed in affected countries worldwide with no sustained human-to-human transmission. Zoonotic transmission to humans from infected birds occurs either directly or through environmental contamination. Hence, almost all human infections have been related to close contact with infected or sick birds or their faecal products in domestic settings – e.g. in ‘wet markets’ in Asia or in backyard farming [9,11].

The most commonly identified risk factors associated with A(H5N1) virus infection include contact with infected blood/organs or bodily fluids of infected poultry via food preparation practices; touching and caring for infected poultry; exposure to A(H5N1) via swimming or bathing in potentially virus-laden ponds and exposure to A(H5N1) at live bird markets in Asia and via backyard poultry in Egypt [11,12]. WHO has published a proposal for candidate vaccine viruses for pandemic preparedness [13].

Since 1996, when they were first observed in China, A(H5N1) viruses have affected poultry, initially in the Far East and later in parts of Europe, the Middle East, Africa and the United States [14]. The virus was introduced into Egypt in 2006, and since then a separate virus clade has evolved from the strains found in Asia [13].

The first human case of A(H5N1) avian influenza in Egypt was diagnosed in 2006 [15]. Raising poultry in households is common in Egypt, where community awareness of the risks of avian influenza seems to remain low. In December 2014, the Egyptian veterinary authorities indicated that the capacity of veterinary services to investigate outbreaks and carry out surveillance was challenged, mainly by limited resources (e.g. manpower, vehicles and equipment). The authorities faced difficulties in controlling the disease due to the high density of commercial and household poultry flocks, the intensity of bird movements and low awareness of the disease in the rural population.

The political unrest in Egypt may have contributed to a reduced surveillance capacity but it is believed that the situation and surveillance activities improved in 2014.

The public health impact of H5 vaccination programmes in poultry has been limited, as the vaccination does not prevent shedding and human exposure to the virus, although it reduces the severity of clinical signs and mortality of vaccinated poultry [16]. Circulation of A(H5N1) viruses in vaccinated flocks has been detected [17].

## Human and avian surveillance of A(H5N1) in Egypt

Influenza is a notifiable disease in Egypt, and the country has well-established sentinel surveillance systems for influenza-like illnesses (ILI) and acute respiratory infections (ARI), covering 12 public (Ministry of Health) hospitals and one polyclinic, including three mutual sites serving for both ILI and SARI. Since 2006, all healthcare facilities have been obliged to notify suspected A(H5N1) cases – ILI/ARI with bird contact – and confirmed, PCR-positive cases to the Ministry of Health. A hospital-based surveillance system was established in 2009 to report ILI/severe acute respiratory infection (SARI)/pneumonia cases, and samples from severe SARI/pneumonia cases or cases without clear diagnosis are sent to laboratory to be tested for influenza viruses and MERS-CoV.

A recent study estimated that the seroprevalence of anti-A(H5N1) antibodies (titre  $\geq 80$ ) among Egyptians who are exposed to poultry was 2% [18].

Egypt implemented a routine nationwide avian influenza surveillance programme after a ministerial decree (number 221) in 2006. The National Laboratory for Veterinary Quality Control on Poultry Production is in charge of the official diagnosis and surveillance of avian influenza virus in Egypt. Between 2009 and 2010, tracheal and cloacal swabs were collected from domestic poultry at 22 024 commercial farms, 1 435 backyard holdings and 944 live bird markets, as well as from 1 297 wild birds representing 28 different migratory types [19]. In mid-2014, ring vaccination of household poultry was re-introduced after several years of only vaccinating the commercial sector. This was increased to mass vaccination of household poultry in December 2014 and January 2015 (communicated by the UN Food and Agriculture Organization office, Egypt).

## Human and avian surveillance of A(H5N1) in Europe

All novel influenza strains are notifiable diseases in the EU under EU legislation and the International Health Regulations\* (IHR) through the Early Warning and Response System (EWRS) and IHR, respectively. Human infections with A(H5N1) are notifiable according to EU Decision 1082/2013/EU [20,21]. Commission Decision 2008/426/EC lays down case definitions for reporting communicable diseases in EU [2008/426/EC: Commission Decision of 28 April 2008 amending Decision 2002/253/EC laying down case definitions for reporting communicable diseases to the Community network under Decision No 2119/98/EC of the European Parliament and of the Council](#).

EU legislation for surveillance and control of highly pathogenic avian influenza viruses is in place [22–24].

## Event background information

### Human cases in the world

Between 2003 and 3 March 2015, 784 laboratory-confirmed human cases of avian influenza A(H5N1) virus infection, including 429 deaths, were reported to WHO from 16 countries (Table 1, Figure 1). The number of human cases at the beginning of March 2015 is already the third highest number of cases reported in any given year, and higher than 2007 when A(H5N1) was affecting nine different countries. The most affected countries cumulatively are Egypt and Indonesia. In 2014 and 2015, Egypt reported the most cases and has become the most affected country with the highest number of human cases (Table 1). So far in 2015, Egypt has had the highest number of cases reported by a country since the emergence of the virus.

Whenever avian influenza viruses are circulating in poultry, sporadic infections or small clusters of human cases are possible in people exposed to infected poultry or contaminated environments, especially in households. Human infections remain rare, and influenza A(H5N1) viruses do not currently appear to transmit easily between people. As such, the risk of these viruses spreading in the community remains low [25].

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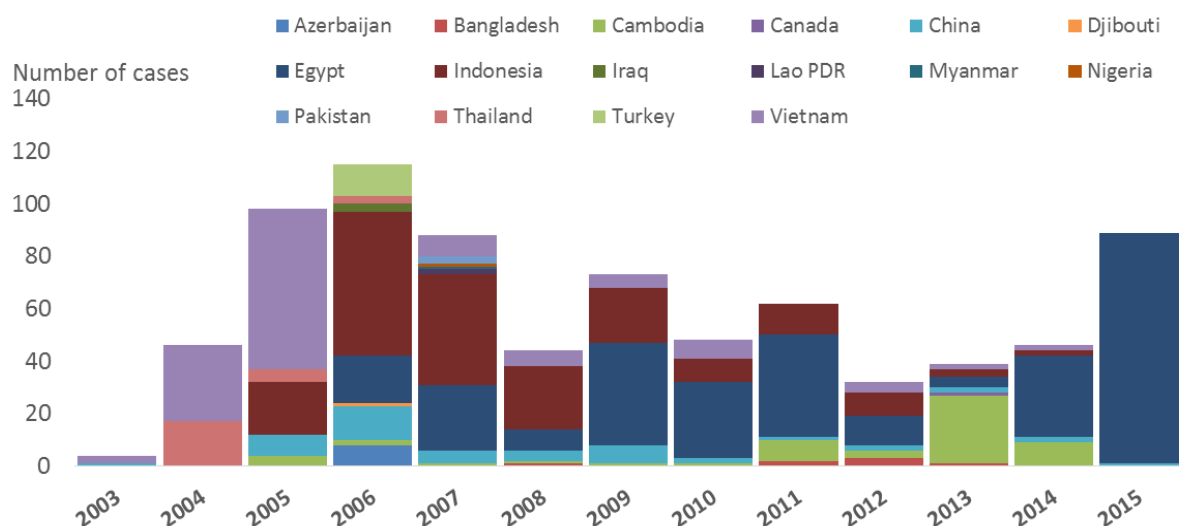
\* Case definitions for the four diseases requiring notification in all circumstances under the International Health Regulations (2005) available at [http://www.who.int/ihr/Case\\_Definitions.pdf?ua=1](http://www.who.int/ihr/Case_Definitions.pdf?ua=1).

**Table 1. Distribution of A(H5N1) cases by country and year, February 2003 to 3 March 2015**

Reporting country	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Total
Azerbaijan				8										8
Bangladesh						1			2	3	1			7
Cambodia			4	2	1	1	1	1	8	3	26	9		56
Canada											1			1
China	1		8	13	5	4	7	2	1	2	2	2	1	48
Djibouti				1										1
Egypt				18	25	8	39	29	39	11	4	31	88	292
Indonesia			20	55	42	24	21	9*	12	9	3	2		197
Iraq				3										3
Laos					2									2
Myanmar					1									1
Nigeria					1									1
Pakistan					3									3
Thailand		17	5	3										25
Turkey				12										12
Vietnam	3	29	61		8	6	5	7		4	2	2		127
<b>Total</b>	<b>4</b>	<b>46</b>	<b>98</b>	<b>115</b>	<b>88</b>	<b>44</b>	<b>73</b>	<b>48</b>	<b>62</b>	<b>32</b>	<b>39</b>	<b>46</b>	<b>89</b>	<b>784</b>

Source: WHO/GIP, data in HQ as of 3 March 2015 [15]

**Figure 1. Cumulative number of global confirmed human cases of avian influenza A(H5N1) reported to WHO, 2003–2015, as of 3 March 2015**



Source: WHO/GIP, data in HQ as of 3 March 2015 [15]

### Human cases in Egypt

According to a global WHO update on 3 March 2015 there have been 88 human cases of influenza A(H5N1), including 26 deaths reported in Egypt in 2015 [14].

The number of laboratory-confirmed human cases of avian influenza A(H5N1) virus infection in Egypt with onsets of illness in December 2014, January and February 2015 is the highest reported by any country in a single month (Figure 2). The number of fatal cases in 2015 is higher than in the previous two years (Table 2). The number of reported cases remained at the same high level for each week since the beginning of 2015 (Figure 3). The case-fatality rate for 2015 so far is 30%, although for recent cases the final outcomes may not yet be known. There appears to have been no discernible trend in the case-fatality rate between 2006 and 2015. Most cases are reported from central Egypt, along the Nile River and in the Nile Delta (Map 1). Location of the human cases overlaps significantly with areas of reported outbreaks of A(H5N1) in domestic poultry. The increase in human cases can be attributed to 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 possibly longer survival of the viruses in the environment [25]. A high-level joint WHO/FAO/OIE\* mission to Egypt to assess the risks associated with the influenza A(H5N1) viruses and to recommend control measures is planned for early March 2015.

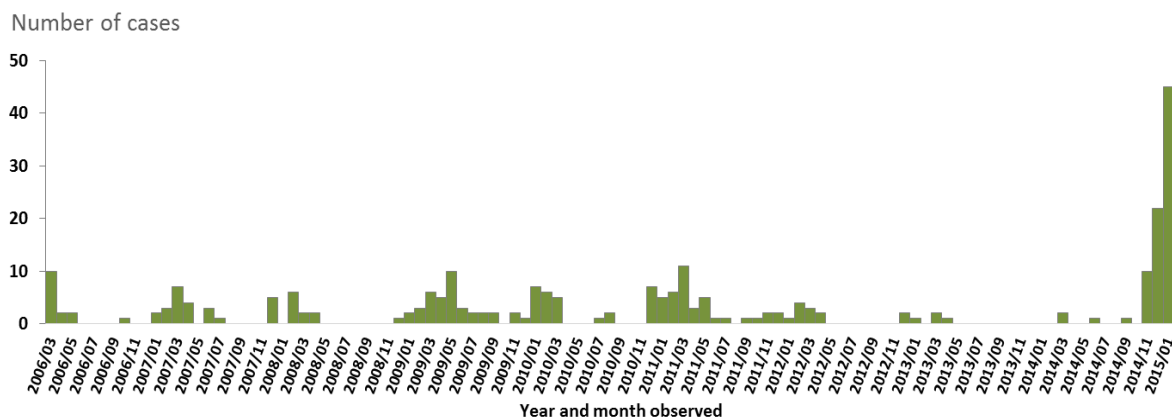
\* OIE - World Organisation for Animal Health

**Table 2. A(H5N1) number of cases and deaths in Egypt, 2006–2015 (as of 3 March 2015)**

Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Number of cases	18	25	8	39	29	39	11	4	31	88
Number of deaths	10	9	4	4	13	15	5	3	9	26
CFR	56%	36%	50%	10%	45%	38%	45%	75%	29%	30%

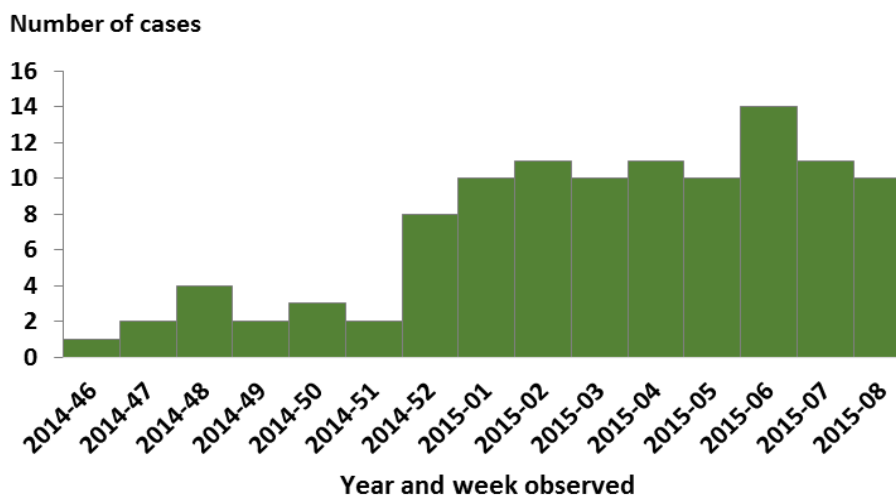
Source: WHO[15]

**Figure 2. Number of human cases of A(H5N1) observed in Egypt, by year and month, March 2006 to February 2015**



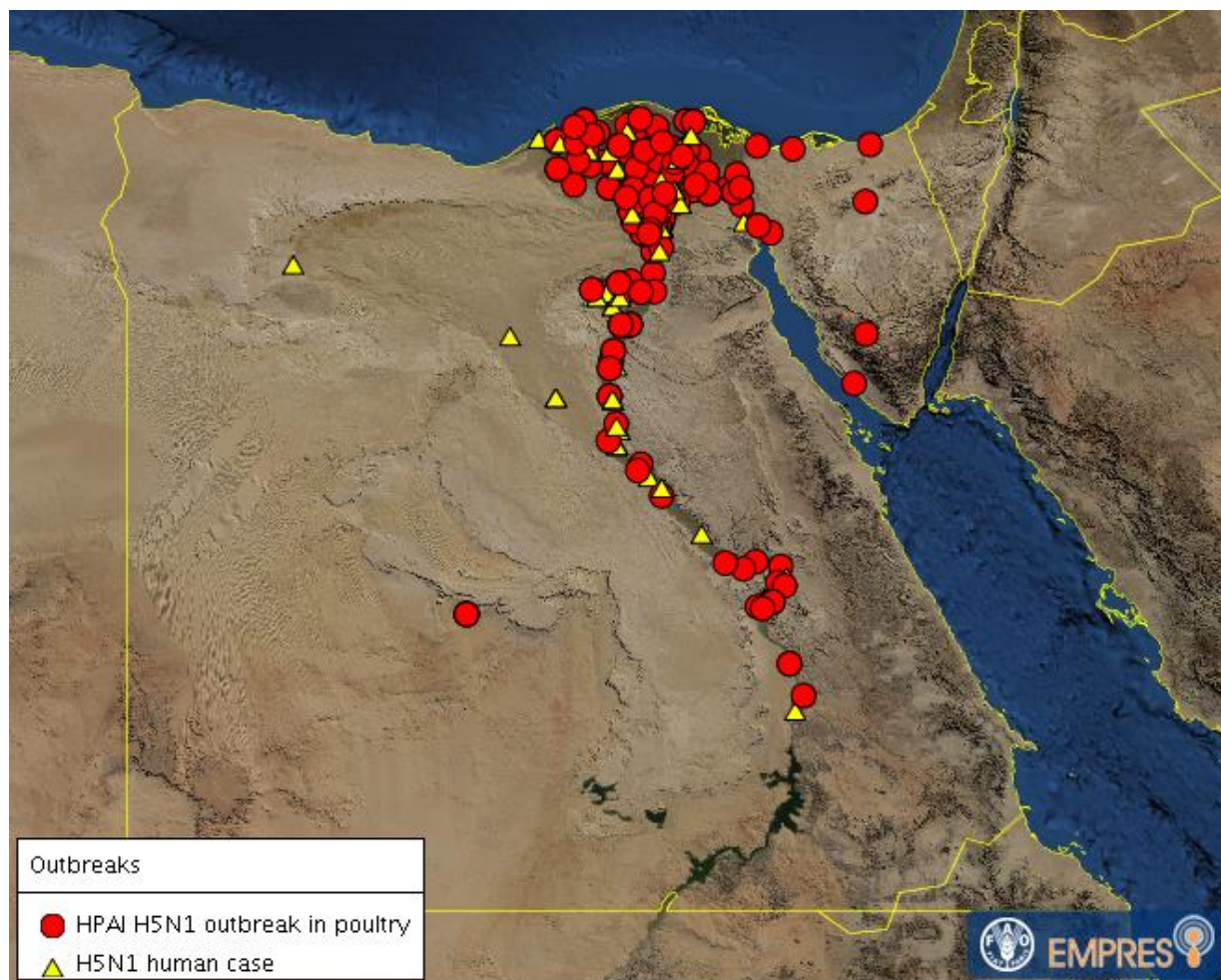
Source: EMPRES-i; available from: <http://empres-i.fao.org/eipws3g>; accessed 9 March 2015

**Figure 3. Number of human cases of A(H5N1) observed in Egypt, by year and week, week 46–2014 to week 8–2015**



Source: EMPRES-i; available from: <http://empres-i.fao.org/eipws3g>; accessed 9 March 2015

**Map 1. Geographical distribution of human cases and outbreaks of A(H5N1) in poultry reported in Egypt, 1 January 2015–12 March 2015**



Source: EMPRES-i; available from: <http://empres-i.fao.org/eipws3q> accessed 12 March 2015, provided by FAO

## Situation of highly pathogenic avian influenza virus A(H5N1) in birds

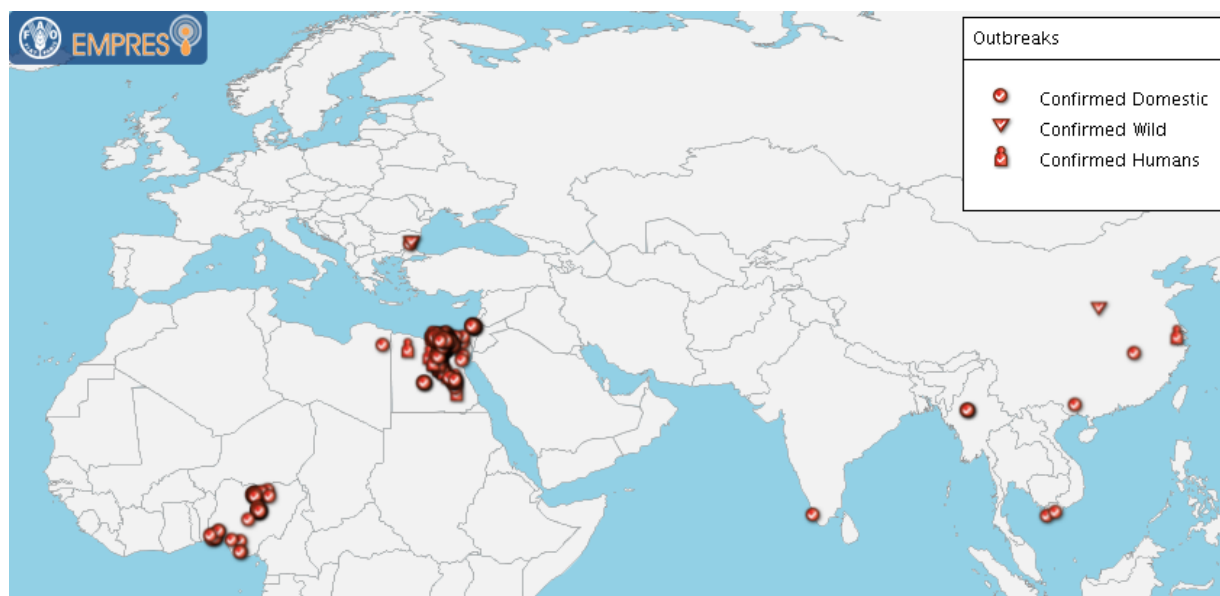
Various influenza A(H5) subtypes, such as influenza A(H5N1), A(H5N2), A(H5N3), A(H5N6) and A(H5N8), have recently been detected in birds in Europe, North America, and Asia, according to reports received by OIE [26]. Although these influenza A(H5) viruses might have the potential to cause disease in humans, so far no human cases of infection have been reported, with the exception of the human infections with influenza A(H5N1) viruses and the three human infections with influenza A(H5N6) virus detected in China since 2014 [25].

In 2015, official notifications of outbreaks or detections of highly pathogenic avian influenza virus A(H5N1) in birds have been reported in Bulgaria, China, Egypt, India, Israel, Myanmar, Nigeria, Palestine\* and Gaza, the United States of America and Vietnam [26] (Map 2). The A(H5N1) virus reported in the United States is a reassortant virus of avian influenza viruses circulating in birds in Asia (HA) and northern America (HA) and is genetically different from the A(H5N1) viruses causing human infections [27].

Egypt's neighbour, Libya, was affected in 2014 [26,28] and cases have been reported in 2015 by the national authorities [5]. The A(H5N1) virus subclade in Israel, Palestine and Gaza is the same as in Egypt (clade 2.2.1.), while recent detections of A(H5N1) in a pelican, a dove and a backyard poultry flock in Bulgaria [26] were due to a virus belonging to a different clade (2.3.2.1c) [13].

\* This designation shall not be construed as recognition of a State of Palestine and is without prejudice to the individual positions of the Member States on this issue.

**Map 2. Geographic distribution of highly pathogenic avian influenza virus A(H5N1) reported in Africa, Asia and Europe in domestic poultry and wild birds with human cases reported in 2015**



Source: EMPRES-i; available from: <http://empres-i.fao.org/eipws3g>; accessed 9 March 2015

## Situation of highly pathogenic avian influenza A(H5N1) in birds in Egypt

FAO stated that during December 2014 and February 2015, 352 poultry outbreaks were notified in Egypt, which is a large increase compared to the 44 poultry outbreaks reported during the same period the year before [5,29]. Outbreaks were reported among vaccinated poultry in commercial farms and households as well as in unvaccinated backyard poultry [5,30]. It is unclear at the moment whether the increase in the number of affected flocks is biased due to increased surveillance activity after the stabilisation of the political system. The locations of poultry outbreaks largely overlap with areas of human cases (Map 2).

## A(H5N1) virus characteristics and circulating A(H9N2) in Egypt

In 2010–2011, viruses of clade 2.2.1 and 2.2.1.1 were co-circulating in Egyptian poultry, with clade 2.2.1 mainly isolated in unvaccinated backyard poultry. Viruses from clade 2.2.1 were responsible for all human cases in Egypt between 2006 to 2013 [31]. During the winter 2014–2015, A(H5N1)-only viruses of clade 2.2.1 were circulating in Egypt and were responsible for outbreaks in Israel as well as Palestine and Gaza [13].

Preliminary laboratory investigations did not detect major characteristic changes in the recently viruses isolated from patients compared to isolates from previously reported cases, but amino acid substitutions have been detected that might influence the reactivity of the available candidate vaccine viruses. Therefore, A/Egypt/N04915/2014-like virus has been proposed as a candidate vaccine virus of this clade for pandemic preparedness [32].

Two mutations in A(H5N1) isolates from poultry have been recorded in Egypt. According to the Reference Laboratory for Veterinary Quality Control on Poultry Production, these mutations were first detected in 2011 and are located at sites  $\alpha$ 129 and  $\alpha$ 151. These mutations in the virus might contribute to an increased avidity for human receptor while retaining the wild-type avidity for avian receptor [33]. However, it is not fully understood how this might contribute to the overall picture of the increase in human cases.

There have been few detections of A(H5N1) viruses in migratory wild birds over the few last years, indicating that wild birds play a minor role in the spread of the virus [19,34]. A(H5N1) has been detected in different species of birds in Egypt (e.g. turkeys, ducks, chickens, pigeons, quail and geese) [31,35]. Sick and dead birds mainly tested positive for A(H5N1) but a high number of apparently healthy birds have also tested positive. Morbidity and mortality might not be present in all affected backyard poultry, indicating that contact with apparently healthy birds might also be a source of infection. Any supporting data will be important in developing future interventions. Furthermore, subclinical infections may be related to prior exposure to A(H9N2) where cross immunity has been reported to attenuate infection/disease [36].

In recent years, an increasing circulation of A(H9N2) in poultry has been observed in Egypt with co-infections of A(H5N1) and A(H9N2) in birds, opening the possibility for viral reassortment [31]. The extent and influence of the enhanced co-circulation of A(H9N2) and co-infection with A(H5N1) in birds on the dramatic increase in A(H5N1) outbreaks and related human cases in Egypt needs to be further analysed to understand the epidemiology of the recent outbreak and to establish prevention and control measures. In January 2015, the first human case of A(H9N2) with exposure to healthy poultry was described [13]. The increase of A(H9N2) circulation in the poultry population yielded in an increase in A(H9N2) seropositivity in humans which was even higher than the seropositivity to A(H5N1) in the studies [37].

This situation is comparable to the circulation of A(H9N2) and the emergence of A(H7N9) in China. The uncontrolled circulation of A(H9N2) viruses in the poultry population has already been shown to be a driver of the emergence of A(H7N9) viruses in China, offering a diverse gene pool for reassortment events [38,39] where co-infections of humans with A(H7N9) and A(H9N2) have also been observed [40,41].

Potential co-infections of A(H5N1) and A(H9N2) in humans in Egypt should be monitored and human A(H5N1) viruses should be sequenced in order to detect reassortment events early on.

## Virus transmission and risk factors

During the recent increase in human cases, one family cluster with two confirmed cases was observed whereby both cases had shared the same exposure to backyard poultry at the same time [32]. No sustained human-to-human transmission has been identified, only small clusters with the same exposure prior to disease onset. Human cases reported direct exposure to live or sick poultry, mostly backyard poultry before onset of disease. A correlation between the practice of disposing of dead poultry or poultry faeces in garbage piles outside and A(H5N1) detection in backyard flocks has been previously shown [42]. Outdoor disposal also increased the risk of A(H5N1) spreading among households within a village. The role of domestic geese and ducks as likely asymptomatic sources of infection, particularly for free-ranging backyard poultry, is not fully understood.

To date, no introduction of A(H5N1) clade 2.2.1 or A(H9N2) viruses from Egypt into Europe with migratory birds has been detected in the EU wild bird surveillance programmes, despite continuous circulation in Egypt. This is possibly due to the fact that A(H5N1) mainly affects backyard poultry and has only been detected sporadically in wild migratory birds in Egypt [19,34]. These recent 2.2.1 viruses are less infectious for domestic waterfowl and therefore presumably also for wild waterfowl. However, the increased number of outbreaks and the higher level of virus circulation in the poultry population within Egypt might open the possibility of spread to Europe through the legal or illegal trade of infected birds or contaminated material.

The detection of A(H5N1) in Israel, Gaza and the West Bank is related to the Egyptian outbreak, since the virus clade is the same as in Egypt [13]. Information about the method of introduction is not available, but could be the result of trade in infected asymptomatic poultry, contaminated material or wild birds. The recent detections of A(H5N1) in a pelican and a dove in Bulgaria [26] are not related to Egypt as the clade was different (clade 2.3.2.1c) [13].

## ECDC threat assessment for the EU

Egypt has reported a dramatic increase in human cases and deaths due to A(H5N1) in recent months. During the same period, a large increase in outbreaks among poultry has been reported, mainly related to backyard farming. A(H5N1) affects all sectors of poultry production, is detected in different bird species and circulates in all geographical areas.

The reason for the current increase in human infections is believed to be the spread of the virus within the backyard poultry population and the intensive virus circulation. There has also been speculation that increased co-circulation of A(H9N2) might have contributed to the intensified spread of A(H5N1) in poultry and associated human cases in Egypt. The current joint WHO/CDC/FAO/OIE mission to Egypt will hopefully provide more information on the reason for the sharp increase in human cases. A strategy needs to be established to prevent further geographical spread.

Although the risk of an introduction of A(H5N1) into Europe via migratory birds seems to be very low, the increase in the number of outbreaks and the higher level of virus circulation in the poultry population in Egypt might increase the likelihood for A(H5N1) infections of migratory birds. In particular, migratory waterfowl are known to be potential vectors for the introduction of A(H5N1) to free areas as they undertake movements at certain times of the year. Therefore in Europe there is a theoretical risk that the virus may spread to poultry and the veterinary sector should maintain vigilance, using well-established surveillance systems for early detection, should new introductions occur.

Whenever avian influenza viruses are circulating in poultry, sporadic infections and small clusters of human cases are possible in people exposed to infected poultry or contaminated environments. Although an increased number of animal-to-human infections has been reported by Egypt over the past few months, these influenza A(H5) viruses do not appear to transmit easily among people at present. As such, the risk of these viruses spreading in the community remains low.



Human infections are related to exposure to infected poultry, with the increase in outbreaks among backyard poultry most probably contributing to the increase in human cases. Increased human infectivity of the circulating virus and protection conferred by the poultry vaccines currently in use should be further investigated. No indications of human-to-human transmission have been reported from Egypt. As such, the risk of these viruses spreading in the community remains low, and the assessment of the last ECDC Rapid Risk Assessment published on 23 December 2014 remains valid.

Although the areas where there has been transmission in poultry are mostly rural, the importation of a sporadic travel-related human A(H5N1) case into the EU is possible and public health authorities should be prepared. The risk of EU citizens being infected in Egypt is extremely low. No cases of A(H5N1) among travellers to Egypt have ever been notified. Travellers should be advised to avoid direct contact with poultry or poultry products.

## Conclusions

The recently reported increase in human cases of A(H5N1) infection during the winter months 2014–2015 may be due to an increase in the circulation of A(H5N1) among backyard poultry and exposure to infected poultry across Egypt. Identification of such sporadic cases or small clusters is not unexpected as avian influenza A(H5N1) viruses are known to be circulating among poultry within the country. Strict implementation of control measures to reduce and eliminate infection in poultry is essential for reducing the risk of zoonotic transmission and human cases. Enhanced human infectivity of the circulating virus and the protection conferred by the poultry vaccines currently in use should be further investigated. Surveillance in poultry as well as in humans needs to be strengthened and, ideally, coordinated. Intervention programmes to reduce virus circulation in the country should be reinforced.

Travellers visiting Egypt should avoid direct contact with poultry and birds or uncooked/untreated poultry products.

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