衞生防護中心
Centre for Health Protection

Scientific Committee on Emerging and Zoonotic Diseases

Avian Influenza Situation Updates

Purpose

This paper provides an update of the situation of avian influenza H5N1 regarding human infections, bird and poultry infections, virology and new clinical management guidelines.

Human infections

Geographical distribution

2. Since the beginning of avian influenza outbreaks in 2003, human cases of avian influenza have been reported in 12 countries - Azerbaijan, Cambodia, China (*Anhui, Beijing, Fujian, Guangdong, Guangxi, Hubei, Hunan, Jiangxi, Liaoning, Shanghai, Sichuan, Xinjiang, Zhejiang*), Djibouti, Egypt, Indonesia, Iraq, Laos, Nigeria, Thailand, Turkey and Vietnam (Figure 1). As of 25 October 2007, there have been 332 confirmed human cases of avian influenza A (H5N1) reported to WHO[1].

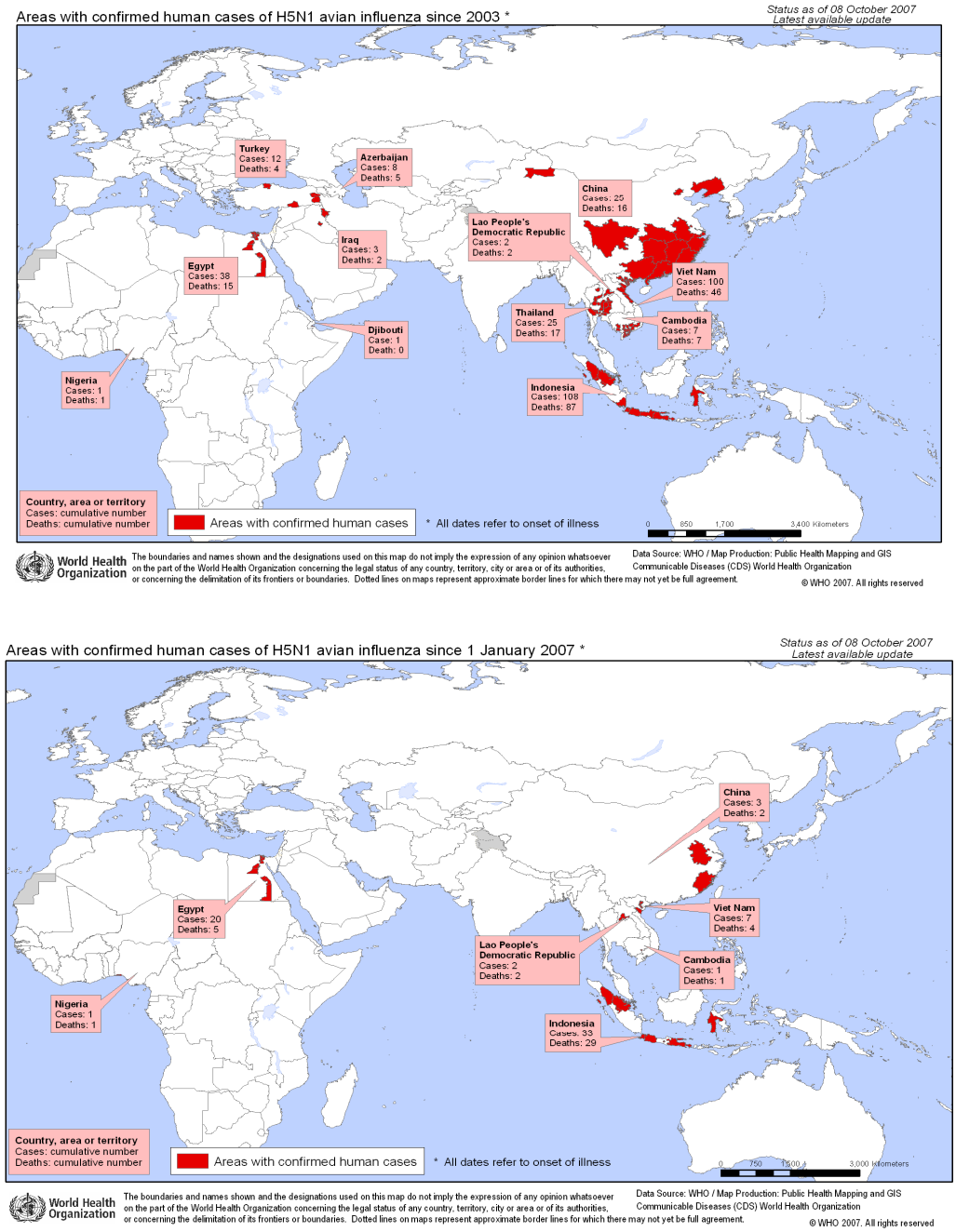

Figure 1. Map of the geographical distribution of human influenza A (H5N1) cases since (i) 2003, and (ii) January 2007.

3. In 2007 (as of 25 October 2007), a total of seven countries were affected involving 69 cases. Indonesia has the highest number of reported cases (35 cases, 50.7%), followed by Egypt (20 cases, 29.0%) and Vietnam (7 cases, 10.1%) (Figure 2).

Figure 2. Number of human influenza A (H5N1) infections with onset in 2007 (as of 25 October 2007) and their outcomes.

Seasonality

4. Cases continued to occur throughout the year (up to 25 October, 2007), with more cases from January to March in the past few years (Figure 3).

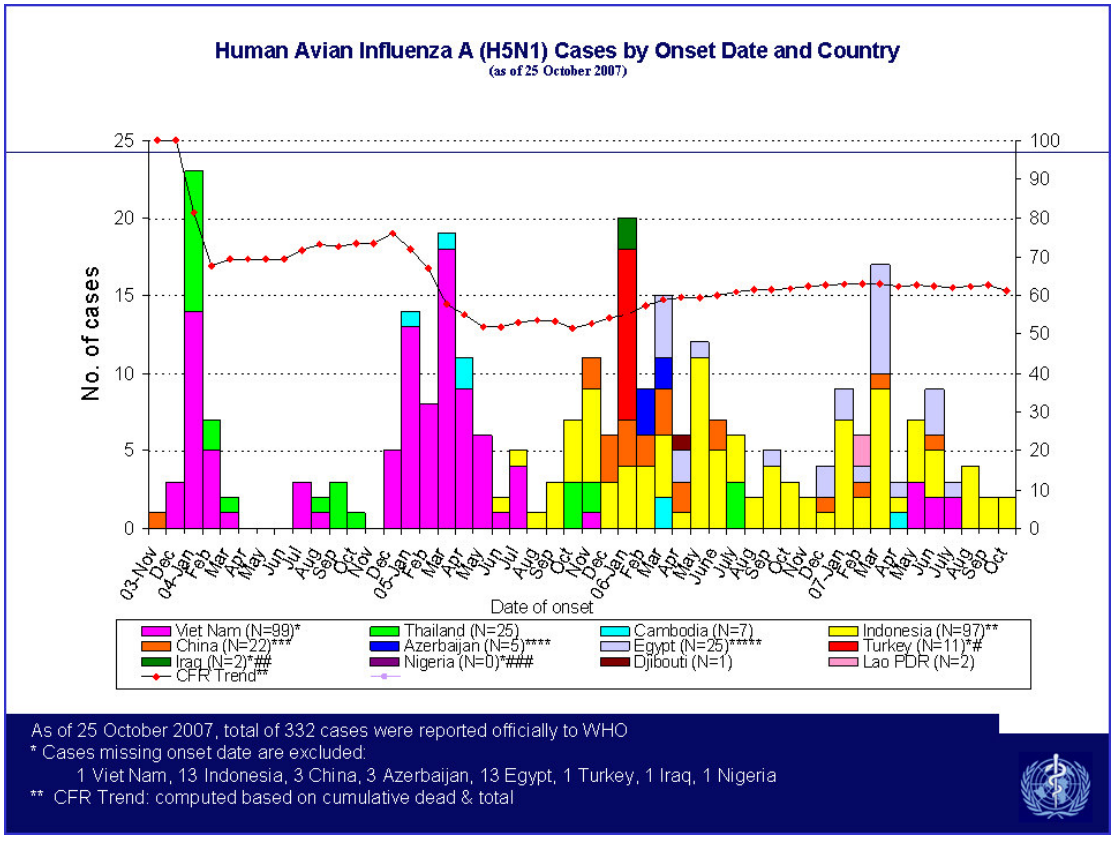

Figure 3. Human avian influenza A (H5N1) cases by onset date and country (as of 25 October 2007).

Age and sex distribution of cases

5. Since 2003, ages of cases ranged from 3 months to 81 years (median 19.0 years) and 28.6% were below 10 years of age[2]. Cases were distributed almost equally in females (51.8%) and males. In 2007, ages of cases ranged from 2 to 45 years old, and more female than male cases (a F:M ratio of 1.56) had occurred[1].

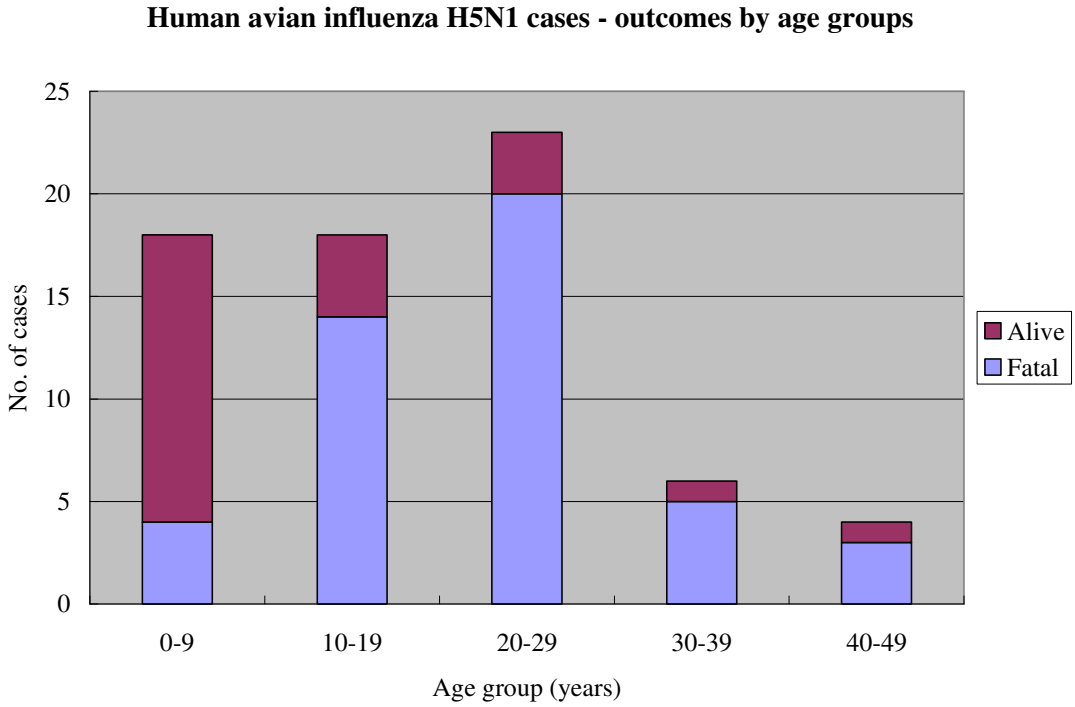

Figure 4. Human avian influenza A (H5N1) cases in 2007 (n=69), by age group and outcome (as of 25 October 2007).

Clinical course

6. H5N1 infection mainly affects the lower respiratory tract, causing diffuse alveolar damage and respiratory failure. Diarrhoea is also a common presenting feature of H5N1, occurring in up to 70% of patients and viral RNA had been detected in some faecal samples tests[3, 4].

7. WHO confirmed cases from 2003 to 25 October 2007 show that the number of days from onset to hospital admission ranged from 0 to 20 days (median 4.5, n=230), and the number of days from onset of symptoms to death ranged from 1 to 30 days (median 9.0, n=179).

Case fatality rate (CFR)

8. As of 25 October 2007, a cumulative of 204 cases out of 332 were fatal, giving an approximate CFR of 61.4% considering all cases since 2003. This has been relatively stable in the past two years (Figure 3). In 2007, the CFR was approximately 66.7%.

9. Cumulatively since 2003, most of the fatal cases had been young, with 50% (102/204) of fatal cases below 20 years of age[2]. In 2007 (as of 25 October 2007), 39.1% of the fatal cases were under 20 years of age and the CFR was highest in the age group of 20 – 29 years (CRF 87.0%) and lowest for children from 0 – 9 years of age (CFR 22.2%) (Figure 4).

10. Among countries with more than 10 cases, Indonesia has the highest CFR (80.9%), compared to about 67% in China and Thailand and 45% in Vietnam. Indonesian and international epidemiologists have been trying to understand why the fatality rate there is so high[5] but no results have yet been published.

11. Regarding risk factors for human H5N1 infection, WHO states that all evidence to date indicates that close contact with dead or sick birds is the principal source of human infection with the H5N1 virus. Especially risky behaviours identified include the slaughtering, defeathering, butchering and preparation for consumption of infected birds[4].

12. A number of academic sources have also attempted to identify prevalent risk factors. A recently published report of a case-control study from Vietnam found that the following risk factors were independently associated with H5N1 infection: (i) preparing sick or dead poultry for consumption in the 7 days before illness onset, (ii) having sick or dead poultry in the household in the 7 days before illness onset, and (iii) lack of an indoor water source[6]. Another recent case report suggests that food markets with live birds may be a source of exposure for avian influenza[7].

13. The apparent clustering of human cases of influenza A (H5N1) among blood relatives had been considered by the World Health Organization as possible evidence of genetic variation in susceptibility[8]. The authors of a mathematical modeling study published in July 2007, suggested that such clusters among blood relatives may occur by chance alone[9].

Birds and poultry infections

14. The worldwide distribution of countries affected by H5N1 outbreaks in wild birds and poultry, respectively, can be seen in Figure 5. Four

countries were newly affected by H5N1 in poultry or birds in 2007, including the United Kingdom, Bangladesh, Kuwait and Saudi Arabia.

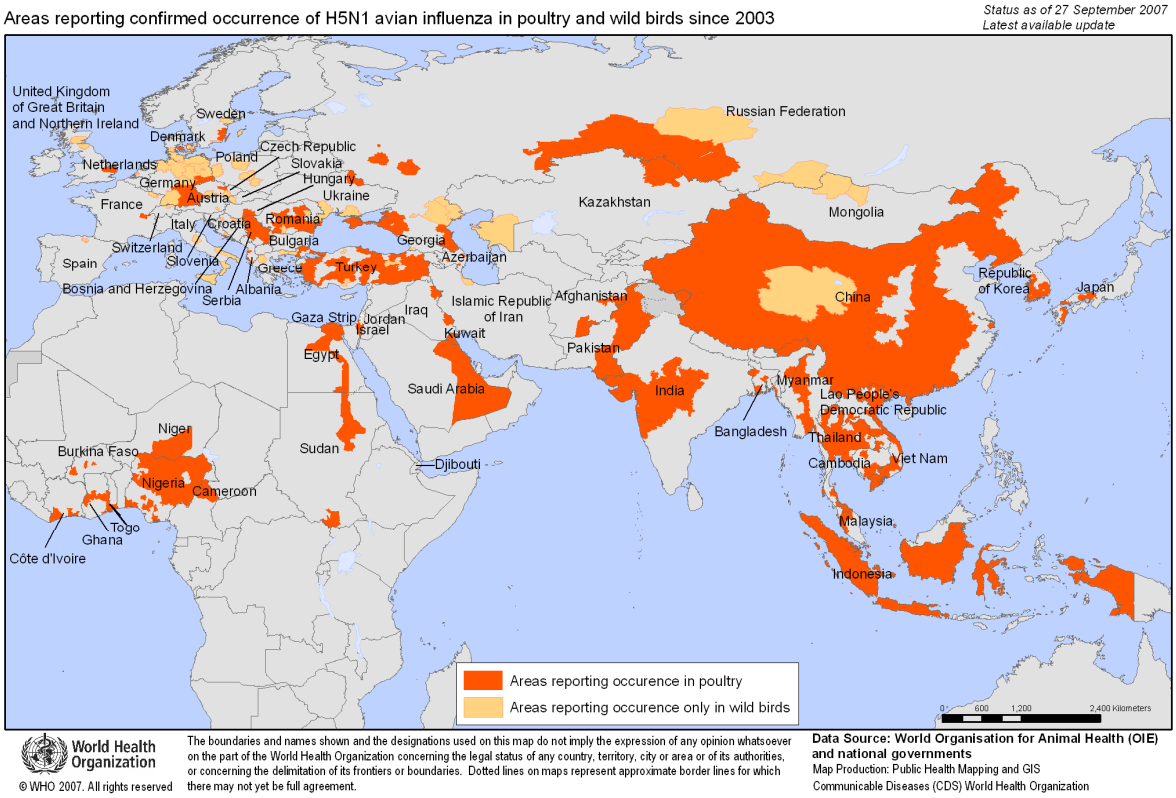

Figure 5. H5N1 in poultry and wild birds since 2003 (as of 27 September 2007).

15. In the UK, investigation of the H5N1 poultry outbreak that occurred in January 2007 suggested that contaminated turkey meat from Hungary may have been the source of the outbreak. The meat was imported and then further processed at a plant in the UK; the plant was in close proximity to a poultry farm [10, 11].

16. In 2007, mainland China reported a few outbreaks of H5N1 in poultry. In March 2007, highly pathogenic avian influenza (HPAI) was found in chickens in Lhassa, capital of the Tibet Autonomous Region, with 680 birds dead amongst a total of 7,670. More recently, in September 2007, HPAI H5N1 was reported on a poultry farm in Panyu, Guangdong. Over 9,800 ducks were affected and 22,800 were culled[12].

17. In 2007, within the framework of the active surveillance programme for avian influenza, 19 cases of HPAI H5N1 in dead wild birds were identified in Hong Kong. The most recent dead wild bird (a Little Egret) H5N1 case was reported in mid-November 2007. An intensive surveillance system is in place on all poultry farms and other locations in Hong Kong. No evidence of HPAI H5N1 has been found on poultry farms.

18. A recent study from Vietnam identified risk factors of H5N1 outbreaks among birds. The risk of outbreak occurrence increased with a greater percentage of rice paddy fields, increasing domestic water bird and chicken density. It also increased with reducing distance to higher population density aggregations, and in the third epidemic wave with increasing percentage of aquaculture. The findings indicate that agri-livestock farming systems involving domestic water birds and rice production in river delta areas are important for the maintenance and spread of infection[13].

19. The presence of H5N1 infection in either wild birds or poultry represents a risk of disease in the other. That risk may depend on the opportunities for interaction between infected wild birds and poultry, which includes both direct contact and a range of indirect means, such as contamination of environments or fomites, by which virus transmission might occur[14]. Apart from possibly one exception in Azerbaijan in 2006, where a number of swans had died in the community, there have been no documentations of direct transmission from wild birds to humans[15].

20. The Director General of the OIE highlighted that in the first half of 2007, countries reported fewer deaths of wild and migratory birds. However, poultry flocks still continue to be infected in some countries and that shows the international community needs to keep up its high level of prevention and control measures of the disease in animals[16].

Virology

21. Recent genetic characterization of H5N1 viruses has demonstrated two distinct phylogenetic clades. Clade 1 viruses have circulated primarily in Cambodia, Thailand, and Vietnam and clade 2 viruses have circulated primarily in China and Indonesia and have spread westward to the Middle East, Europe, and Africa. Six different subclades of clade 2 have been recognized, three of which (subclades 1, 2 and 3) have been largely responsible for human cases in Indonesia, in countries in the Middle East, Europe and Africa, and in China, respectively[17, 18].

22. The number of mammalian species susceptible to H5N1 has seemed to increase. We now know that asymptomatic infection can happen in domestic cats[19] and FAO recommends that avian influenza in cats should be closely monitored[20]. Moreover, a recent report involving cats experimentally infected with H5N1 demonstrated that infected cats excreted the virus via the respiratory tract and the digestive tract, suggesting that in addition to the respiratory route, other routes of transmission may play a role in spread among mammalian hosts[21].

23. In humans, the H5N1 virus may also spread beyond the lungs to other organ systems, even the foetus. Viral genomic sequences and antigens

were found in type 2 epithelial cells of the lungs, epithelial cells of the trachea, T cells of the lymph nodes, and neurons of the brain. In intestinal mucosa, viral sequences, but not antigens, were detected[3]. The authors suggested that infection of the epithelial cells in the trachea is of concern. It may suggest that other viral mediators exist or that the virus might develop mechanisms to overcome respiratory tract defenses and further assessments are needed.

24. As for antivirals, in January 2007, some indication of reduced susceptibility of oseltamivir was noted in a small cluster of human H5N1 cases in Egypt. Laboratory tests suggested that the virus had "moderately reduced susceptibility" to osteltamivir. However, the clinical level of resistance of the mutations was uncertain and WHO did not change treatment recommendations due to this event. Resistance to oseltamivir had been previously identified in a Vietnamese case in 2005[22]. Other incidents of reduced susceptibility or resistance to oseltamivir have not been noted since.

Clinical Management Guidelines

25. In August 2007, WHO published updated advice on clinical management of human infection with avian influenza A (H5N1) virus[23] (Appendix I). Pharmacological and supportive treatment modalities and case management advice were reviewed. The highlights are described below.

26. Oseltamivir remains the primary recommended antiviral treatment. Evidence that the A(H5N1) virus continues to replicate for a prolonged period indicates that treatment with oseltamivir is also warranted when the patient presents to clinical care at a later stage of illness. Once treatment has been initiated in a suspected A(H5N1) patient, a standard 5-day course of therapy (which may be extended) should be administered, unless an alternative diagnosis is established[23].

27. It was also suggested that modified regimens of oseltamivir treatment, including two-fold higher dosage (i.e. 150 mg twice daily for adults), longer duration and possibly combination therapy with amantadine or rimantadine (in countries where A(H5N1) viruses are likely to be susceptible to adamantanes) may be considered on a case by case basis, especially in patients with pneumonia or progressive disease[23].

28. Corticosteroids should not be used routinely, but may be considered for septic shock with suspected adrenal insufficiency requiring vasopressors. Prolonged or high dose corticosteroids can result in serious adverse events, including opportunistic infection[23].

29. Antibiotic chemoprophylaxis should not be used. However, when pneumonia is present, antibiotic treatment according to prevailing guidelines for community-acquired pneumonia is appropriate. When available, results of

microbiologic studies should be used to guide antibiotic usage for suspected bacterial co-infection in patients with A(H5N1) virus infection[23].

Summary

30. The world is presently in phase 3 of WHO pandemic alert: a new influenza virus subtype is causing disease in humans, but is not yet spreading efficiently and sustainably among humans[24].

31. Avian influenza remains endemic in at least three countries (Indonesia, Nigeria and Egypt)[25]. The endemic nature of the disease in these countries constitutes a permanent source of potential contamination for humans and could also be a source of contamination for other countries, for example, through the illegal movement of animals. Therefore, HPAI H5N1 in animals remains a threat to public health[25].

Centre for Health Protection
5 December 2007

References

1. Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1) Reported to the World Health Organization. WHO. http://www.who.int/csr/disease/avian_influenza/country/cases_table_2007_10_08/en/index.html 2007. Accessed 19 November 2007.

2. Avian Influenza Update Number 119 (30 Oct 2007). Western Pacific Regional Office of the World Health Organization 2007.

3. H5N1 infection of the respiratory tract and beyond: a molecular pathology study. Gu J, Xie Z, Gao Z, et al. Lancet 2007; 370:1137-45.

4. Avian influenza (" bird flu") - Fact sheet. WHO 2006.

5. Epidemiology: Human cases create challenges and puzzles. Dennis Normile. Science 5 January 2007: Vol. 315. no. 5808, p. 32.

6. Risk factors for human infection with avian influenza A H5N1, Vietnam, 2004. Dinh PN, Long HT, Tien NT, et al. Emerg Infect Dis 2006; 12:1841-7.

7. Food markets with live birds as source of avian influenza. Wang M, Di B, Zhou DH, et al. Emerg Infect Dis 2006; 12:1773-5.

8. Influenza research at the human and animal interface. WHO 2006.

9. Little Evidence for Genetic Susceptibility to Influenza A (H5N1) from Family Clustering Data. Pitzer VE. Emerging Infectious Diseases 2007; 13:1074.

10. Link between H5N1 in UK and recent outbreaks in Hungary is investigated. Mayor S. BMJ 2007; 334:335.

11. Outbreaks of highly pathogenic avian influenza (A/H5N1) in commercial poultry in Hungary and the UK--public health implications. Euro Surveill 2007; 12.

12. Avian influenza - Follow up report No. 7. OIE. http://www.oie.int/wahid-prod/reports/en_fup_0000006213_20070917_155704.pdf 2007. Accessed 19 November 2007.

13. An analysis of the spatial and temporal patterns of highly pathogenic avian influenza occurrence in Vietnam using national surveillance data. Pfeiffer DU, Minh PQ, Martin V, Epprecht M, Otte MJ. Vet J 2007; 174:302-9.

14. Summary of the discussions on avian influenza and wild birds of a special meeting of the OIE Wildlife Working Group on 21 February with an invited group of experts and recommendations of the Wildlife working group. OIE 2006.

15. Avian influenza – situation in Azerbaijan - update 2. WHO Disease Situation Updates. 21 March 2006. http://www.who.int/csr/don/2006_03_21a/en/index.html. Accessed on 19 November 2007.

16. Press Release, OIE 2007. http://www.oie.int/eng/press/en_070521.htm. Accessed on 19 November 2007.

17. Antigenic and genetic characteristics of H5N1 viruses and candidate H5N1 vaccine viruses developed for potential use as pre-pandemic vaccines. WHO Global Influenza Programme. 2006. http://www.who.int/csr/disease/avian_influenza/guidelines/recommendationvaccine.pdf. Accessed on 19 November 2007.

18. H5N1 influenza--continuing evolution and spread. Webster RG, Govorkova EA. N Engl J Med 2006; 355:2174-7.

19. Subclinical infection with avian influenza A (H5N1) virus in cats. Leschnik M, Weikel J, Mostl K, et al. Emerg Infect Dis 2007; 13:243-7.

20. Avian influenza in cats should be closely monitored. FAO Newsroom 2007.

21. Influenza A virus (H5N1) infection in cats causes systemic disease with potential novel routes of virus spread within and between hosts. Rimmelzwaan GF, van Riel D, Baars M, et al. Am J Pathol 2006; 168:176-83.

22. Avian influenza - situation in Egypt - update. WHO 2007. http://www.who.int/csr/don/2007_01_18/en/index.html. Accessed 19 November 2007.

23. Clinical management of human infection with avian influenza A (H5N1) virus. WHO 2007. http://www.who.int/csr/disease/avian_influenza/guidelines/clinicalmanage07/en/index.html.

24. Current WHO phase of pandemic alert. WHO 2007. http://www.who.int/csr/disease/avian_influenza/phase/en/index.html. Accessed on 19 November 2007.

25. Technical Meeting on Highly Pathogenic Avian Influenza and Human

H5N1 Infection. FAO, WHO and OIE with the collaboration of UNSIC and UNICEF 2007. http://www.fao.org/avianflu/en/conferences/june2007/index.html. Accessed on 19 November 2007.