INFORMATION NOTE

Recent Developments in Avian Influenza

1. Introduction

1.1 At its meeting on 13 November 2006, the Panel on Health Services requested the Research and Library Services Division to provide information on recent developments in avian influenza.

1.2 Avian influenza, or bird flu, is a contagious disease of birds caused by influenza A viruses. The avian influenza virus currently affecting poultry and humans is the highly pathogenic H5N1 strain of the virus. The purpose of this information note is to provide the Panel with background information on recent developments in avian influenza, in terms of the spread of the disease in 2006, the availability of antiviral drugs, the development of a human vaccine and the studies recently conducted on the H5N1 virus.

2. Spread of H5N1 infections in humans

2.1 While avian influenza viruses are highly species-specific[1], they, on rare occasions, cross the species barrier to infect humans.[2] As of 29 November 2006, the total number of confirmed worldwide human cases of H5N1 infections reported to the World Health Organization (WHO) amounted to 258. Within this total, 154 or 60% were fatal cases. The breakdown of the cumulative number of confirmed human H5N1 cases by country is shown in the Table on the following page.

[1] Influenza viruses are normally highly species-specific, meaning that viruses that infect an individual species stay "true" to that species, and only rarely spill over to cause infection in other species. See World Health Organization (2006a).

[2] See Department of Health (2006) and World Health Organization (2005b).

Table — Cumulative number of confirmed human cases of H5N1 avian influenza reported to the World Health Organization (as of 29 November 2006)

Country	2003		2004		2005		2006		Total	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
Azerbaijan	0	0	0	0	0	0	8	5	**8**	**5**
Cambodia	0	0	0	0	4	4	2	2	**6**	**6**
China	1	1	0	0	8	5	12	8	**21**	**14**
Djibouti	0	0	0	0	0	0	1	0	**1**	**0**
Egypt	0	0	0	0	0	0	15	7	**15**	**7**
Indonesia	0	0	0	0	19	12	55	45	**74**	**57**
Iraq	0	0	0	0	0	0	3	2	**3**	**2**
Thailand	0	0	17	12	5	2	3	3	**25**	**17**
Turkey	0	0	0	0	0	0	12	4	**12**	**4**
Vietnam	3	3	29	20	61	19	0	0	**93**	**42**
Total	**4**	**4**	**46**	**32**	**97**	**42**	**111**	**76**	**258**	**154**

Source: World Health Organization (2006b).

2.2 The 258 human H5N1 cases reported have come from ten countries: Vietnam (93), Indonesia (74), Thailand (25), China (21), Egypt (15), Turkey (12), Azerbaijan (8), Cambodia (6), Iraq (3) and Djibouti (1). Before 2006, all the human H5N1 cases had occurred in East Asian countries, namely Vietnam, Indonesia, Thailand, China and Cambodia. The situation changed in January 2006, when Turkey and Iraq reported their first cases of human H5N1 infections, the first outbreaks outside East Asia. In March 2006, Azerbaijan and Egypt confirmed their first cases of human infections. Later on, Djibouti confirmed H5N1 infections in people in May 2006.

Human-to-human transmission

2.3 Direct contact with infected poultry, or surfaces and objects contaminated by their faeces, is presently considered as the main route of human infections.[3] However, isolated clusters of probable limited human-to-human transmission of the H5N1 virus have also been observed. For example, Indonesia reported a human-to-human spread case in May 2006. In that case, eight people in an extended family were infected. The first family member was thought to have become ill through contact with infected poultry, and passed the disease to her six relatives. One of those relatives, a 10-year-old boy, then infected his father. No further spread outside of the exposed family was documented or suspected.[4]

2.4 In any event, WHO considers that the instances of human-to-human transmission of the H5N1 virus are rare and should not be a cause for alarm. In no instance has the virus spread beyond a first generation of close contacts or caused illness in the general community.[5] The Centers for Disease Control and Prevention in the United States (US) shares a similar view, arguing that the spread of the H5N1 viruses from an ill person to another has been reported very rarely, and transmission has not been observed to continue beyond one person.[6] Likewise, the Department of Health in the United Kingdom (UK) considers that the instances of human-to-human transmission have been isolated one-off occurrences with no further spread to people, and that the route of transmission remains unconfirmed.[7]

2.5 Meanwhile, WHO has developed a global alert system, based on six pre-defined phases, as a way of signalling the seriousness of the risk of an influenza pandemic (see Appendix I for details). The world is presently at phase 3, where a new influenza virus subtype is causing disease in humans, but is not yet spreading efficiently and sustainably among humans.

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3 See Centers for Disease Control and Prevention (2006b) and World Health Organization (2005b).

4 Another case happened in 2004 when Thailand reported a probable human-to-human spread in a family resulting from prolonged and very close contact between an ill child and her mother. See Centers for Disease Control and Prevention (2006c).

5 See World Health Organization (2005b).

6 See Centers for Disease Control and Prevention (2006c). The Centers for Disease Control and Prevention is an agency of the US Department of Health and Human Services, which is responsible for protecting the public health and safety of people.

7 See Department of Health (2006). The Department of Health is a government department, which is responsible for government policies on health and social care.

3. Spread of H5N1 infections in animals

3.1 H5N1 infections in animals have continued its spread in 2006, reaching India, Pakistan, Afghanistan, Myanmar, Azerbaijan, Georgia and a number of countries in Europe, Africa and the Middle East. Appendix II shows the countries which reported their first outbreak of H5N1 infections in animals in the January-November 2006 period.

3.2 Europe saw the outbreak of the H5N1 virus in early 2006, with the detection of the virus in wild birds and/or poultry in a number of European countries in the first quarter of the year. The outbreak continued into the ensuing months, with the report of the first animal case in Spain in June 2006.[8]

3.3 As of 23 November 2006, 14 European Union (EU) member states had reported their first cases of H5N1 infections in animals to the World Organization for Animal Health.[9] These infections were mostly but not entirely in wild birds. The countries where there were only wild birds infected included Greece, Italy, Slovenia, Austria, Slovakia, Poland, Czech Republic, the UK and Spain. In Hungary, Germany, France, Sweden and Denmark, both wild birds and poultry were infected.

3.4 In the EU, there were also cases where other animals became infected with the H5N1 virus in 2006. In February 2006, Germany confirmed H5N1 infection in a dead domestic cat[10], the first time the virus being identified in a mammal in the EU. A month later, Sweden detected H5N1 in a mink and Germany confirmed H5N1 infection in a stone marten.

3.5 Africa experienced the first sighting of the H5N1 virus in the first quarter of 2006, with poultry infections spotted in Nigeria, Niger, Egypt, Cameroon, Burkina Faso, Sudan and Cote d'Ivoire. Both Nigeria and Egypt also reported H5N1 infections in wild birds. In April 2006, Djibouti discovered its first cases of H5N1 infections in poultry. In the Middle East, H5N1 infections in wild birds and/or poultry were detected in Iraq, Iran, Israel, Palestine and Jordan also in early 2006.

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8 The affected countries, listed in the order of the start date of the outbreak, were Greece, Bulgaria, Italy, Hungary, Germany, Slovenia, Austria, Albania, Bosnia-Herzegovina, France, Slovakia, Sweden, Switzerland, Serbia and Montenegro, Poland, Denmark, Czech Republic, the UK and Spain.

9 The World Organization for Animal Health is an international inter-governmental organization founded in 1924. Its missions are to: (a) guarantee the transparency of animal disease status world-wide; (b) collect, analyze and disseminate veterinary scientific information; (c) provide expertise and promote international solidarity for the control of animal diseases; and (d) guarantee the sanitary safety of world trade by developing sanitary rules for international trade in animals and animal products.

10 The virus was first reported in felines in December 2003, when two tigers and two leopards at a zoo died after exhibiting clinical signs suggestive of the avian influenza.

3.6 While there are views tracing the recent spread of the virus to migratory birds[11], circumstantial evidences suggest otherwise. For example, the outbreak in the African countries in early 2006 mostly originated within the poultry industry, and the timing and locations of the outbreak did not match the movements of migratory birds. In addition, the first case in Nigeria was detected in a large commercial farm, and not among backyard flocks which would be expected to have a greater chance of coming into contact with wild birds.[12]

4. Availability of antiviral drugs

4.1 Two classes of drugs are currently available for the treatment of the avian influenza. They are the M2 inhibitors (amantadine and rimantadine) and the neuraminidase inhibitors (oseltamivir and zanamivir). Amantadine and rimantadine inhibit the action of M2, a virus protein which enables the virus to take over the infected cell and order it to start making replicas of the virus itself. By M2 inhibition, amantadine and rimantadine inhibit virus replication. Meanwhile, oseltamivir and zanamivir block the function of viral neuraminidase protein, thus preventing the virus from penetrating the cell wall of the infected cell to spread across to other cells. By neuraminidase inhibition, the viral chain reaction is thus broken.

Amantadine and rimantadine

4.2 According to WHO[13], amantadine and rimantadine could potentially be used against influenza pandemic, but resistance to these drugs may develop rapidly, which could significantly limit their effectiveness. Some currently circulating avian influenza strains are fully resistant to these M2 inhibitors. For example, genetic sequencing of the H5N1 viruses from human cases in Vietnam and Thailand shows resistance to amantadine and rimantadine.[14]

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[11] According to World Health Organization (2006a), scientists are increasingly convinced that at least some migratory waterfowl are carrying the H5N1 virus in its highly pathogenic form, sometimes over long distances, and introducing the virus to poultry flocks in areas that lie along their migratory routes. The American Council on Science and Health (2006) argues that *"[m]igration of infected wild birds is believed to be responsible for the most recent appearance of H5N1 in some European nations"*.

[12] In the African countries, it is thought that the spread could be linked to the movements of infected poultry, such as imports of poultry products from contaminated countries. See Economist (2006) and BirdLife (2006).

[13] See World Health Organization (2005a).

[14] See Centers for the Disease Control and Prevention (2006a).

Oseltamivir and zanamivir

4.3 According to WHO, oseltamivir (commercially known as Tamiflu) and zanamivir (commercially known as Relenza), have been shown, in laboratory studies, to reduce the severity and duration of illness caused by seasonal influenza. The protective efficacy of Tamiflu and Relenza in preventing laboratory confirmed clinical human influenza is between 60% and 90%.[15] The efficacy of these two drugs hinges on their administration within 48 hours after symptom onset. For cases of human infections with H5N1, the drugs may reduce the severity of disease and improve prospects of survival, if administered early, but clinical data are limited. The H5N1 virus is expected to be susceptible to Tamiflu and Relenza.

4.4 Apart from medical treatment, antiviral drugs could also be used for containing the outbreak of human influenza. According to WHO, recent studies, based on mathematical modelling, suggest that antiviral drugs could be used in the prevention of illness near the start of a pandemic to reduce the risk that a fully transmissible virus will emerge or at least to delay its international spread, thus gaining time to augment vaccine supplies.[16]

4.5 In August-September 2005, two science journals published papers[17] suggesting that, under certain conditions, the tactical deployment of antiviral drugs might contain, or even eliminate, an outbreak of human influenza. Both papers concluded that between 100 000 and 3 million doses of antiviral drugs would be needed to stamp out an outbreak, if deployed within the first few weeks of detection of the first case and combined with household quarantine. Where the virus was more transmissible or where the pandemic emerged simultaneously in many places, the number of doses needed would be at the top of this range. To prevent the spread of disease, antiviral drugs would also have to be given to a high proportion of people in the surrounding areas of the pandemic centre.[18]

Stockpiling of Tamiflu

4.6 In recent years, WHO and the governments of many countries have been stockpiling antiviral drugs[19], primarily Tamiflu, for prophylaxis (prevention of illness)[20] and treatment. Tamiflu is a popular choice for stockpiling, since it is available in both pill form and a drinkable liquid suspension.[21] Unlike Tamiflu, Relenza comes in an inhaler.

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15 See World Health Organization (2005a) and Public Health Agency of Canada (2006).

16 See World Health Organization (2005a).

17 See Ferguson et al (2005) and Longini et al (2005).

18 See Economist (2005).

19 For example, the UK government purchased enough courses (each containing of 10 capsules) of Tamiflu to treat 25% of the population in September 2006. See Department for Health (2006).

20 Tamiflu is being used for protection of individuals involved in the culling of animals infected by H5N1 virus as well as healthcare workers involved in the management of people infected by the virus. See Roche Laboratories Inc. (2006a).

21 See Revill (2005).

4.7 The manufacturing of Tamiflu is complex and involves 10 main steps, some of which have been identified as complicated. The manufacturing process takes approximately six to eight months once all the raw materials have been sourced. As such, Roche Laboratories Inc., the Swiss company that produces Tamiflu, has faced a backlog of orders amid the global stockpiling of this antiviral drug.

4.8 More recently, Roche Laboratories Inc. has worked with its external contractors to dramatically jack up the production of Tamiflu. It is expected to be capable of producing 400 million treatments (each consisting of 10 capsules) of Tamiflu annually by end-2006, significantly exceeding government orders of 200 million treatment received to date. Supply of Tamiflu will be boosted further because a handful of generic drug makers have started producing their own version of Tamiflu with a sub-licence from Roche Laboratories Inc.[22] For example, Roche Laboratories Inc. has granted sub-licences to companies in China and India to manufacture Tamiflu for pandemic use.

Warning against the use of Tamiflu

4.9 In November 2006, the US Food and Drug Administration revised the product labeling requirement of Tamiflu to include new warnings about the possibility of self-injury and delirium associated with the drug.[23] The revision was based on reports of more than 100 people, mostly in Japan, who suffered unusual psychiatric effects, including cases of self-injury and suicide, when taking the drug.

4.10 Under the new regulation, a manufacturer of Tamiflu is required to include the following information and guidance in its package insert: *"There have been postmarketing reports (mostly from Japan) of self-injury and delirium with the use of TAMIFLU in patients with influenza. The reports were primarily among pediatric patients. The relative contribution of the drug to these events is not known. Patients with influenza should be closely monitored for signs of abnormal behavior throughout the treatment period"*.

4.11 In addition, the following statement must be added to the "What are the possible side effects of TAMIFLU" section: *"People with the flu, particularly children, may be at an increased risk of self-injury and confusion shortly after taking TAMIFLU and should be closely monitored for signs of unusual behavior. A healthcare professional should be contacted immediately if the patient taking TAMIFLU shows any signs of unusual behavior."*[24]

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22 See Enserink (2006).

23 See US Food and Drug Administration (2006) and Roche Laboratories Inc. (2006b).

24 It was reported that the decision by the US Food and Drug Administration to update the product labeling requirement of Tamiflu was to keep in line with the practice in Japan, where the Japanese Tamiflu label had already warned of possible abnormal behaviours associated with the drug. See CNN.com (2006) and Washingtonpost.com (2006).

5. Development of a human avian influenza vaccine

5.1 According to WHO, vaccines are considered as the first line of defence for reducing the excess morbidity and mortality that invariably accompany pandemics. However, vaccines to protect humans against the H5N1 virus are not yet available. Although the development of a human avian influenza vaccine is currently under way in several countries, no vaccine is ready for commercial production. Even if such vaccine is invented, large-scale commercial production will not start until several months after the outbreak of a pandemic, since the vaccine needs to closely match the prevailing pandemic virus.

5.2 Some clinical trials have already been conducted to test whether experimental vaccines will be fully protective and to determine whether different formulations can economize on the amount of antigen[25] required, thus boosting production capacity. Strategies for stretching limited antigen supplies – by adding an adjuvant to the vaccine formulation or injecting the vaccine into the skin rather than into muscle – have been proposed.[26] Adjuvants are chemicals that can be added to the vaccine formulation to boost the immune response, theoretically allowing the use of smaller dosage of antigen to achieve an immune response. Such antigen-sparing strategies using adjuvants are currently being tested by several manufacturers.

5.3 In July 2006, a British-based pharmaceutical company reported that it had made an experimental vaccine for avian influenza that appeared to work at much lower dosage than other H5N1 vaccines in development to date. According to the company, a clinical trial involving 400 healthy volunteers in Belgium revealed that two adjuvanted vaccine shots of just 3.8 micrograms each were enough to elicit antibodies against the flu strain.[27] Previously, a French-based pharmaceutical company tested that pandemic vaccines were efficacious only at much higher dosage of up to adjuvanted 30 micrograms of vaccines injected twice.[28]

6. Recent studies on the H5N1 virus

6.1 In recent years, a number of studies have been conducted on the H5N1 virus, particularly on its possible mutation into a new strain capable of infecting both animals and humans easily. The paragraphs below summarize the researches conducted during 2006 on the following four areas of the H5N1 virus:

(a) spread of the H5N1 virus;

(b) human infections with the H5N1 virus;

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25 Antigen is the component of the vaccine that elicits an immune response.
26 See World Health Organization (2005c).
27 See GlaxoSmithKline (2006).
28 See Bresson et al (2006).

(c) emergence of a new Fujian-like strain of the H5N1 virus; and

(d) mutations in the H5N1 virus.

The studies under (a) and (b) have been quoted by WHO[29], whereas the studies under (c) and (d) provide more recent findings on the mutations in the H5N1 virus.

Research on the spread of the H5N1 virus

6.2 On 21 February 2006, a research team led by Guan Yi of the University of Hong Kong, and Robert Webster of St. Jude Children's Research Hospital in Memphis, published a paper in the *Proceedings of the National Academy of Sciences* on the spread of the H5N1 virus.[30] Guan's research team helps clarify the role of the migratory birds in the recent spread of the H5N1 virus. Previously, some researchers have expressed scepticism on the role of the migratory birds, by arguing that infected birds would die before travelling very far.

6.3 Since 2002, Guan's research team has collected samples from 13 115 migratory birds at Mai Po Marshes in Hong Kong and Poyang Lake in Jiangxi Province, China. In early 2005, they isolated the H5N1 virus from six apparently healthy migratory ducks at Poyang Lake. The research team also collected samples from 1 092 captured migratory ducks and found that 3.1% had antibodies to H5N1, indicating a prior infection. These findings confirm that wild birds can carry the virus over long distances.

6.4 The research team has also regularly sampled poultry brought to markets in six provinces in southeastern China since 2000. Among the 51 121 birds studied, they have found the H5N1 virus in about 2% of ducks and geese, and some chickens. The research team finds that the virus has persisted in southern China for almost a decade and has been repeatedly introduced into the neighbouring Asian countries. Viruses from Vietnam and Thailand match Guangdong viruses, while Indonesia has its own related cluster. As such, multiple distinct sub-lineages of the H5N1 virus are now established in poultry in various geographical areas of Southeast Asia. The movement of poultry and poultry products, rather than that of migratory birds, is thought to sustain endemicity of the virus in these areas.

29 See World Health Organization (2006d).
30 See Chen et al (2006).

6.5 Against the above background, the research team concludes that *"H5N1 viruses can be transmitted over long distances by migratory birds. However, viruses in domestic poultry have evolved into distinct regional clades*[31]*, suggesting that transmission within poultry is the major mechanism for sustaining H5N1 virus endemicity in this region."*[32]

Research on the human infections with the H5N1 virus

6.6 In March 2006, two research teams independently published findings in *Nature* and *Science* respectively on why the H5N1 virus was so lethal to humans but so difficult to spread.[33] One team was led by Yoshihiro Kawaoka, a virologist at both the University of Tokyo and the University of Wisconsin, while the other team was led by Thijs Kuiken of Erasmus University in Rotterdam.

6.7 Both papers suggest that human influenza viruses attach themselves to molecules in cells lining the nose and throat. Unlike human influenza viruses, the H5N1 viruses prefer to bind to molecules located deep in the lungs. In addition, they have difficulty in infecting the cells that line the nose and the upper part of the lungs. Such findings are consistent with the clinical picture of H5N1 infection, in which most patients are diagnosed with symptoms of infection in the lower respiratory tract, with rapid progression to pneumonia. Since the H5N1 viruses preferentially infect cells in the lower respiratory tract, they reside deep in the airways and are not easily expelled by coughing and sneezing, the usual route of spread of human influenza.

Research on the emergence of a new Fujian-like strain of the H5N1 virus

6.8 On 7 November 2006, Guan Yi, along with his colleagues at the University of Hong Kong and at St. Jude Children's Research Hospital, published a paper in the *Proceedings of the National Academy of Sciences*[34] on the identification of a new Fujian-like strain of the H5N1 virus, and a general upswing in the overall H5N1 infection through their ongoing surveillance of poultry markets in six provinces of southern China.

6.9 The research team tested 53 220 birds from live-poultry markets in six southern Chinese provinces from July 2005 through June 2006. Within this total, 1 294 birds or 2.4% tested positive for the H5N1 virus, more than double the 0.9% positive rate in the previous year.

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31 A clade is a group of organisms consisting of a single common ancestor and all the descendants of that ancestor. See Wikipedia (2006).

32 See Chen et al (2006).

33 See Shinya et al (2006) and Riel et al (2006).

34 See Smith et al (2006).

6.10 The researchers then analyzed the genomes of 390 birds of the 1 294 birds tested positive for the H5N1 virus and found that 68% of them were in the new Fujian-like lineage. The prototype of this lineage was first detected in March 2005, but few viruses like it were found in the ensuing few months. However, the prevalence of the strain had increased dramatically from October 2005, and accounted for 95% of all samples collected from April to June 2006.

6.11 At the same time, the research team determined that the hemagglutinin genes[35] of five recent human H5N1 viruses from different Chinese provinces belonged to the Fujian strain, thus confirming that the new virus did infect humans. Fujian-like strains were also detected from wild birds and/or poultry in Hong Kong, Laos and Malaysia, indicating that the new virus had already spread beyond southern China.

6.12 To assess the effects of China's poultry vaccination programme, the research team conducted tests on 1 113 poultry samples collected from markets in two provinces between November 2005 and April 2006. The test showed that 16% or 180 of the samples had antibodies against a 2002 strain of H5N1. A subset of 76 of the 180 positive samples was then tested for neutralizing antibodies against the Fujian-like strain and two other recent H5N1 strains. Most of the samples had low levels of antibodies against the Fujian-like strain, although they had relatively high levels for the other two strains.

6.13 The research team concludes that an H5N1 variant (Fujian-like strain) has emerged and becomes predominant, replacing those previously established multiple sub-lineages in different regions of southern China. This virus has also transmitted to Hong Kong, Laos, Malaysia and Thailand, resulting in a new transmission and outbreak wave in Southeast Asia. The research team speculates that the new virus may be resistant to current vaccines and that it may have emerged in response to the widespread poultry vaccination in southern China.

China's response to the study

6.14 On 10 November 2006, the Chinese government held a press conference on the aforementioned findings regarding the identification of a Fujian-like virus in southern China. At the press conference, Chinese officials and experts put forward the following arguments:

(a) the Fujian-like variant was by no means a new variant. It was highly homogeneous to the H5N1 virus subtype isolated in Hunan and other provinces during a bird flu outbreak in early 2004;

[35] The H5N1 hemagglutinin gene makes a protein that allows the virus to enter cells and is responsible for its most lethal effects. The protein fuses the influenza virus to the surface of the cell, rips open the cell wall and allows the viral genetic material to flow in and take over the cell.

(b) the Ministry of Agriculture isolated only new mutant virus of H5N1 avian influenza during a surveillance campaign in early 2006 in Shanxi and Ningxia Provinces. No new virus had been discovered in southern China;

(c) vaccines currently in use were very effective on known bird flu viruses, including those found in waterfowls in southern China. In addition, China had been developing new vaccines to cope with mutated viruses. A new vaccine had been developed against mutated viruses found in Shanxi and Ningxia Provinces earlier this year;

(d) the evaluation of the effectiveness of the Chinese poultry vaccine by Guan Yi's research team was not scientific, as the researchers did not specify the locations and vaccination of the chickens they tested;

(e) about 95% of domestic poultry were vaccinated between January and October 2006. It appeared that along with increased density of vaccination, the number of avian influenza cases had reduced significantly; and

(f) 16 variants of bird flu viruses had been found in the 20 confirmed cases of human infections in China since October 2005. A total of 15 strains were isolated from the cases in southern China and they belonged to the same gene type. There was no ground for five human cases to be caused by mutated strains in southern China.[36]

Research on mutations in the H5N1 virus

6.15 On 16 November 2006, a research team led by Yoshihiro Kawaoka published a paper in *Nature* on the mutations in the H5N1 virus.[37] For years, scientists have observed that avian and human influenza viruses differ in the types of receptor proteins they recognize. Receptors sit on the surface of each species' cells, and allow particular viruses into a cell to trigger a cascade of lethal cellular responses. Most avian viruses seem to prefer binding to a bird receptor molecule. However, it is thought that the H5N1 virus would be able to infect people efficiently if it mutates in a way that facilitates its binding to human cell receptors. To search for such mutations, Kawaoka's research team has screened viral samples collected from both birds and humans.

[36] See State Council Information Office (2006) and 國務院新聞辦公室 (2006).

[37] See Yamada et al (2006).

6.16 The research team has found that the samples from birds could only recognize receptors on bird cells. However, in three of the samples from humans, the virus recognized both human and bird receptors. Researchers have also discovered two spots on the H5N1 virus which would need to mutate for the virus to infect people more easily. That recognition should help scientists understand what genetic changes are required for the virus to easily infect human cells and test H5N1 virus samples for the changes. If the changes start to be found more frequently, that might signal that a pandemic is drawing near.

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Appendix I

World Health Organization phases of pandemic alert

Inter-pandemic phase New virus in animals, no human cases	Low risk of human cases	1
	Higher risk of human cases	2
Pandemic alert New virus causes human cases	No or very limited human-to-human transmission	3
	Evidence of increased human-to-human transmission	4
	Evidence of significant human-to-human transmission	5
Pandemic	Efficient and sustained human-to-human transmission	6

Source: World Health Organization (2006c).

Appendix II

Outbreak of the first case of H5N1 infections in wild bird/poultry by country, January-November 2006

	H5N1 infections in wild birds		H5N1 infections in poultry	
	Start of the outbreak	**Initial species affected**	**Start of the outbreak**	**Initial species affected**
Europe				
Greece	30-Jan	Swans	x	x
Bulgaria	31-Jan	Mute swans	x	x
Italy	1-Feb	Mute swans	x	x
Hungary	4-Feb	Mute swans	4-Jun	Geese
Germany	8-Feb	Mute swans, whooper swans and goshawks	2-Apr	Turkeys
Slovenia	11-Feb	Mute swans and grey herons	x	x
Austria	13-Feb	Swans	x	x
Albania	x	x	16-Feb	Chickens and turkeys
Bosnia-Herzegovina	16-Feb	Swans	x	x
France	17-Feb	Common pochards (ducks)	23-Feb	Turkeys
Slovakia	17-Feb	Ducks	x	x
Sweden	24-Feb	Tufted ducks	17-Mar	Mallards
Switzerland	26-Feb	Common mergansers	x	x
Serbia and Montenegro	28-Feb	Mute swans	9-Mar	Chickens
Poland	1-Mar	Swans and hawks	x	x
Denmark	12-Mar	Common buzzards	16-May	Backyard poultry
Czech Republic	20-Mar	Mute swans	x	x
United Kingdom	30-Mar	Whooper swans	x	x
Spain	30-June	Grebes	x	x

Note: (x) No reported case.

Appendix II (cont'd)

	H5N1 infections in wild birds		H5N1 infections in poultry	
	Start of the outbreak	**Initial species affected**	**Start of the outbreak**	**Initial species affected**
Africa				
Nigeria	3-Mar	Vultures	10-Jan	Poultry
Niger	x	x	13-Feb	Poultry
Egypt	17-Feb	Migratory birds	17-Feb	Backyard poultry
Cameroon	x	x	21-Feb	Ducks
Burkina Faso	x	x	1-Mar	Guinea fowls
Sudan	x	x	25-Mar	Poultry
Cote d'Ivoire	31-Mar	Sparrow hawks	30-Mar	Chickens and ducks
Djibouti	x	x	6-Apr	Poultry
Middle East				
Iraq	x	x	18-Jan	Pigeons
Iran	2-Feb	Whooper swans	x	x
Israel	x	x	16-Mar	Turkeys
Palestine	x	x	21-Mar	Chickens and ducks
Jordan	x	x	23-Mar	Turkeys and chickens
Asia				
India	x	x	27-Jan	Chickens
Pakistan	x	x	23-Feb	Poultry
Afghanistan	19-Mar	Crows	2-Mar	Chickens and turkeys
Myanmar	x	x	8-Mar	Chickens and quails
Eurasia				
Azerbaijan	29-Jan	Migratory birds	22-Feb	Poultry
Georgia	23-Feb	Swans	x	x

Note: (x) No reported case.

Sources: United States Department of Agriculture (2006), World Organization for Animal Health (2006), World Health Organization (2006d), and Food and Agriculture Organization of the United Nations (2006).

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