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Strengthening pandemic-influenza preparedness and response, including application of the International Health Regulations (2005)

Report by the Secretariat

SITUATION ASSESSMENT

1. Beginning in mid-2003, eight countries in south-east Asia experienced the largest and most severe outbreaks of highly pathogenic avian influenza in poultry on record. The causative agent, the H5N1 strain of *Influenzavirus A*, has since become endemic in domestic birds in several of the initially affected countries.
2. From July 2005 to the end of the year, the virus expanded its geographical presence in birds beyond the initial focus in Asia. Countries reporting their first outbreaks, in both wild and domestic birds, included (in order of reporting) the Russian Federation, Kazakhstan, Turkey, Romania and Ukraine. Croatia and Mongolia reported detection of the virus in wild birds only.
3. Beginning in February 2006, the geographical presence of the virus in birds expanded again, this time dramatically: between then and early April 2006, 32 countries, located in Africa, Asia, Europe and the Middle East, had reported their first cases of infection in wild or domestic birds, or both. This development marks the fastest and most extensive geographical spread of any highly pathogenic avian influenza virus recorded since the disease was first described in 1878. The virus has now affected poultry in some of the world's most densely populated and impoverished areas poorly served by systems for health care and disease surveillance. This situation increases the likelihood that human cases may not be detected promptly or at all, thus weakening the early warning system that signals the need to intensify pandemic preparedness or launch an effort to contain an emerging pandemic virus.
4. Evidence has mounted that at least some species of migratory birds have acquired an ability to carry the H5N1 virus in its highly pathogenic form over long distances. This new role of migratory birds, first observed in 2005, is considered partly responsible for the dramatic recent spread of the virus to new areas. The involvement of migratory birds in the epidemiology of this disease increases the likelihood of further spread and adds greatly to the complexity of control measures in animals, as elimination of the virus in wild birds is universally considered impossible.

5. The spread of the virus to new areas is of concern for human health as it broadens opportunities for human exposures and infections. Each human case gives the virus an opportunity to develop into a form that spreads efficiently and sustainably among humans, at which point a pandemic is expected to start.
6. Infections in poultry and wild birds during the first part of 2006 have been accompanied by the detection of H5N1 virus in a small number of dead domestic cats in some countries, and in two additional mammalian species that prey on wild birds, the stone marten and the mink. At present, infection in these additional mammalian species is not thought to play a significant role in the epidemiology of the disease or to introduce added risks for human infection. However, given the close association between domestic cats and people, vigilance for signs that cats are becoming more widely infected is essential.
7. The first human cases in the present outbreak occurred in December 2003 in Viet Nam. By early April 2006, close to 200 laboratory-confirmed human cases had been reported from nine countries: Azerbaijan, Cambodia, China, Egypt, Indonesia, Iraq, Thailand, Turkey, and Viet Nam. In humans, the virus causes severe disseminated disease affecting multiple organs and systems. Infection has been fatal in more than half of the cases. For unknown reasons, most cases have occurred in previously healthy children and young adults.
8. Resolution WHA58.5 acknowledged the serious threat to human health represented by the outbreaks in poultry and the associated human cases, and stressed the need for all countries to collaborate with WHO and the international community in order to lessen the risk of the H5N1 influenza virus causing a pandemic among humans.
9. Although neither the timing nor the severity of the next pandemic can be predicted, the risk that a pandemic virus will emerge is directly linked to the presence of the virus in poultry and is expected to persist. Since mid-2003 (as of early April 2006), 48 countries had reported the virus in domestic or wild birds. Of the 29 countries with outbreaks in poultry, only two have successfully eliminated the virus from their territories and maintained a disease-free status.
10. On present evidence, the species barrier is substantial: the virus does not cross easily from birds to humans. Behaviours associated with a high risk of infection include the slaughter, butchering, defeathering, and preparation for consumption of infected birds. Properly cooked poultry and poultry products are safe to eat.
11. Investigation of instances of possible human-to-human transmission is difficult, as family members are usually exposed to the same animal or environmental sources as well as to one another. Several instances of limited human-to-human transmission have occurred, but in no case has the virus spread beyond a first generation of close contacts or caused illness in the general community. Data from these incidents suggest that transmission requires very close contact with an ill person. The WHO level of pandemic alert remains at phase 3: a novel influenza virus subtype is causing human infections, but does not spread efficiently or sustainably from one person to another.

ACTIONS UNDERTAKEN BY WHO

12. In resolution WHA58.5 the Health Assembly requested the Director-General to undertake several actions, including (a) to improve surveillance for H5N1 cases in humans and outbreaks in animals; (b) to reduce the shortage of vaccines and antiviral agents; (c) to assess the feasibility of

using a stockpile of antiviral agents to alter the course of a pandemic near its start; and (d) to evaluate non-pharmaceutical measures, including the use of surgical masks, for limiting transmission during a pandemic.

13. In August 2005, all Member States were sent a document outlining recommended strategic actions for responding to the avian influenza pandemic threat. Recommended actions respond to different opportunities to intervene at different phases, moving from the present pre-pandemic situation, through the emergence of a pandemic virus, to the declaration of a pandemic and subsequent international spread. Actions requested in resolution WHA58.5 are embodied in the recommended strategic actions for each of these phases.

14. In the present phase, where interventions aim to reduce opportunities for a pandemic virus to emerge, activities concentrate on preventing human infections and strengthening the early warning system. In May 2005, FAO and OIE, in collaboration with WHO, issued "A global strategy for the progressive control of highly pathogenic avian influenza", giving priority to countries where human cases have occurred.¹ The three organizations have collaborated also in drawing up preventive measures, to be jointly implemented by the health and animal sectors, adapted to conditions in small backyard flocks, which have been associated with most human cases to date. Nonetheless, surveillance of both human cases and poultry outbreaks remains weak in most affected countries in Africa and Asia. In humans, surveillance is complicated by the non-specific early symptoms of influenza caused by the H5N1 virus, the high incidence of other respiratory diseases in affected countries, and the technical difficulty of diagnostic confirmation.

15. Direct support continues to be provided for field investigations of cases and laboratory confirmation of diagnosis, and laboratories in the WHO Global Influenza Surveillance Network continue to assess viruses for changes that could signal improved transmissibility or altered virulence. Some evidence of adaptive mutation during 2005 has emerged. Recent studies of the virus responsible for the exceptionally lethal pandemic of 1918-1919 have yielded better understanding of the genetic determinants of both transmissibility and virulence, and this understanding should improve the precision of early warning signals derived from virological investigations. These studies have also found some genetic similarities between the 1918 virus and H5N1 viruses circulating in 2005.

16. Vaccines are considered to be the first line of defence for reducing morbidity and mortality during a pandemic. The Secretariat has undertaken several activities aimed at expediting the development of a pandemic vaccine and increasing manufacturing capacity. Around 10 countries have domestic companies engaged in work on a pandemic vaccine. Some candidate vaccines are now undergoing clinical trials. Vaccine formulations that economize on the use of antigen are also undergoing clinical trials and, if successful, could help stretch limited antigen supplies and thus increase the number of doses that can be produced at current capacity. As a second line of action, the Secretariat has provided direct support to some developing countries engaged in work on a pandemic vaccine. In the first half of 2006, WHO is convening workshops on regulatory preparedness, aimed at expediting the licensing of pandemic vaccines, and a consultation on access to pandemic vaccines, aimed at developing a global action plan.

17. Countries that are building domestic stockpiles of antiviral agents need to have plans to distribute them, decide whether these drugs are to be used for treatment or prophylaxis, and be ready with appropriate prescribing advice. Because the medicines are costly and supplies are limited, it is

¹ <http://www.fao.org/ag/againfo/subjects/documents/ai/HPAIGlobalStrategy31Octzero5.pdf>.

recommended that antiviral agents be used at the start of a pandemic, pending the availability of vaccines, for the treatment of patients and the protection of workers in essential services, including health care. Some circulating H5N1 viruses are fully resistant to the one class of antiviral agents, the M2 inhibitors (amantadine and rimantadine), but other viruses are fully susceptible to these agents. Because of the risk that the virus will develop resistance to the second class of antiviral agents, the neuraminidase inhibitors (oseltamivir and zanamivir), it is not recommended that these agents be given to large numbers of healthy people, for prophylactic purposes, for extended periods.

18. Antiviral agents are effective in preventing influenza. Neuraminidase inhibitors have been shown, in laboratory studies, to reduce the severity and duration of illness caused by seasonal influenza. The efficacy of these inhibitors depends on their administration within 48 hours of onset of symptoms. For cases of human infection with the H5N1 virus, these agents, if administered early, may reduce the severity of disease and improve prospects of survival but clinical data are limited.

19. Supplies of oseltamivir (administered as tablets) and zanamivir (administered by use of an inhaler) remain extremely limited. Because of the complex and time-consuming manufacturing process, the sole manufacturer of oseltamivir is unable fully to meet demand and faces a backlog of orders. Manufacturing technology is not easily transferred to other production facilities, but strategies for doing so are being explored as a matter of urgency; particular attention is being given to the option of manufacturing oseltamivir in developing countries.

20. Following a donation by industry, WHO will have a stockpile of antiviral agents (oseltamivir), sufficient for three million treatment courses, by early 2006. Recent studies, based on mathematical modelling, suggest that these drugs could be used prophylactically 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. From 6 to 8 March 2006, WHO convened a global technical meeting to finalize an early containment protocol for pandemic influenza. The results of this meeting were made publicly available the following week.¹ To increase the likelihood that early intervention using an international stockpile of antiviral agents will be successful, surveillance in affected countries needs to improve, particularly the capacity to detect clusters of cases closely related in time and place. Should the emerging pandemic virus behave epidemiologically in ways that preclude early intervention, medicines in the stockpile can be used for treatment and prophylaxis in the initially affected countries.

21. As supplies of antiviral agents and vaccines will be inadequate in all countries at the start of a pandemic, governments will need to advise their populations on the use of non-pharmaceutical measures to protect them from infection or, at the population level, to slow transmission. Several non-pharmaceutical interventions have been evaluated. The effectiveness of some will depend on the characteristics of the virus (e.g. virulence, attack rate, transmissibility and pathogenicity in groups at different risk), which cannot be known in advance and will need to be evaluated as the pandemic evolves. Plans are in place to undertake this activity. For example, should schools prove to play an important role in disease dissemination, as has happened in past pandemics, their temporary closure could be recommended as a means of slowing spread. Any measure that flattens the peak incidence of cases over time will relieve some of the burden on health services and reduce some of the social disruption that accompanies high rates of worker absenteeism.

¹ WHO pandemic influenza draft protocol for rapid response and containment. Accessible at: http://www.who.int/csr/disease/avian_influenza/guidelines/pandemicfluprotocol_17.03a.pdf.

22. The potential effectiveness of other non-pharmaceutical interventions can be assessed based on what is known about the behaviour of normal seasonal influenza. In February 2006, WHO issued interim guidelines, specific to the H5N1 virus, for infection control in health-care facilities.¹ These guidelines include recommendations on a broad range of issues, including the use of masks by both health professionals and patients, isolation precautions for suspected or confirmed cases, and the prioritized use of personal protective equipment when supplies are limited. Because influenza has a short serial interval (one person can infect another within an average of only two days), the disease spreads rapidly within a community, allowing little time for the tracing and management of contacts. Once the number of cases begins to increase significantly, the tracing and isolation of contacts will become neither feasible nor sensible as a measure for reducing transmission.

23. A document submitted to the Board at its 117th session² reported on the outcome of a meeting on avian influenza and human pandemic influenza (Geneva, 7-9 November 2005), at which delegates discussed the possibility of voluntary compliance with the relevant provisions of the International Health Regulations (2005) before entry into force. The Board adopted resolution EB117.R7 in that regard.

24. In its discussion of this item, the Board underscored the seriousness of the present threat and its relevance to all countries³. Many countries which lie along the flight paths of migratory birds were perceived to be at enhanced risk of the virus being introduced into wild and domestic birds; some countries doubted their ability to cope with a disease as challenging as this one. Should a pandemic begin, all countries could be rapidly affected. Many Board members expressed the need to improve access to antiviral medicine and pandemic vaccines as a strategy for mitigating morbidity and mortality during a pandemic. WHO was asked to play a leadership role in this regard.

ACTION BY THE HEALTH ASSEMBLY

25. The Health Assembly is invited to consider the draft resolution contained in resolution EB117.R7.

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¹Avian influenza (including influenza A (H5N1), in humans: WHO interim infection control guidelines for health-care facilities. Accessible at: http://www.who.int/csr/disease/avian_influenza/guidelines/infectioncontrol1/en/.

² Document EB117/31.

³ See document EB117/2006/REC/2, summary record of the second, third and eighth meetings.