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Strengthening pandemic-influenza preparedness and response

Report by the Secretariat

SITUATION ASSESSMENT

1. Since mid-2003, parts of south-east Asia have 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 crossed the species barrier to infect more than 120 people in five countries: Cambodia, China, Indonesia, Thailand, and Viet Nam. In humans, the virus causes severe disseminated disease affecting multiple organs and systems. Infection has been fatal in more than half the cases. For unknown reasons, most cases have occurred in previously healthy children and young adults.
2. 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.
3. While 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. The virus is now considered endemic in domestic birds in large parts of Indonesia and Viet Nam and in some parts of Cambodia, China, Thailand, and possibly also the Lao People's Democratic Republic. Time frames for controlling the disease in animals are now being measured in years.
4. In mid-2005, the virus expanded its geographical range in poultry beyond the initial focus in south-east Asia. The Russian Federation reported its first outbreak of H5N1 influenza in poultry, in Siberia, in late July 2005. Reports of disease in adjacent parts of Kazakhstan followed in early August. Deaths of wild birds from H5N1 influenza were reported in both countries. Almost simultaneously, Mongolia reported the detection of H5N1 virus in dead migratory birds. In October 2005, Turkey and Romania confirmed outbreaks of H5N1 influenza in poultry, and Croatia detected the virus in dead migratory birds. Deaths of wild and domestic birds in several other areas are under investigation. Vigilance is high, outbreaks have been quickly detected and reported, and extensive control measures have followed immediately. No human case has been associated with any of these most recent animal outbreaks. Patient samples and viruses have been shared internationally and are undergoing analysis at WHO reference laboratories.

5. The spread of the virus to poultry in any new area 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 begin.

6. 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. Yet, with the virus now pervasive in large parts of Asia and apparently healthy domestic ducks shedding large quantities of virus, it has become increasingly difficult to find an exposure source for new cases. Nor is it known why, in cases where several people have shared the same exposure, only some fall ill.

7. Investigation of instances of possible human-to-human transmission is also 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.

8. The possibility that the virus will spread to poultry in new areas or be reintroduced to areas where outbreaks have been controlled is now high. Recent evidence indicates that at least some species of migratory birds are now directly carrying highly pathogenic H5N1 viruses to new areas located along migratory flyways. The episode in the second quarter of 2005, when more than 6000 wild waterfowl died at a nature reserve in central China of influenza due to highly pathogenic H5N1 virus, was highly unusual and probably historically unprecedented. This event, which suggests an important change in the relationship between the virus and its natural avian reservoir host, adds greatly to the complexity of control measures in animals, as elimination of the virus in wild birds is universally considered impossible. WHO advises countries located on the flyways from central Asia and Siberia to be vigilant for deaths in migratory birds and outbreaks in poultry, and to investigate and report such events quickly. When outbreaks of highly pathogenic H5N1 avian influenza in birds are confirmed, vigilance for human cases should increase.

ACTIONS UNDERTAKEN BY WHO

9. Resolution WHA58.5 requested the Director-General to undertake several actions to (a) improve surveillance for H5N1 cases in humans and outbreaks in animals; (b) reduce the shortage of vaccines and antiviral agents; (c) assess the feasibility of using a stockpile of antiviral agents to alter the course of a pandemic near its start; and (d) evaluate non-pharmaceutical measures, including the use of surgical masks, for limiting transmission during a pandemic.

10. 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.

11. 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 the *Office International des Epizooties*, 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 Asia. In humans, surveillance is complicated by the non-specific early symptoms of influenza caused by H5N1 virus, the high incidence of other respiratory diseases in affected countries, and the technical difficulty of diagnostic confirmation.

12. 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.

13. 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, which is the component of the vaccine that elicits the immune response, 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 assistance to some developing countries engaged in work on a pandemic vaccine.

14. 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 drugs are costly and supplies are limited, it is 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.

15. 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.

¹ http://www.fao.org/ag/againfo/resources/documents/empres/AI_globalstrategy.pdf.

16. 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.

17. 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. The success of this strategy, which has never been tested, depends on several assumptions: (a) the first viruses that show an ability to sustain transmission among humans will not yet be highly transmissible; (b) the emergence of such viruses will be geographically circumscribed; (c) the first clusters of human cases caused by the virus will be rapidly detected and reported; (d) antiviral medications will be rapidly mobilized from the stockpile, made available to the affected populations, and administered to sufficiently large numbers of people; and (e) movement of people in and out of the area will be effectively restricted. The first two assumptions depend on the behaviour of the virus and cannot be known before its emergence. The remaining assumptions imply excellent surveillance and logistics capacity in the initially affected areas, combined with an ability to enforce movement restrictions. 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 concerning 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, drugs in the stockpile can be used for treatment and prophylaxis in the initially affected countries.

18. 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 will relieve some of the burden on health services and reduce some of the social disruption that accompanies high rates of worker absenteeism.

19. The potential effectiveness of other non-pharmaceutical interventions can be assessed based on what is known about the behaviour of normal seasonal influenza. Assuming that pandemic influenza is spread by droplets, simple surgical masks should confer protection and are recommended for use by patients and their close contacts. Respiratory masks are recommended for health staff caring for patients and other emergency-response providers. 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.

20. An addendum to this document¹ reports 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. Proposals in this regard are being submitted to the Board in the addendum.

ACTION BY THE EXECUTIVE BOARD

21. The Executive Board is invited to take note of the report.

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¹ Document EB117/5 Add.1.