WORLD HEALTH ORGANIZATION

EXECUTIVE BOARD **EB115/44**
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Influenza pandemic preparedness and response

Report by the Secretariat

1. In resolution WHA56.19 the Health Assembly expressed concern about the general lack of preparedness for an influenza pandemic. The resolution urged Member States to draw up and implement national preparedness plans, and requested the Director-General to continue to provide leadership in pandemic preparedness, particularly by strengthening global influenza surveillance.

2. Since January 2004, events affecting both human and animal health have brought the world closer to an influenza pandemic than at any time since 1968. Whereas past pandemics have consistently announced themselves with an explosion of cases, events during 2004, supported by epidemiological and virological surveillance, have given the world an unprecedented warning that a pandemic may be imminent. They have also opened an unprecedented opportunity to enhance preparedness.

3. Given the constantly changing nature of influenza viruses, the occurrence of pandemics defies precise predictions concerning timing, causative strain, and severity of the disease and its international impact. Conditions favouring the emergence of a pandemic virus are, however, well known, and are increasingly being met. It is therefore prudent for all countries, supported by WHO, to undertake or intensify preparedness activities as a matter of urgency.

THE PANDEMIC THREAT

4. Concern that an influenza pandemic might be imminent began in January 2004, when Thailand and Viet Nam reported their first human cases of avian influenza, caused by the H5N1 strain of *Influenzavirus A*. These cases were directly linked to historically unprecedented outbreaks of highly pathogenic H5N1 avian influenza in poultry that began in 2003 and rapidly affected eight Asian nations;[1] all prerequisites for the start of a pandemic were met save one: efficient human-to-human transmission.

5. Two waves of avian influenza have struck. The initial spread of H5N1 in poultry, which saw the death or destruction of more than 120 million birds, was accompanied by 35 human cases, of which 24 were fatal. The human cases occurred in Thailand and Viet Nam only, from January 2004 through

[1] Cambodia, China, Indonesia, Japan, Lao People's Democratic Republic, Republic of Korea, Thailand and Viet Nam.

March 2004. Epidemiological investigations, conducted with WHO support, linked most human cases to direct contact with diseased poultry in household, as opposed to commercial, flocks.

6. Massive control efforts were introduced in most countries with the aim of eliminating the virus from its poultry host. The largest outbreaks among poultry, in Thailand and Viet Nam, declined sharply near the beginning of March 2004. After a brief lull, however, disease activity began to increase in July, with fresh outbreaks reported in Cambodia, China, Indonesia, Thailand, and Viet Nam. In August, Malaysia reported its first outbreak. Although the number of affected poultry has been much smaller in this second wave (less than one million), there have again been human cases. From August through October, nine cases, of which eight were fatal, were reported in Thailand (five) and Viet Nam (four). Viet Nam reported an additional case in late December.

7. These cases include the first instance of probable human-to-human transmission, reported in a family cluster in Thailand in September 2004. Intensive door-to-door surveillance failed to detect further instances of such transmission, and the event appears to have been isolated and limited.

8. As of 5 January 2005, the H5N1 virus has caused 45 confirmed human cases, of which 32 were fatal. Among all these cases, two features are striking: the overwhelming concentration of cases in previously healthy children and young adults, and the very high mortality. No explanation for this unusual disease pattern is presently available. Nor is it possible to calculate a reliable case-fatality rate, as mildly symptomatic disease may be occurring in the community yet escape detection.

EVOLUTION OF THE THREAT

9. Although the second wave of outbreaks has been far less conspicuous in the numbers of human beings and animals affected, it has demonstrated several unusual features. Confirmed by findings from recent epidemiological and laboratory studies, these features suggest that the virus may be evolving in ways that increasingly favour the start of a pandemic.

10. Evidence indicates that H5N1 virus is now endemic in parts of Asia, having established a permanent ecological niche in poultry. The risk of further human cases will continue, as will opportunities for a pandemic virus to emerge. Studies comparing virus samples over time show that the H5N1 strain has become progressively more pathogenic for poultry, and is now hardier than in the past, surviving several days longer in the environment. Evidence further suggests that H5N1 virus is expanding its mammalian host range. For example, the virus has recently been shown to cause severe disease and deaths in species, including captive tigers (*Pantera tigris*) and experimentally infected domestic cats, not previously considered susceptible to disease caused by any influenza A virus.

11. Another surprising finding is the detection of highly pathogenic H5N1 virus in dead migratory birds. Wild waterfowl are the natural reservoir of all influenza A viruses and have historically carried these viruses, in evolutionary equilibrium, without showing symptoms or succumbing to disease. Most recently, asymptomatic domestic ducks have been shown to excrete highly pathogenic H5N1 virus, suggesting an important silent role in maintaining transmission. As these ducks can excrete large quantities of lethal virus without the warning signal of visible illness, it has become difficult to give rural residents realistic advice on how to avoid exposure. The role of domestic ducks as a silent reservoir of H5N1 virus may help to explain why several recent human cases could not be traced to contact with diseased poultry.

12. The present concentration of outbreaks of avian influenza in poultry in rural areas, where most households maintain free-ranging flocks and ducks and chickens mingle freely, is of particular concern, especially as households depend on these birds for income and food. Such outbreaks may escape detection, are difficult to control, and increase the likelihood of human exposures, which may occur when children play in areas shared by poultry or when families slaughter or prepare birds for consumption.

ASSESSMENT OF THE THREAT

13. Taken together, these changes in the ecology of the disease and behaviour of the virus have created multiple opportunities for a pandemic virus to emerge, either after a reassortment event, when genetic material is exchanged between human and avian viruses during coinfection of a human being or pig, or through a more gradual process of adaptive mutation. Nobody can predict how the present situation will evolve. Experts readily agree, however, that H5N1 virus has demonstrated considerable pandemic potential. With the virus now endemic, the probability that this potential will be realized has increased.

14. Of the three pandemics of the previous century, those beginning in 1957 and 1968 caused large numbers of cases and a combined mortality estimated at more than three million deaths, mostly in the very young, the elderly and people with underlying chronic conditions. In stark contrast, the 1918 pandemic probably caused more than 40 million deaths, mainly in persons aged 15 to 35 years. The reasons for this exceptional lethality are not fully understood.

15. The present situation may resemble that leading to the 1918 pandemic. Similarities between the H5N1 and 1918 viruses have been suggested in the gradual adaptation of an avian to a human-like virus, the severity of disease, its concentration in young and healthy people, and the occurrence of primary viral pneumonia in addition to secondary bacterial pneumonia (which responds to antibiotics). It should be remembered, however, that an avian influenza virus would probably lose pathogenicity when it acquires the improved transmissibility needed to ignite a pandemic. More relevant to preparedness planning is the fact that no virus of the H5 subtype has probably ever circulated among human beings, and certainly not within the lifetime of today's world population; population vulnerability to an H5N1-like pandemic virus is universal.

16. Experts regard pandemic influenza as one of the most significant global public health emergencies caused by a naturally occurring pathogen. Although the timing of this event cannot be predicted, rapid international spread is certain once a virus with the appropriate characteristics appears. Historically, pandemics have travelled along sea lanes, with global spread completed within six to eight months. As demonstrated by severe acute respiratory syndrome (SARS), spread along the routes of international air travel can shorten this time considerably. The speed of international spread has no direct effect on mortality, but could compromise response capacity should large parts of the world experience almost simultaneous outbreaks. Many of the public heath interventions that successfully contained SARS will not be effective against a disease that is far more contagious, has a short incubation period, and can be transmitted before to the onset of symptoms. Apart from causing a surge of cases requiring health care, such rapid contagion typically results in a crippling shortage of workers in health care and other essential services. The resulting social and economic disruption may be greater in today's closely interconnected and interdependent world. For these reasons, every effort must be made to take advantage of the present unique opportunity for intensified preparedness.

17. By May 2004, the three complementary objectives for the international public health response were considered to be: to avert a pandemic, to control the human outbreaks and prevent further spread, and to conduct the research needed for better preparedness and response, including the immediate development of a vaccine against the pandemic virus. The subsequent evolution of events has forced reconsideration of these three objectives.

18. Prospects for averting a pandemic initially depended on elimination of the virus in its animal reservoir. Despite massive control efforts, outbreaks in poultry have continued. Field investigations of recent cases indicate that rural farmers and their families are the most important risk group. Governments in affected countries must continue to reach these people with information, appropriate to rural farming practices, on dangerous behaviours to avoid. Investigations have linked some recent cases to the practice, common among rural subsistence farmers, of killing and eating poultry once birds within a flock show signs of disease or start to die. Rapid detection and culling of infected birds remain essential. Opportunities for the successful treatment of patients are reduced by the tendency of cases to be detected late in the course of the illness. Work on the development of a vaccine against a pandemic virus has moved forward, but not with a speed appropriate to the urgency of the situation.

PREPAREDNESS MEASURES

19. Vaccines are the most important intervention for preventing influenza and reducing its health consequences during a pandemic. In November 2004, WHO convened a meeting to explore ways to expedite the development of a vaccine against a pandemic virus.[1] All the major influenza vaccine manufacturers were represented. The meeting specifically considered what needs to be done by industry, regulatory authorities, governments and WHO to make such vaccines available rapidly and in as large a quantity as possible.

20. Several manufacturers are engaged in development of a vaccine against a pandemic virus, and various strategies, both short-term and long-term, are being pursued. As a new vaccine for seasonal influenza is produced almost every year, the steps required for vaccine development, licensing and production are familiar to both industry and regulatory agencies. The H5N1 virus, however, raises special problems, including its threat to personnel at manufacturing sites and its lethal effect on embryonated chicken eggs, the current standard medium in vaccine production. Specific problems involve more complex production technologies, heightened biosafety requirements, intellectual property rights for patented technologies, liability for adverse reactions, and some regulatory complexities.

21. As agreed during the meeting, all these problems can be solved through a collaborative effort involving governments, industry and academia; roles and responsibilities for doing so were identified. Some solutions depend on public funding; others require research support; still others will benefit from international coordination by WHO. To gain time, the meeting identified several activities that can be undertaken now to lay the groundwork for rapid marketing authorization and production of a safe and effective vaccine once a pandemic starts.

[1] Informal meeting of WHO, influenza vaccine manufacturers, national licensing agencies, and government representatives on influenza pandemic vaccines (Geneva, 11-12 November 2004). A summary report is available at: http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_GIP_2004_3/en/.

22. The greatest problem is the inadequacy of supplies to meet global needs. Manufacturing capacity is finite and cannot be expanded quickly. Should a pandemic begin now, no company could meet its production targets. Resolution WHA56.19 noted that better use of vaccines for seasonal epidemics will help to ensure that manufacturing capacity meets demand in a future pandemic, and set a goal for improved coverage of the elderly population during seasonal epidemics. Even though this approach is considered to be the best long-term strategy for expanding the manufacturing base for all influenza vaccines, more immediate solutions are needed.

23. High priority has been given to the investigation of strategies that economize on the use of antigen. Intradermal vaccination might extend vaccine supply several-fold. Inclusion of an adjuvant in the vaccine formulation could enhance the effectiveness of antigen in low doses, thus making the most of limited antigen supplies and limited manufacturing capacity. Such strategies currently represent the best hope that countries without manufacturing facilities will have some access to a vaccine against a pandemic virus. At the start of a pandemic, manufacturers will halt production of trivalent seasonal vaccines (protective against three strains) and begin manufacturing of a monovalent vaccine protective against the pandemic virus only, thus greatly increasing the number of doses that can be produced during a given time. Two doses may, however, be needed to assure protection in immunologically naïve populations.

24. Manufacturing capacity for influenza vaccines is concentrated in Australia, Europe, Japan and North America. Vaccine development is undertaken by companies and governments in these areas, but the need for a vaccine will be global. It is expected that, should a pandemic begin, countries with manufacturing facilities will regulate production nationally.

25. Antigen, protective against the H5 virus subtype, can be produced in bulk and stored. Advance stockpiling of a vaccine against a pandemic virus is not possible, as the vaccine must closely match the actual strain of the pandemic virus and must therefore await its emergence.

26. Antiviral agents, which can be stockpiled in advance, have important but different roles, both now and at the start of a pandemic. These roles are, however, constrained by high costs and limited supplies. There are three opportunities for using antiviral medications, some of which are considered effective against H5N1 infection in humans. In the first such set of circumstances, these medicines can be used to treat H5N1-infected patients and to prevent infection in close contacts, including family members and health-care workers; this is currently being put into practice. As all antiviral agents need to be administered shortly after the onset of symptoms, a critical problem is the tendency of cases to be detected late in the course of their illness.

27. A second opportunity to use antiviral agents arises when surveillance indicates that the transmissibility of the virus is beginning to become more efficient. Administration of medications to all members of a community in which clusters of cases are occurring might either stop the virus from further improving its transmissibility or delay international spread.

28. The third opportunity presents once a pandemic has been declared. Pending the availability of vaccines, antiviral agents will be the principal medical intervention for reducing morbidity and mortality, which becomes the most important priority once a pandemic is under way. Several countries are now stockpiling antiviral medications, and these advance orders are expected to drive expansion of manufacturing capacity for the future. Increased capacity will place the world in a better position to respond to any future pandemic caused by any influenza virus.

29. A wide range of non-medical interventions, such as improved personal hygiene, quarantine, contact tracing and travel restrictions, can potentially reduce opportunities for transmission at the start of a pandemic and slow international spread. They have relevance to all countries. Consideration of their use during a pandemic is particularly important, as they will be the principal protective tools, pending the augmentation of vaccine supplies. WHO has issued recommendations concerning the use of more than 30 non-medical interventions at different phases during the progression from a pre-pandemic situation to declaration of a pandemic.[1] As another measure of their importance, any slowing of international spread at the start of a pandemic gains time to increase vaccine supplies; each day gained could mean an additional five million doses of vaccine.

30. Another WHO consultation, held in December 2004, recommended several revisions to the WHO preparedness plan for an influenza pandemic.[2] This document, which forms the basis for most national preparedness plans, presents a phased approach, in which sequential epidemiological events trigger a range of national and international activities, including those required for vaccine development. Revisions take into account the additional levels of alert and related activities needed when the threat of a pandemic arises from an outbreak in animals, and will be particularly useful in countries experiencing outbreaks of avian influenza in animals.

31. Given the seriousness of the present situation, all countries need to undertake preparedness activities. In affected countries, a high level of vigilance for clusters of cases of respiratory disease provides an early warning mechanism important for all countries. The best opportunity for international collaboration to improve preparedness and to expedite vaccine development is now, before the start of a pandemic.

ACTION BY THE EXECUTIVE BOARD

32. The Board is invited to note the report.

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[1] WHO consultation on priority public health interventions before and during an influenza pandemic (Geneva, 16-18 March 2004), document WHO/CDS/CSR/RMD/2004.9, available at: http://www.who.int/csr/disease/avian_influenza/consultation/en/.

[2] Influenza pandemic plan: the role of WHO and guidelines for national and regional planning (Geneva, April 2004), document WHO/CDS/CSR/EDC/99.1, available at: http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_EDC_99_1/en/.