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Avian influenza and human health

Report by the Secretariat

BACKGROUND

1. In January 2004, health authorities in Thailand and Viet Nam reported their first human cases of infection with avian influenza, caused by the H5N1 strain of *Influenzavirus A*. The cases in humans are directly linked to outbreaks of highly pathogenic H5N1 avian influenza in poultry first reported in the Republic of Korea in mid-December 2003 and subsequently confirmed in an additional seven Asian countries (Cambodia, China, Indonesia, Japan, Laos, Thailand, and Viet Nam). As at mid-March 2004, no countries other than Thailand and Viet Nam had reported human cases. Despite the comparatively small number of cases reported to date, the situation has features of public health concern that warrant careful monitoring. Of foremost concern is the risk that conditions present in parts of Asia could give rise to an influenza pandemic.
2. Concern about a future influenza pandemic has a strong historical base. Although the timing cannot be predicted, influenza pandemics have followed a recurring pattern and invariably cause great loss of life, social disruption, and economic costs. The previous century experienced three pandemics. Of these, the great pandemic of 1918-1919 is regarded as the most deadly disease event in the history of humanity.
3. Conditions favourable to the start of an influenza pandemic are now much better understood than in the previous century. Influenza research was greatly stimulated in 1997, when the world's first cases of human infection with the H5N1 strain of avian influenza virus were documented in Hong Kong Special Administrative Region, China. Investigations launched by that outbreak, including studies in molecular biology and epidemiology, helped elucidate the mechanisms by which pandemic viruses emerge and further clarified the conditions that favour such an event. These studies also demonstrated, for the first time, that the H5N1 strain can infect humans directly without prior adaptation in a mammalian host. Some experts believe that this improved understanding, when combined with good surveillance and reporting, might make future pandemics both predictable and preventable.
4. In Hong Kong Special Administrative Region, China, the outbreak in humans, which involved 18 cases, six of them fatal, coincided with outbreaks of infection due to highly pathogenic H5N1 virus in domestic poultry on farms and in live markets. The culling within three days of the entire poultry population of Hong Kong SAR is thought to have averted a pandemic on that occasion. Interspecies transmission occurred again in Hong Kong SAR in February 2003, when H5N1 virus caused two human cases, one of which was fatal.

THE OUTBREAK IN POULTRY

5. In birds, highly pathogenic avian influenza is an extremely contagious and aggressive disease that causes rapid systemic illness and death in susceptible birds. Domestic chickens and turkeys are most severely affected; mortality in these birds often exceeds 50%. Until now, the disease was considered rare. From 1959 to 2003 only 21 outbreaks occurred worldwide, mainly in the Americas and Europe. Although all had serious consequences for the poultry industry, most remained geographically circumscribed. Culling, quarantine, disinfection, restrictions on animal movement, and strict biosecurity on farms are standard measures, recommended by FAO and the Office International des Epizooties, for control and the prevention of reinfection. Even under favourable circumstances (concentration in commercial production facilities, limited geographical spread), control has taken as long as two to three years.

6. The present outbreaks in poultry are historically unprecedented in their geographical scope, international spread, and economic consequences for the agricultural sector. They have several features that will make short-term control and long-term prevention of reinfection extremely difficult to achieve. In several affected countries, up to 80% of poultry production occurs in small rural farms and backyard holdings. Such large numbers of free-ranging birds are largely incompatible with the application of biosecurity measures, including bird-proof, ecologically controlled housing; treatment of water supplies; disinfection of all incoming persons, equipment, and vehicles; and prevention of contact with insects, rodents, and other mechanical vectors.

7. Another problem is the lack of coping capacity, including surveillance and response capacity and resources, in several affected countries. During the first two months of the recent outbreaks, more than 100 million birds died or were destroyed. Compensation of farmers has often been inadequate, thus discouraging the reporting of further cases and encouraging the hiding or smuggling of valuable birds, such as fighting cocks.

8. In many Asian countries, poultry production has increased dramatically over the past decade and now carries great significance for the national economy. Poultry and poultry products have also become a staple food, providing as much as 30% of total protein in the diets of large populations, including rural households.

9. More than half of the affected countries are experiencing outbreaks of highly pathogenic avian influenza for the first time in their histories. Because the present situation has no historical precedent, national authorities and international agencies have no body of experience to guide the selection and implementation of the most effective control measures. With so many countries affected over such large geographical areas, the risk is great that successful control in one country will be compromised by inadequate control elsewhere.

IMPLICATIONS FOR HUMAN HEALTH

10. Although the outbreaks in poultry have weakened economies and jeopardized food security, the greatest concern for human health is the risk that present conditions could give rise to an influenza pandemic. Research has identified three prerequisites for the start of a pandemic. First, a novel influenza virus must emerge to which the general population will have no or little immunity and against which no existing vaccine will be effective. Second, the new virus must be able to replicate in humans and cause disease. Third, the new virus must be efficiently transmitted from one human to

another; efficient human-to-human transmission is expressed as sustained chains of transmission causing community-wide outbreaks. The first two prerequisites have been met.

11. The small number of human cases to date compared with the magnitude of the outbreak in birds suggests that H5N1 virus is not easily transmitted from birds to humans at present. Investigations to date have found no evidence of efficient human-to-human transmission. The virus could, however, rapidly improve its transmissibility via two mechanisms. Efficient human-to-human transmission could follow the exchange of gene segments (reassortment) when humans or pigs are simultaneously infected with H5N1 and a currently circulating human influenza virus, which is already adapted for efficient transmission. Mutation during human infection is a second mechanism for improving transmissibility; scientists believe that only a small number of mutational changes in the virus may be needed.

12. No one can predict if or when the third prerequisite for the start of a pandemic will be met. The chances have, however, been greatly increased by the scale of the outbreaks in poultry, the inherent difficulty of their control, and the resulting continuing opportunities for human exposure and infection to occur. These conditions make the present situation sufficiently serious to warrant urgent acceleration of pandemic preparedness plans.

THE INTERNATIONAL RESPONSE

13. Improved understanding of the conditions that favour pandemics supports a rational response with three complementary objectives: to avert a pandemic; to control the outbreak in humans and prevent further spread; and to conduct the research needed for better preparedness and response, including the immediate development of a vaccine protective against infection with H5N1 virus. The first step towards averting a pandemic is to eliminate the animal reservoir of the virus and thus reduce opportunities for human exposure and infection. Activities that contribute to this goal include rapid detection of infected flocks followed by immediate culling, quarantine, disinfection, and introduction of strict biosecurity measures on farms. Cullers are at risk of brief but intensive exposure and should receive adequate personal protective equipment. They should also be vaccinated against circulating strains of normal seasonal influenza. Although these vaccines will not protect against infection with H5N1 virus, they do reduce the risk of reassortment following co-infection of humans with avian and human influenza viruses.

14. Control of the outbreak in humans has relied on heightened surveillance and case detection, laboratory diagnosis according to international standards, and infection control to prevent amplification of cases in health-care settings. Experience in the clinical management of this disease is very limited, and case fatality has been high in this and previous outbreaks. H5N1 virus may also be causing milder cases of disease, which are not being detected and reported, and which would influence estimates of the case fatality ratio.

15. The present situation provides opportunities to advance knowledge further by conducting appropriate research. Within affected countries, several case-control studies are under way to determine the risk to poultry workers and cullers and to investigate whether limited human-to-human transmission has occurred. Other lines of research have been undertaken by laboratories in the WHO Global Influenza Surveillance Network. These laboratories have provided diagnostic support and rapidly conducted the research, including virus characterization, needed to understand the outbreaks better and to prepare a prototype virus that can then be supplied to manufacturers as the “seed lot” for

vaccine production. Studies designed to assess the potential of H5N1 virus to mutate or reassort, and thus improve its transmissibility, should greatly strengthen the scientific base for risk assessment.

16. Particular problems could arise in the use of antivirals during a pandemic caused by H5N1. Studies conducted by laboratories in the WHO Global Influenza Surveillance Network have shown that most current H5N1 strains are resistant to one of the two classes of antiviral drugs. Should viral replication outside the human respiratory tract be confirmed, as is currently suspected by some scientists, one of the two antivirals in the second class will also be ineffective. Other problems include high costs, uncertain efficacy, and extremely limited supplies, with no surge capacity.

17. In response to these concerns, WHO convened a technical consultation on preparedness for an influenza pandemic (16 to 18 March 2004). Attended by more than 100 experts, it assessed the objectives, feasibility, and effectiveness of a wide range of measures that could be introduced by WHO and national authorities to slow national and international spread of an influenza pandemic and to reduce associated morbidity, mortality, and social disruption. Possibilities for averting a pandemic were also explored.

18. The consultation concluded that supplies of vaccine, the first line of defence for preventing high morbidity and mortality, would be grossly inadequate at the start of a pandemic and well into the first wave of international spread. Manufacturing capacity is finite, and production and stockpiling of a vaccine against a pandemic strain face a number of constraints. Limited production capacity, largely concentrated in Europe and North America, would exacerbate the problem of inequitable access.

19. In the absence of a vaccine, other measures would take on importance as a means of reducing national and international spread pending build-up of vaccine stocks. The consultation considered these measures in terms of their relevance to different phases, defined by epidemiological criteria, during the progression from an incipient pandemic situation to the declaration of a pandemic. The establishment of human-to-human transmission was considered to be the key epidemiological trigger for intense international efforts aimed at interrupting further transmission, or at least delaying it. Surveillance systems should therefore be oriented towards early detection, reporting and investigation of clusters of human cases, followed by aggressive containment measures, including tracing and management of contacts, targeted prophylactic use of antivirals, and travel-related measures. Establishment of an international stockpile of antivirals for use exclusively during this critical period should be considered. Should early containment fail, pandemic response plans should include provisions for stopping preventive measures in order to conserve resources for reducing case fatality while vaccine supplies were increased and mass vaccination strategies put in place.

CONCLUSIONS

20. At the beginning of the twenty-first century, the world has experienced two unusually alarming infectious disease events: the emergence and subsequent spread of SARS in 2003, and the looming threat of an influenza pandemic in 2004. Together, these events underscore the need for international solidarity against threats that can spread readily and widely – with highly adverse consequences for economies and societies as well as public health – in a closely interconnected and highly mobile world. The control of such threats depends on prompt and transparent reporting of cases and a robust system of global surveillance and response. Such a system will also strengthen protection against a third infectious threat that became prominent in 2001, namely, the risk that biological agents would deliberately be used to cause harm.

21. Strong international mechanisms for responding to emergencies can never fully compensate for weak national capacity. During the SARS outbreak, one of the greatest fears was that the disease would gain a foothold in a developing country with inadequate response capacity, thus allowing the virus to establish endemicity. In the present situation, the H5N1 strain has established a strong presence in the poultry populations of large areas in Asia, and is likely to prove extremely difficult – if not impossible – to eliminate. Regardless of whether the virus becomes endemic in birds, the international community needs to be prepared for a long-term struggle against the risk of further infections and opportunities for a novel virus with pandemic potential to emerge.

22. The possibility of recognizing conditions conducive to a pandemic brings with it the opportunity to take appropriate corrective actions and thus prevent the great loss of life and social disruption invariably caused by pandemics. To do so, surveillance and reporting need to be strengthened, as does collaboration between the public health and agricultural sectors. Research set in motion by WHO's Global Outbreak and Response Network, national authorities, and laboratories in the influenza surveillance network will contribute to both risk assessment in the present situation and better preparedness to act when a similar situation inevitably arises.

ACTION BY THE EXECUTIVE BOARD

23. The Executive Board is invited to note this report.

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