

Avian and pandemic influenza: developments, response and follow-up, and application of the International Health Regulations (2005)¹

Report by the Secretariat

RECENT DEVELOPMENTS

1. The present WHO level of pandemic influenza alert, set in place in January 2004, remains at phase 3: a novel influenza virus is causing sporadic human cases, but is poorly adapted to humans. Highly pathogenic avian influenza, caused by the H5N1 virus, remains primarily a disease of domestic birds.
2. The number of countries reporting human cases grew from two in 2004 to five in 2005. During the first 10 months of 2006, 109 cases and 74 deaths were reported from nine countries, representing a case-fatality rate of 68%. Some instances of limited human-to-human transmission have occurred. In all such instances, the virus had multiple opportunities to spread into the general community or to infect unprotected health-care workers, but did not do so. Chains of human-to-human transmission have been short, and most have been limited to relatives in close contact with an infected family member. These findings further confirm that the H5N1 virus is at present poorly adapted to humans.
3. Although some countries severely affected by poultry outbreaks have controlled those outbreaks, the virus has become firmly entrenched in populations of domestic birds elsewhere. Moreover, evidence has continued to mount that wild migratory birds can transport highly pathogenic H5N1 viruses over long distances, thus further complicating efforts to eliminate the virus from avian species. The threat that a pandemic virus may emerge is serious and expected to persist. A WHO working group on influenza research at the human and animal interface (Geneva, 21–22 September 2006) acknowledged that the seriousness of the present situation, including the risk that a pandemic virus may emerge, is not likely to diminish in the near future.²
4. As influenza A viruses lack a “proof-reading” mechanism for DNA repair and fail to correct small errors that occur in viral replication, constant genetic mutation is a characteristic feature of all influenza A viruses, including H5N1. The H5N1 virus has evolved, in animals, in several ways since the start of the current poultry outbreaks in mid-2003. In terms of implications for human health, one of the most significant evolutions has been the divergence of viruses into distinct genetic groups,

¹ See document EB120/16 for information on application of the International Health Regulations (2005).

² Document WHO/CDS/EPR/GIP/2006.3.

called clades. At present, scientists in the WHO network of laboratories specialized in research on H5 viruses have identified two clades; within one, a further three distinct subclades have been identified. Viruses belonging to all these clades and subclades are circulating simultaneously, each clade and subclade characterized by distinctive genetic sequences and antigenic properties and each tending to be predominance in one particular geographical area. This divergence underscores the difficulty of developing a predictably protective vaccine before the emergence of the actual pandemic virus.

RESPONSE

5. Continuing vigilance for human cases has been accompanied by national and global preparedness measures on several levels. Almost all countries have now formulated preparedness plans for an influenza pandemic, many of which have been tested in national or regional exercises. Manufacturing capacity for oseltamivir, the principal antiviral medicine for prophylaxis and treatment, has increased considerably, and manufacturing licences have been granted to several developing countries. WHO has a stockpile of oseltamivir, amounting to three million treatment courses, for use in a rapid containment intervention near the start of a pandemic; to support such an intervention, a detailed operational protocol, with clearly defined responsibilities, time frames for action, and standard operating procedures, was issued in draft form in May 2006.¹ Several candidate pandemic vaccines are under development and some have entered clinical trials.

6. The Secretariat is addressing urgent concerns related to limited vaccine-production capacity and limited access to vaccines. In October 2006, it issued a global action plan for increasing the supply of pandemic influenza vaccines.² This plan outlines three major approaches, each supported by short- and long-term objectives and a range of strategies and actions for meeting them: (a) an increase in seasonal use of vaccine, which will gradually result in greater overall capacity to manufacture pandemic vaccines; (b) a more immediate increase in production capacity, through improvements in vaccine-production technologies and formulations of vaccines, the construction of new plants, or the partial conversion of existing facilities used to produce vaccines for veterinary purposes; and (c) further research and development, including the development of novel vaccines that induce broad-spectrum and long-lasting immune responses.

7. On 24 and 25 October 2006, WHO convened a consultation to explore the ethical issues that are likely to arise during national and international responses to a pandemic and thus need to be considered in preparedness planning. Its objectives included consideration of the need to promote equitable access, at both national and international levels, to therapeutic and prophylactic measures, including vaccines. For clinicians and laboratory personnel working on the diagnosis of human cases of H5N1 influenza, an illustrated guide to the collection, preservation and shipment of specimens for diagnostic purposes was issued, also in October 2006.³ For epidemiologists, a step-by-step guide to the

¹ WHO pandemic influenza draft protocol for rapid response and containment. Available at: http://www.who.int/csr/disease/avian_influenza/guidelines/protocolfinal30_05_06a.pdf.

² Document WHO/IVB/06.13 – WHO/CDS/EPR/GIP/2006.1.

³ Document WHO/CDS/EPR/ARO/2006.1.

field investigation of cases is being finalized, with particular emphasis on the investigation of possible instances of human-to-human transmission.¹

8. The Secretariat has recently formulated a set of best practices for the sharing of influenza viruses, which were endorsed during the first meeting of the Influenza Pandemic Task Force (25 September 2006), convened pursuant to resolution WHA59.2. These recommended practices make a clear distinction between procedures specific to the sharing of H5N1 viruses and other long-standing procedures for the sharing of seasonal influenza viruses. Routine sharing of seasonal influenza viruses, coordinated internationally by WHO since 1947, functions smoothly to guide the composition of annual vaccines for seasonal influenza and maintain vigilance for the emergence of novel virus strains, including those with pandemic potential.

9. The sharing of H5N1 viruses raises a unique set of issues not seen during the routine sharing of seasonal influenza viruses. These issues stem from three characteristics of H5N1 viruses: (a) their high pathogenicity for animals and humans, which restricts research to a limited number of specially equipped laboratories; (b) the need to use a patented technology, called reverse genetics, when rendering these viruses safe for use in the development of candidate pandemic vaccines; and (c) the great significance of H5N1 viruses as an agricultural threat and a pandemic threat to international public health, which increases the need for collaborative research on these viruses and the global need for access to medical interventions that may be a product of this research.

FOLLOW-UP

10. The recent divergence of H5N1 viruses into genetically and antigenically distinct clades and subclades complicates the selection of an optimal strain for the development of a vaccine. Candidate vaccine viruses representing all presently known clades and subclades have been developed through reverse genetics by laboratories in the WHO network, and intense efforts are under way to develop pandemic vaccines. Some candidate H5N1 vaccines have shown cross-protection in animal studies against the various strains but the effectiveness of cross-protection of people is not known. Moreover, scientists are unable to predict which currently circulating strain, if any, might start a pandemic.

11. This divergence has also intensified the need for rapid sharing with WHO laboratories of all recently isolated viruses, from both animals and humans, data on genetic sequences, and information collected from clinical and epidemiological investigations of humans infected with these viruses. Such international sharing of viruses, sequence information and clinical/epidemiological findings is needed for overall pandemic risk assessment, the production of up-to-date diagnostic reagents and diagnostic kits, and surveillance of resistance to antiviral medicines as well as for the development of effective pandemic vaccines.

12. An influenza pandemic is expected to spread throughout the world in a matter of months, if not weeks. The sharing of H5N1 viruses and sequence data for vaccine research and development is therefore crucial for the protection of public health in all countries and is a collective responsibility. At the same time, however, the countries most severely affected by avian outbreaks and human cases are largely located in the developing world, and few have the capacity to manufacture pandemic vaccines. A call for more rapid routine sharing of H5N1 viruses needs to be accompanied by measures that

¹ Document WHO/CDS/EPR/GIP/2006.4, in press.

improve the prospects of access to pandemic vaccines in all countries and increase the supply of pandemic vaccines. These challenges are great and being given a correspondingly high priority by WHO and its international partners.

ACTION BY THE EXECUTIVE BOARD

13. The Executive Board is invited to consider the following draft resolution:

The Executive Board,

Having considered the report on avian and pandemic influenza: developments, response and follow-up, and application of the International Health Regulations (2005),¹

RECOMMENDS to the Sixtieth World Health Assembly the adoption of the following resolution:²

The Sixtieth World Health Assembly,

Having considered the report on avian and pandemic influenza: developments, response and follow-up;

Recalling resolutions WHA58.5 and WHA59.2, which expressed concern about the potential of the H5N1 avian influenza virus to cause a pandemic and urged Member States to disseminate to WHO collaborating centres information and relevant biological materials, including clinical specimens and viruses;

Recognizing, in particular, the importance of international sharing, with WHO collaborating centres, of clinical specimens and viruses as a contribution to assessment of the pandemic risk, the development of pandemic vaccines, the updating of diagnostic reagents and test kits, and surveillance for resistance to antiviral medicines,

1. URGES Member States:

(1) to continue to support the WHO Global Influenza Surveillance Network and its procedures for the routine collection, exchange and characterization of circulating strains of seasonal influenza viruses;

(2) to establish mechanisms that ensure the routine and timely sharing of biological materials related to novel influenza viruses posing a pandemic threat, including H5N1 virus isolates from both humans and animals, and the placement of data on the genetic sequences of these viruses in the public domain;

¹ Documents EB120/15 and EB120/16.

² See document EB120/15 Add.1 for the administrative and financial implications for the Secretariat of this resolution.

(3) to support implementation of the WHO global pandemic influenza action plan to increase vaccine supply¹ as a means of increasing availability and access to pandemic influenza vaccines;

(4) to continue to conduct rapid clinical and epidemiological investigation of human infections, and to share findings in a timely manner with WHO and the international community;

2. REQUESTS the Director-General:

(1) to continue to coordinate international surveillance of seasonal influenza viruses and viruses with pandemic potential;

(2) to ensure that the results of research on influenza viruses, including the H5N1 virus, lead to the broadest possible access to practical products, including pandemic influenza vaccines;

(3) to ensure broader regional distribution of production capacity for influenza vaccine and increasing production capacity for pandemic vaccines by leading implementation of the WHO global pandemic influenza action plan to increase vaccine supply, emphasizing those activities that help to increase access to pandemic vaccines in developing countries and other countries that lack domestic manufacturing capacity;

(4) to continue to assess the evolving threat of an influenza pandemic and keep the international community informed.

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¹ Document WHO/IVB/06.13 – WHO/CDS/EPR/GIP/2006.1.