Avian Influenza

in South-East Asia Region: Priority Areas for Research

World Health Organization

Regional Office for South-East Asia

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Contents

Background

The first cases of human Influenza A H5N1 reported in 1997 from Hong Kong (China) coincided with H5N1 outbreaks in poultry in farms and in wet markets. The destruction of the entire poultry population at that time in Hong Kong (China) resulted in cessation of human cases. In early 2003, however, cases were reported from a Hong Kong (China) family who had travelled to mainland China. In mid-2003, H5N1 began to circulate in poultry in some countries of South-East Asia and these were followed in December 2003 by human cases in Viet Nam which were followed by subsequent epidemics among poultry in several countries in Asia and human cases in Thailand, Indonesia, Cambodia and China.

Global and regional situation

Since mid-2005, the spread of avian influenza (AI) among poultry across the globe has been rapid with H5N1 outbreaks in birds in 54 countries; in addition a total of 251 human cases and 148 deaths have been reported from 10 countries across central Asia, Africa, Europe and the Middle East. Two of the 11 countries in the South-East Asia Region – Indonesia and Thailand – have reported human cases since 2003. Thailand's last human case was reported in September 2006 after no reports for six months. Indonesia continues to report human cases. Thailand and Indonesia account for about 32% of the total global human cases. Outbreaks of H5N1 in poultry have been reported from India and Myanmar in addition to Thailand and Indonesia. Of the current figures for the reported human cases, the case fatality is very high – 65%. It is uncertain whether milder cases of human H5N1 infection have occurred.

The full disease spectrum in man is critical and requires vigilant surveillance. The surveillance system will provide epidemiological, clinical and virological data on influenza strains. Moreover, efforts have been made to ensure close collaboration between the public health, agricultural sectors and veterinary services.

The need for research

There are many unanswered questions about AI H5N1. Research leads to a better understanding of the disease while at the same time developing the evidence base from which to appropriately target effective interventions in the face of limited resources. As part of preparedness, a research agenda has to be prepared because the timing of another pandemic is unpredictable. During the recent AI outbreaks, research on the natural history of the disease has been localized and disjointed. Some data have been available from small-scale investigations but international merging of data has been difficult because of the lack of standardization and compatibility of study protocols. Experiences from the recent H5N1 outbreak and SARS have shown that research on emerging infectious diseases cannot be conducted properly when initiated after the outbreak has occurred. By using an international or regional multi-site research network instead of individual efforts, the necessary capability to understand the disease better can be developed which in turn will help in its prevention and control. In this report, the current knowledge on AI available from studies, and the gaps in knowledge that in order to be filled need the cooperation of all affected countries, have been reviewed and further steps to be taken in this direction recommended.

What is known about Avian Influenza

Evolving virus

The highly pathogenic Influenza A H5N1 virus is endemic in avian populations in some countries in South-East Asia and represents a real

pandemic threat. The continued evolution of H5N1, initially a mild disease, has led to a more pathogenic disease in poultry with a risk of mutation or genetic reassortment which can result in a virus with increased transmissibility; the virus survival characteristics have changed, surviving at 37C for 6 days in 2004 compared to 2 days in 1997.

Genetically and antigenically distinct sub-lineages of H5N1 virus have become established in poultry in different geographical regions of South-East Asia indicating the long term endemicity of the virus. H5N1 virus has also been isolated from apparently healthy migratory birds in southern China.

Animal-to-human transmission

The first documented outbreak of human respiratory disease caused by AI A (H5N1) viruses occurred in Hong Kong (China) in 1997. The kinetics of the antibody response to the avian virus in H5N1-infected persons was similar to that of a primary response to human influenza A viruses; serum neutralizing antibody was detected, in general, greater than or equal to 14 days after symptom onset. A study among swine residents and employees in the USA indicated that pig contact was associated with seropositivity to swine influenza viruses. The study indicated possible risk of transmission from animals to the human population. A study to evaluate the potential for avian-to-human transmission of H5N1 was conducted by a cohort study among poultry workers (293 Hong Kong (China) government workers (GWs) who participated in a poultry culling operation and 1525 poultry workers (PWs)). Paired serum samples collected from GWs and single-serum samples collected from PWs were considered to be anti-H5 antibody positive if they were positive by both microneutralization and Western blot testing. Among GWs, 3% were seropositive, and 1 seroconversion was documented. Among PWs, approximately 10% had anti-H5 antibody. More intensive poultry exposure, such as butchering and exposure to ill poultry, was associated with having anti-H5 antibody. These findings suggested an increased risk of AI infection from occupational exposure. A 2004 study in Viet Nam

among confirmed cases of H5N1 patients identified that in eight of the nine patients in whom history was taken, there was a clear evidence of either direct handling of poultry (chickens and ducks) or exposure to sick poultry in the week before the onset of illness. This study showed exposure to sick poultry as the main risk factor. It also documented an average incubation period of 3 days (range 2-4 days).

A 2004 study in Thailand among confirmed cases of H5N1 indicated that all significant risk factors were related to exposure to affected birds, including contact with sick or dead chickens and keeping dead chickens in the house. The study documented an average incubation period of 3 days (range 2-8 days). Molecular biological analysis of viral nucleic acid supports the hypothesis that animals, particularly birds and pigs, may have contributed to earlier influenza pandemics. Some animal viruses containing genes, e.g. H1, H2 and H3, might infect humans directly and become adapted to the human host. Alternatively, reassortment of the genes in different animals or human influenza viruses might appear in an infectious human virus.

Expanding host range

The host range is also expanding to include wild and domestic birds and other animals such as cats and tigers. Ducks are a critical factor in highly pathogenic AI (HPAI) persistence and spread; HPAI replicates in respiratory and intestinal tracts of ducks and large amounts are excreted via the respiratory tract and faeces and can spread from ducks to chickens; in Thailand H5N1 was found to be prevalent among free-grazing and backyard ducks compared to ducks raised in areas with high biosecurity. AI can infect not only chickens and ducks but also pigs. Ducks are important because they can be infected with mild or asymptomatic infection and can transmit large quantities of the virus through their excretion and faeces. Pigs are important in crossing the species barrier as they have cell surface receptors for both human and AI viruses. In addition, viral mutations can also lead to the emergence of a strain with the potential to cross the species barrier and efficiently infect humans and other mammals.

Person-to-person transmission

Person-to-person spread can occur – this was first documented in Hong Kong (China) in 1997 and is most likely when contact is close. It may increase the chances for the emergence of a novel influenza virus with pandemic potential. The detection of clusters of cases closely related in time and place is likely to be the most important epidemiological signal of improved human-to-human transmission. The decision to initiate rapid containment activities will be based on clinical, epidemiological and virological findings.

In 1999, a retrospective cohort study in Hong Kong (China) found no serological evidence of infection among family members and health care workers who had close contact with two laboratory confirmed H9N2 subtype AI cases. This finding suggested that H9N2 subtype was not easily transmitted from human to human. However, the H9N2 viruses are widely distributed in avian populations, can infect humans, and could evolve or undergo genetic reassortment with potential for transmissibility in humans.

Cohort studies were conducted to assess the risk of human-to-human transmission of the virus. By the use of a combination of serological assays, 6 out of 51 household contacts, 1 out of 26 tour group members and none of 47 co-workers exposed to H5N1-infected persons were positive for H5 antibody. One H5 antibody-positive household contact, with no history of poultry exposure, provided evidence that human-to-human transmission of the avian virus may have occurred through close physical contact with H5N1-infected patients. In contrast, social exposure to case patients was not associated with H5N1 infection.

A case control study conducted to assess the risk of influenza A (H5N1) among health care workers, who were exposed to patients with confirmed H5N1 in Hong Kong (China) found that 3.7% of the exposed health care workers and only 0.7% of the non-exposed workers were H5N1 seropositive. The difference remained significant after controlling for poultry exposure ($p = 0.01$). This finding supports human-to-human transmission of AI (H5N1). A 2004 case report in Thailand indicated

that clinical signs and symptoms of AI H5N1 may be more protean than originally described. The case, with gastrointestinal symptoms with no early respiratory symptoms, was reported. This underscores the importance of continuing infection control precautionary measures among health care workers. The observations from clusters of cases in close contact from Viet Nam and Thailand suggest the possibility of human-to-human transmission. However, further research is required.

Antivirals and vaccines

Mixed resistance patterns to antiviral drugs have been demonstrated – most human isolates are resistant to M2 class of drugs – amantadine, rimantidine; few H5N1 isolates have been shown to be resistant to oseltamivir. Based on modelling using a specific reproductive number, quantities of antivirals to be stockpiled can be predicted. However, what is crucial is how quickly cases are diagnosed and the speed at which antiviral drugs can be distributed. The impact of influenza on morbidity and hospitalization in the tropics and subtropics is not well defined. Better utilization of the vaccine during annual epidemics will enhance global vaccine production capacity and allow for better preparedness to meet the surge in demand that would be inevitable in confronting a pandemic.

Studies have been carried out to identify sources of infection, assess the risk of human infection and the potential for mutation and to determine the potential for infection across species. More research is needed to fully understand the extent and implications of a pandemic among humans. High population exposure and low perceived risk are potentially important health threats in AI.

Potential areas for future research

Epidemiology

Understanding the epidemiology of AI in humans will facilitate better detection and control of the disease. Knowing about risk factors and

understanding the natural history of the disease will assist in refining the case definition for better case ascertainment. Specific research areas include:

(1) Studies on the mode of transmission in human beings, infectiousness and communicability.

(2) Obtain data on the incubation period of H5N1.

(3) Determining the presence of asymptomatic infection in humans through seroprevalence studies.

(4) Identifying risk factors/risk behaviours associated with AI transmission among human beings.

(5) Determining the role of other animals such as tigers, pigs and cats in disease transmission.

Laboratory

Determining the laboratory profile of suspect cases will assist in detecting H5N1 cases, optimizing treatment and possible utilization of the virus as a vaccine strain. Specific areas of work should include:

(1) Reviewing the etiology of severe pneumonia cases and deaths by setting up sentinel sites with research capacity and sufficient laboratory support which, in addition to detecting H5N1, will detect other emerging pathogens.

(2) Characterization of isolates from the South-East Asia Region to understand their sources, determine resistance to oseltamivir and their utilization as a potential vaccine strain.

(3) Developing user-friendly sensitive and specific rapid diagnostic kits for H5 diagnosis which can be used at peripheral levels.

(4) Conducting genetic analysis of virus isolates to determine mutation or reassortment. This requires sharing of clinical samples from cases in family clusters with laboratories in the WHO Global Influenza Surveillance Network.

(5)	Supporting vaccine research; virus characterization of influenza subtypes (H5 and non H5) to trace mutation or reassortment to provide a scientific basis for risk assessment. This will also help prepare a prototype virus that can be supplied to manufacturers as the 'seed virus' for vaccine production. Continue human H5N1 vaccine research and development using the research network sites as a multi-center field trial.

(6)	Assessing capacity within the region to carry out vaccine development.

Clinical

Data on the clinical course of the disease will help to understand the disease progression thereby facilitating early detection and appropriate management. Specific research could include:

(1)	Describing the clinical manifestation of confirmed cases to better describe the clinical profile and use it to improve the case definition for surveillance purposes.

(2)	Reviewing the clinical course of illness in cases to determine the natural history of the disease.

(3)	Examining why the case fatality rates are high in certain areas.

(4)	Evaluating possibility of person-to-person transmission by paying particular attention to clusters of pneumonia cases and pneumonia in health care workers.

(5)	Reviewing medical histories of cases to determine if particular patient profiles are more susceptible to disease.

(6)	Undertaking autopsy studies where possible to determine the cause of death.

(7)	Studying the effects of various disinfectants on H5N1 survival for infection control purposes.

(8) Conducting human clinical trials with oseltamivir to determine optimum doses, duration and frequency.

(9) Testing the efficacy of oseltamivir in reducing the case fatality rate.

(10) Studying the effects of neuraminidase inhibitors alone or in combination with M2 inhibitors or ribavirin; study should include pregnant women and less than one year old children.

(11) Evaluating the effectiveness of antivirals and monitoring drug resistance during outbreaks.

Social, behavioural, economic and policy-related issues

There is a gap in knowledge regarding factors likely to promote or hinder effective implementation of effective behaviour change interventions. Specific projects in this area could include:

(1) Determining behaviours and practices among communities likely to promote or hinder effective implementation of behaviour change interventions

(2) Reviewing knowledge, attitudes and practices of health care workers and the general population in relation to risk factors

(3) Determining the role of culture, communication, policy coherence in promoting behaviours that reduce transmission of AI from animals to humans

(4) Assessing community knowledge about antiviral availability and use

(5) Evaluating the role of the media and health promotion practices and of health promotion materials disseminated during outbreaks for refining risk communication messages

(6)   Documenting the evidence of the effectiveness of behaviour change interventions and sharing experiences and lessons learnt from managing cases and clusters of H5N1

(7)   Carrying out comparative analysis of the impact of culling vs vaccination

(8)   Determining the prevalence of asymptomatic infection in ducks in Asia to allow a focused approach to the prevention of human cases arising from exposure to apparently healthy domestic ducks

WHO's role in supporting research

WHO will consider organizing a consultation to fine tune the research agenda and identify few research areas that would provide critical input for AI control and preparing for a pandemic. In each of the priority research areas there is a need to develop a generic protocol that can be applied at the field level with the understanding that most research can only be carried out in areas where outbreaks have occurred or are ongoing.

A regional workshop to further discuss the methodology and to ascertain support for this activity could therefore be organized. Regional workshops to bring principal investigators from collaborating sites together to ensure international cooperation, coordination and sharing of information would be useful.

WHO could promote collaboration among laboratory, epidemiology, social science and veterinary medicine institutions across the Region to complement the research network and also consult national authorities to identify collaborating research sites for emerging diseases including AI. Members from each collaborating site, WHO and partners from research institutions will have a role in establishing standards for protocol implementation as demonstrated in the WHO pandemic influenza protocol for rapid response and containment.

The resources and infrastructure needed to assist a site to perform the study, bearing in mind that each site may have different capacity and need should be discussed. Technical and financial assistance will be required to respond to those needs. Data generated will be used for local clinical management decisions, national policy development and international pandemic preparedness.