By Dr Wong Sin Yew

Avian Influenza:
Are we on the brink of an influenza pandemic?

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Since October 2005, hardly a week goes by without a media report on highly pathogenic avian influenza (HPAI) due to H5N1 either causing avian outbreaks in a new geographic locale or highlighting yet another human being infected with this virus. Indeed, many influenza experts (virologists, infectious disease physicians, public health officials) are concerned that the continuing spread of HPAI in wild and domestic poultry represents the most serious human influenza pandemic risk for decades.

Why is there this concern? Is this just media hype? After all, HPAI due to H5N1 remains an avian influenza with only humans infected '*incidentally*'. The following is a short summary of recent articles on HPAI due to H5N1 and their implications on pandemic influenza. Hopefully, this article will spur closer interest into this topic and improve appreciation of the concerns that have been voiced by many in the medical and scientific community.

Firstly, many believe that history usually repeats itself. In the past century, influenza pandemics have occurred at approximately 30 to 40 year intervals with the 1918 Spanish flu (H1N1), 1957 with Asian flu (H2N2), and 1968 with Hong Kong flu (H3N2). We are past the 30-year mark and close to the 40-year mark since the last influenza pandemic of 1968. In fact, this concern with history has prompted influenza experts to predict an influenza pandemic within

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the first decade of the 21st century. As early as April 2003, at the WHO assembly, countries were already encouraged to develop an influenza pandemic plan. As the events of HPAI due to H5N1 unfolded, WHO identified H5N1 avian influenza as the most significant influenza pandemic threat. One of the main reasons is that influenza pandemics occur when there is a major antigenic shift. Immunity of humans to influenza is thought to be subtype specific and since most humans have never been infected by H_5 influenza virus before, an influenza pandemic is likely to occur if the H5N1 virus develops efficient human-to-human transmission.

The geographic reach of HPAI due to H5N1 has extended beyond Asia to the Middle East and Eastern Europe. H5N1 is now endemic in domestic and wild poultry in several Asian countries. Unfortunately, sporadic H5N1 human cases continue to occur in these countries. Although H5N1 at present remains an avian disease, these human cases allow interaction between the H_5N_1 avian influenza and human influenza viruses. The H1N1 Spanish flu that caused 20 to 40 million deaths in 1918 was avian in origin. Therefore, it came as no surprise that health authorities are concerned that re-assortment of H5N1 avian influenza with human influenza viruses such as H3N2, or direct adaptive mutation by the H5N1 virus will result in H5N1 becoming the next pandemic influenza strain.

TIMELINE OF AVIAN INFLUENZA H5N1 SINCE 1997

H5N1 influenza virus first came to medical attention when human cases were reported in Hong Kong in 1997. In the ensuing outbreak, several million poultry died or were culled before the human cases ceased. In all, there were 18 human cases, of which 6 were fatal. Not much was heard until February 2003 when 2 cases (1 fatal) of H5N1 were reported in Hong Kong.

The current H5N1 avian influenza outbreak has been described to have occurred in three waves. The first wave started in December 2003, when countries including Thailand, Korea, Vietnam, Japan, Cambodia, Laos, Indonesia and China reported outbreaks of H5N1 avian influenza occurring in poultry farms. In January 2004, both Vietnam and Thailand reported human cases with high mortality rate. This first wave ended in March 2004 and there were in total, 12 human cases (8 fatal) in Thailand and 23 cases (16 fatal) in Vietnam.

The second wave started four months later in July 2004 when some of the abovementioned countries started reporting outbreaks in poultry again. One new country, Malaysia also reported outbreaks in poultry. From August 2004 until November 2004, sporadic human cases were reported in Thailand (5 cases with 4 fatal) and Vietnam (4 cases with 4 fatal).

The third wave started in December 2004 and is ongoing. New poultry outbreaks were reported in Vietnam, Indonesia, Thailand and Laos. Vietnam reported human cases in December 2004 and continued to report cases sporadically up to November 2005. In February 2005, Cambodia reported 4 human cases and all 4 died. In July 2005, Indonesia first reported human cases and new cases continued up to December 2005. From July 2005 to October 2005, numerous countries including Russia, Siberia, Kazakhstan, Tibet, Mongolia, Turkey, Kuwait reported HPAI due to H5N1 in wild and domestic poultry. Thailand reported human cases again in October 2005 and China first reported human cases from November 2005. Avian outbreaks have also been recently reported in Croatia and Romania. In January 2006, Turkey reported human cases and the numbers appear to be increasing in the first two weeks of January. The outbreak in Turkey is still under investigation but it appears to be widespread within the country involving both rural and urban areas.

CUMULATIVE HUMAN CASES (LAB CONFIRMED 10.1.2006): WHO

Countries	26.12.2003 – 10.3.2004	19.7.2004 – 8.10.2004	16.12.04 – to-date	Total to-date
Indonesia: cases	0	0	16	16
Indonesia: deaths	0	0	11	11
Vietnam: cases	23	4	66	93
Vietnam: deaths	16	4	22	42
Thailand: cases	12	5	5	22
Thailand: deaths	8	4	2	14
Cambodia: cases	0	0	4	4
Cambodia: deaths	0	0	4	4
China: Cases	0	0	8	8
China: Deaths	0	0	5	5
Turkey: Cases	0	0	4	4
Turkey: Deaths	0	0	2	2
Total Cases	35	9	103	147
Total Deaths	24	8	46	78

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The table shows the cumulative cases that have been laboratory-confirmed by WHO up to 10 January 2006. To date, there have been 147 laboratory-confirmed cases with 78 fatalities. There are some points that are worthy of note. The mortality rate appears to be decreasing from 2003 to 2005. This finding of 'milder cases' suggests that the local virus strains may be adapting to humans. The number of cases has steadily increased every year and in 2005, three more new countries (Cambodia, China and Indonesia) have reported human cases. In 2006, Turkey has been added to the list of countries reporting human infections.

H5N1 INFECTION IN HUMANS

For the specific clinical features and evaluation of H5N1 infection in humans, readers are referred to the Directive 2A/2005 dated 15 December 2005 from Ministry of Health (MOH) that was sent to all registered medical practitioners. Further details can be obtained from the review article on avian influenza (H5N1) in humans published in the 29 September 2005 issue of *New England Journal of Medicine*.

Suffice to state that most patients infected with H5N1 have fever >38ºC (94-100%) and the usual influenza-like symptoms of headache, myalgia, cough and rhinorrhea. Gastrointestinal symptoms including diarrhea (41-70%) have been reported frequently and may be the initial presenting symptom in some patients and may precede the respiratory symptoms by up to a week. Many of the infected patients have rapid progression to pneumonia and multi-organ failure. Most hospitalised patients with H5N1 have required ventilatory support within 48 hours after admission.

Incubation period is short and been reported to be 2 to 4 days with a range up to 8 days. The virus excretion and 'infectious period' has not been fully characterised but available data is that it may be prolonged in hospitalised cases and positive viral cultures have been reported up to 16 days after the onset of illness.

Human-to-human transmission of H5N1 virus has been suggested in several household clusters and in one case of child-mother transmission. At this time, human-to-human transmission of H5N1 is 'inefficient' and if mutations occur that result in efficient transmission, its pandemic potential will be fully realised.

EVOLUTION OF THE H5N1 INFLUENZA VIRUS

In the October 2005 issue of *Emerging Infectious Diseases*, the WHO Global Influenza Program Surveillance Network reported on the phylogenetic, phenotypic and antigenic analysis of the H5N1 viruses isolated from birds and humans in the outbreak that occurred between January 2004 to April 2005. One important finding of this study was that the haemagglutinin (HA) gene isolated from H5N1 viruses of human specimens was closely related to those from the avian isolates. This is consistent with the epidemiological conclusion that humans acquired their infections by direct or indirect contact with poultry or poultry products.

There were two distinct lineages identified: H5N1 viruses from the Indochina peninsula (Cambodia, Thailand, Vietnam and Malaysia) were tightly clustered within Clade 1 whereas H5N1 isolates from other surrounding countries (China, Indonesia, South Korea) were distinct from Clade 1 and belonged to the more divergent Clade 2. Up to April 2005, all human infections due to H5N1 were from the Indochina peninsula and were therefore from Clade 1. It would be interesting what the study of the H5N1 viruses from human cases from China, Indonesia and Turkey reveal.

The HA of viruses isolated in the first three months of 2005 showed several amino acid changes relative to the 2004 viruses. This suggests that several of the amino acid changes near the receptor-binding site which had undergone change in 2005 may affect antigenicity or transmissibility. These findings have implications on the choice of prototype H5N1 vaccines.

From this study, there was no evidence that the 2004-2005 H5N1 isolates have acquired non-avian influenza genes by re-assortment. While this is reassuring, it is important that sustained and aggressive efforts to control H5N1 circulation in poultry be mandatory to avoid the possible catastrophic public health consequences that may occur from interaction between H5N1 and human influenza viruses such as H3N2.

STATUS OF H5N1 INFLUENZA VACCINES

An effective H5N1 vaccine is a public health priority and the cornerstone for pandemic prevention and control. After the pandemic H5N1 virus is isolated, it is estimated that it would take 6 to 8 months before vaccines will become commercially available for use. Therefore, antiviral agents would be one of

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the few options to contain the first wave of pandemic influenza.

From its surveillance of the H5N1 viruses so far, the WHO Global Influenza Program Surveillance Network has developed several candidate H5N1 pandemic vaccine viruses. These have been made available to vaccine manufacturers to produce pilot lots for clinical trials and are available for possible large scale manufacturing should the need arise. Vaccine efficacy, dosing schedules, route of administration and so on will need to be studied carefully.

A recent review on the archival records of the Cleveland Family Study participants during the 1957 H2N2 pandemic provided interesting data that suggested cross-subtype influenza immunity may exist. In the article published in the January 2006 issue of *Journal of Infectious Diseases*, Suzanne Epstein reported that only 5.6% of adults who had symptomatic influenza A in earlier study years developed influenza during the 1957 pandemic. In contrast, 55.2% of children who had had symptomatic influenza contracted it again. These findings may suggest an impact of accumulated hetero-subtypic immunity during a pandemic and has possible implications on vaccination strategies.

Whilst we await an 'ideal' H5N1 influenza vaccine for humans that would produce high protective levels of neutralising antibodies and superior efficacy, from a public health perspective, a vaccine with even 50% efficacy will have an important impact on disease control.

THE STATUS OF ANTIVIRAL AGENTS

We know from the analysis of the M proteins of the isolated H5N1 viruses that older agents such as amantadine and rimantadine will not be useful. In contrast, most of the H5N1 isolates have been susceptible to the neuraminidase inhibitors until recently. The neuraminidase inhibitors may be used for treatment, pre-exposure prophylaxis or post-exposure prophylaxis. Using a stochastic epidemic simulation model in which close contacts of suspected influenza cases take antiviral agents prophylactically for 8 weeks, Longini et al reported that the influenza illness attack rate could be reduced from 33% to 2%. Longini et al further elaborated on this with a simulation model on an outbreak occurring in rural Thailand. Their simulation model showed

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that a prepared response with targeted antivirals would have a high probability of containing an epidemic. Similarly, Ferguson et al reported that using a combination of geographically targeted prophylaxis and social distancing measures, a nascent influenza pandemic could be eliminated with a stockpile of 3 million courses of antiviral drugs.

The cautionary note on these mathematical models is that the success of such interventions will require early case detection and 'immediate' institution of these interventional measures. These studies have provided the scientific basis for governments and WHO to stockpile the neuraminidase inhibitors and to use them not only for early treatment but also as prophylaxis to contain an influenza pandemic. Unfortunately, media interest, governments stockpiling have also resulted in 'individuals hoarding or attempting to stockpile' these agents.

Oseltamivir (Tamiflu) had been used in Vietnamese and Thai patients infected with influenza H5N1. The limited data available revealed that there was little clinical benefit to infected patients but oseltamivir may have been prescribed too late in the course of disease as the median time to commencement of the antiviral was 4 to 5 days after the onset of illness. Oseltamivir resistance to other influenza A viruses has been reported to occur in 14 to 18% of children. Thus, it came as no surprise that de Jong reported oseltamivir resistance developing during treatment of influenza H5N1 infection in Vietnam. Some health authorities have already suggested that treatment of H5N1 virus infections in humans may require higher doses

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of oseltamivir and for longer periods than the usual 5 days that is currently prescribed. This will require further detailed study.

Zanamivir, the other registered neuraminidase inhibitor, is presently available only in inhaled form. There is concern that this agent may not be able to treat the systemic disease associated with influenza H5N1 and has not yet been used in human cases of H5N1 infection. The major benefit of zanamivir is that it does not share the structural concerns of oseltamivir and no resistance has yet been reported for zanamivir to any of the influenza viruses.

What should our response be to patients who walk into our clinics requesting for the 'bird flu drug'? Even with 'current appropriate' therapeutic use of oseltamivir, oseltamivir-resistant H5N1 has occurred during prophylaxis and treatment. With improper use of personal stockpiles of oseltamivir, resistance is likely to be further promoted thereby lessening this agent as a frontline defence against influenza. I beseech you to reconsider prescribing neuraminidase inhibitors, especially oseltamivir.

HOW IS SINGAPORE PREPARING FOR AN INFLUENZA PANDEMIC?

Using FluAid (CDC, Atlanta) and assuming an attack rate of 25%, MOH estimates that an influenza pandemic will result in 550,000 cases requiring outpatient treatment, 11,240 requiring hospitalisations, and approximately 1,900 deaths in Singapore in the first wave, which is expected to last 6 to 8 weeks. The next wave of pandemic influenza may occur 3 to 6 months later.

MOH has drafted an influenza pandemic readiness and response plan that details various alert levels and plans to be implemented at each level. It not only covers the healthcare settings but also community measures, border controls and others, so that essential services are maintained, and social and economic disruptions are limited. The national strategy is to establish an effective surveillance system, detect early the importation of the virus, mitigate the consequences when the first pandemic wave hits and then race to achieve national immunity. This draft plan may be accessed at www.moh.gov.sg and the latest draft is the December 2005 version. This draft plan has been reported in the press and was most recently detailed in the *Straits Times* on 28 December 2005.

MOH is utilising the Disease Outbreak Response System (DORS) as the framework to respond to any outbreak. For the pandemic influenza example, Alert Green Level 1 is when there are human cases but the threat of human-to-human infection remains low. Alert Yellow refers to the current situation where there is inefficient human-to-human transmission and infections have only occurred outside of Singapore. Alert Orange is when there are larger clusters of human cases but they are localised in specific geographic locales overseas. Alert Red is when there is a significant risk of acquiring the infection from the local community. At this level, the healthcare system will be stretched and is likely to be overwhelmed. Alert Black occurs when the morbidity and mortality is exceedingly high. Not only will the healthcare system be overwhelmed, the social support structure will be seriously affected and economic activities will be severely disrupted. Let us hope, that we never reach this alert stage.

AVA is another government agency that is closely monitoring the situation and has banned imports of poultry from affected countries. In addition to the stockpile of antivirals and other equipment, the government will also conduct simulation exercises to fine-tune the influenza readiness and response plan. As more information on H5N1 becomes available, further adjustments to the plan will be necessary.

Many companies, especially multinationals, are also preparing for a possible pandemic in the near future. Some of the specific areas that these companies are addressing include putting in place robust communications and internet business models to ensure business continuity. In addition, redundancies are put in place in case one specific country centre is particularly severely affected and it may need to be 'shut down'.

UP-TO-DATE RESOURCES FOR H5N1 AND INFLUENZA

While the lay press may provide very rapid information on 'breaking news', some of the information may not be factual but 'opinions'. Physicians should rely on up-to-date, peer-reviewed (or at least scientifically moderated) information from reliable, non-commercially sponsored websites for the latest on pandemic influenza. My suggestion is to visit the websites listed below at least once or twice per week.

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World Health Organization
The WHO website at **www.who.int** provides basic information on avian influenza and also discussion summaries at the various WHO-organised conferences on avian and pandemic influenza. It also provides regular updates on the number of human cases infected and who have died from H5N1. You will note that WHO provides data on laboratory-confirmed cases only. For example, in the rapidly evolving situation in Turkey, 4 laboratory-confirmed cases (with 2 deaths) are reported in the WHO table of 10 January 2006 but Turkish government has officially notified 15 human cases on the same date. The latest, hottest news/opinions often get reported earlier in ProMed Mail (see below).

ProMed Mail
The latest information on any infectious disease (human and animal) is often first contributed by 'local' scientists, veterinarians and physicians on ProMed Mail at **www.promedmail.org**. This publicly accessible internet-based reporting system is dedicated to rapid global dissemination of information on outbreaks of infectious diseases that affect human health. The information is moderated by eminent scientists/physicians before it is released for general reading by the subscribers of ProMed Mail. Subscriptions are free but donations to maintain this website are welcomed by the International Society of Infectious Diseases (ISID) who sponsor this programme.

Centers for Disease Control and Prevention, Atlanta
The CDC website at **www.cdc.gov** provides regular updates on avian influenza. This website is also useful for original and review articles on H5N1 in its monthly free online journal entitled *Emerging Infectious Diseases*.

WHAT SHOULD DOCTORS DO TO PREPARE FOR PANDEMIC INFLUENZA?

If an influenza pandemic occurs as predicted, there is no place to hide. In Singapore, the government through MOH is actively developing, updating and testing their plan to contain pandemic influenza. This will hopefully provide some comfort at the effort and resources put in by the government to deal with this potential threat.

May I suggest that doctors make an effort to:

1. Keep updated on the influenza situation.
2. Educate your staff and patients on avian influenza and the risks of pandemic influenza. This should also include good personal hygiene practices, responsible social behaviour and simple infection control measures.
3. Early notification of any human case suspected to have avian influenza. (The case definition for suspected cases of Influenza H5N1 has been provided in the MOH Directive 2A/2005.)
4. Continue to vaccinate yourself and your staff against seasonal influenza.
5. Ensure an adequate supply of masks, personal protection equipment for yourself, staff and patients attending your clinic.

Certainly, much of the data on avian influenza H5N1 and its potential to cause an influenza pandemic are frightening and overwhelming. If the pandemic does occur, it will be worse than SARS. As SARS was a defining moment for the medical community, so too will the next influenza pandemic. Whilst SARS descended upon us unannounced, we now have time to educate ourselves, staff and patients for a pandemic influenza. Our preparedness, diligence and early interventions will make the difference in controlling the disease and reducing morbidity and mortality. ■

Suggested Reading:

1. *Epstein SL. Prior H1N1 Influenza infection and susceptibility of Cleveland Family Study participants during the H2N2 pandemic of 1957: An experiment of nature. J Infect Dis 2006;193:49-53.*
2. *WHO Global Influenza Program Surveillance Network. Evolution of H5N1 avian influenza viruses in Asia. Emerg Infect Dis 2005;10: 1515-21.*
3. *The writing committee of WHO Consultation on human influenza A/H5. Avian influenza A(H5N1) infection in humans. New Engl J Med 2005;353:1374-85.*
4. *Longini IM, Nizam A, Xu S et al. Containing pandemic influenza at the source. Science 2005; 309:1083-7.*
5. *Ferguson NM, Cummings DAT, Cauchemez S et al. Strategies for containing an emerging influenza pandemic in SE Asia. Nature 2005;437:209-14.*
6. *De Jong MD, Thanh TT, Khanh TH et al. Oseltamivir resistance during treatment of influenza A(H_5N_1) infection. New Engl J Med 2005;353:2667-72.*