Review of Recent Publications on Avian and Pandemic Influenza: A Selected Annotated Bibliography
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Introduction

This annotated bibliography is intended as a resource for policy-makers, programme managers and other personnel working in influenza control in developing countries. The aim of this bibliography is to provide representative examples of recent published reviews and research articles on various aspects of avian and seasonal influenza which may have the potential to cause a pandemic. The publications included here are in areas of programme and policy, epidemiology, clinical, antivirals and vaccine, non-pharmaceutical interventions and risk communication.

The simultaneous occurrence in several countries of large epidemics of highly pathogenic H5N1 influenza in domestic poultry is historically unprecedented. The potential for further spread of ongoing poultry epidemic to humans, both within affected countries and to others, is real.

This first edition of the bibliography is intended to provide answers to many of the questions faced by national policy-makers in developing strategies for the prevention and control of avian influenza and pandemic influenza in resource-poor settings. The bibliography also aims to be a useful reference material in view of the recent WHO declaration of pandemic influenza as a global emergency and subsequent national preparedness efforts. However, the bibliography was selected based on the relevance and accessibility of the references and several other materials may not have been included due to their non-availability through the Internet or a medical library.

Comments and suggestions for the improvement of future editions of the bibliography would be welcome.
Programme and Policy


This document sets out activities that can be undertaken by individual countries, the international community and WHO to prepare the world for the next influenza pandemic and mitigate its impact once the international spread has begun. Recommended activities are specific to the threat posed by the continuing spread of the H5N1 virus. Addressed to policy-makers, the document also describes issues that can guide policy choices in a situation characterized by both urgency and uncertainty. Recommendations are phase-wise in their approach, with levels of alert and corresponding activities, changing according to epidemiological indicators of increased threat.


This brief looks at the possible economic consequences for Asia of a mutation of avian flu leading to human-to-human transmission, using different assumptions about the duration and virulence of the flu pandemic. The analysis looks at a relatively mild outbreak, based on the historical experience of previous flu outbreaks and SARS. It focuses on the short-run impact of a pandemic on aggregate economic activity. The study concluded that avian flu presents a major potential challenge to the development of the region. A pandemic will likely slow or halt economic growth in Asia and lead to a significant reduction in trade, particularly of services. In the long run, potential economic growth will be lower and poverty will increase. Under a mild scenario (attack rate of 20% and a case-fatality rate of 0.5%), this pandemic would cost the lives of around 3 million Asians. For economic impact, Asia will face a demand shock of around $110-$300 billion in its 2006 GDP, the equivalent of 2.3 to 6.5 percentage points of GDP with the risk that growth in Asia would virtually stop. The global trade of goods and services may contract around 14%, the equivalent of $2.5 trillion. So, beyond death and suffering,
Asia would see its growth reduced, its fight against poverty set back and its hope to reach the Millennium Development Goals (MDGs) disappear.


This paper explores the implications of a pandemic influenza outbreak on the global economy through a range of scenarios (mild, moderate, severe and ultra) that span the historical experience of influenza pandemics of the twentieth century. An influenza pandemic would be expected to lead to: a fall in the labour force to different degrees in different countries due to a rise in mortality and illness; an increase in the cost of doing business; a shift in consumer preferences away from exposed sectors; and a re-evaluation of country risk as investors observe the response of governments. The paper finds that even a mild pandemic has significant consequences for global economic output. The mild scenario is estimated to cost the world 1.4 million lives and close to 0.8% of GDP (approximately US$ 330 billion) in lost economic output. As the scale of the pandemic increases, so do the economic costs. A massive global economic slowdown occurs in the ultra scenario with over 142.2 million people killed and a GDP loss of US$ 4.4 trillion. The composition of the slow down differs sharply across countries with a major shift of global capital from the affected economies.


A containment policy alone is unlikely to prevent a pandemic entirely. The authors argue that if a single introduction of a pandemic-capable strain is expected, multiple introductions should also be expected. Each containment effort would likely be more difficult than the last as manpower, antiviral stockpile and other scarce resources get depleted. Even if each successive containment effort is no more difficult than its predecessor, the chance of at least one failure increases with the number of introductions. At best, a containment policy will only postpone the emergence of a pandemic, to prepare for its effects. In this article, the authors consider the risk of multiple introductions and its implications for pandemic planning.

Highly pathogenic H5N1 influenza A viruses are now endemic in avian populations in South-East Asia, and human cases continue to accumulate. Although currently incapable of sustained human-to-human transmission, H5N1 represents a serious pandemic threat owing to the risk of a mutation or reassortment generating a virus with increased transmissibility. Identifying public health interventions that might be able to halt a pandemic in its earliest stages is therefore a priority. The investigators use a simulation model of influenza transmission in South-East Asia to evaluate the potential effectiveness of targeted mass prophylactic use of antiviral drugs as a containment strategy. Other interventions aimed at reducing population contact rates are also examined as reinforcements to an antiviral-based containment policy. The results show that elimination of a nascent pandemic may be feasible using a combination of geographically targeted prophylaxis and social distancing measures if the basic reproduction number of the new virus is below 1.8. It also predicts that a stockpile of 3 million courses of antiviral drugs should be sufficient for elimination. Policy effectiveness depends critically on how quickly clinical cases are diagnosed and the speed with which antiviral drugs can be distributed.


Highly pathogenic avian influenza A (H5N1) is threatening a human pandemic of potentially devastating proportions. The investigators use a stochastic influenza simulation model for rural South-East Asia to investigate the effectiveness of targeted antiviral prophylaxis, quarantine and pre-vaccination in containing an emerging influenza strain at the source. If the basic reproductive number (R0) were below 1.60, the simulations show that a prepared response with targeted antivirals would have a high probability of containment. In this case, an antiviral agent stockpile of the order of 100,000 to one million courses would be sufficient. If pre-vaccination occurs, then the targeted antiviral prophylaxis could be effective for containing strains with an R0 as high as 2.1. Combinations of targeted antiviral prophylaxis, pre-vaccination and quarantine could contain strains with an R0 as high as 2.4.

The impact of influenza on morbidity and hospitalization in the tropics and subtropics is poorly quantified. Uniquely, the Hong Kong Special Administrative Region has computerized hospital discharge diagnoses on 95% of total bed-days, allowing the disease burden for a well-defined population to be accurately assessed. The influenza-associated morbidity and hospitalization was assessed by Poisson regression models for weekly counts of hospitalizations in Hong Kong during 1996 to 2000, using proportions of positive influenza types A (H1N1 and H3N2) and B isolations in specimens sent for laboratory diagnosis as measures of influenza virus circulation and adjusted for annual trend, seasonality, temperature and relative humidity, as well as respiratory syncytial virus circulation. The results revealed that influenza was significantly associated with hospitalization for acute respiratory disease (International Classification of Diseases version 9 codes [ICD9] 460–466 and 480–487) and its subcategory pneumonia and influenza (ICD9 480–487) for all age groups. The annual rates of excess hospitalization per 100 000 population for acute respiratory diseases for the age groups 0–14, 15–39, 40–64, 65–74 and 75 were 163.3 (95% confidence interval [CI], 135–190), 6.0 (95% CI, 2.7–8.9), 14.9 (95% CI, 10.7–18.8), 83.8 (95% CI, 61.2–104.2) and 266 (95% CI, 198.7–330.2) respectively. Influenza has a major impact on hospitalization due to cardio-respiratory diseases as well as on cerebrovascular disease, ischaemic heart disease and diabetes mellitus in the tropics and subtropics. Better utilization of influenza vaccine during annual epidemics in the tropics will enhance global vaccine production capacity and allow for better preparedness to meet the surge in demand that is inevitable in confronting a pandemic.


Recent studies in Hong Kong and Singapore suggest that the annual impact of influenza in these wealthy tropical cities may be substantial, but little is known about the burden in middle-income tropical countries. The investigators reviewed the status of influenza surveillance, vaccination, research and policy in Thailand as of January 2004. From 1993 to 2002, 64-91 cases of clinically diagnosed influenza were reported per 100 000 persons per year. Influenza
viruses were isolated in 34% of the 4305 specimens submitted to the national influenza laboratory. Vaccine distribution figures suggest that less than 1% of the population is immunized against influenza each year. In January 2004, Thailand reported its first documented outbreak of influenza A H5N1 infection in poultry and the country's first human cases of avian influenza. Thailand's growing economy, well-developed public health infrastructure and effective national immunization programme could enable the country to take more active steps towards influenza control.


The recent spread of highly pathogenic strains of avian influenza has highlighted the threat posed by pandemic influenza. In the early phases of a pandemic, the only treatment available would be neuraminidase inhibitors, which many countries are considering stockpiling for pandemic use. The investigators estimate the effect on the hospitalization rates of using different antiviral stockpile sizes to treat the infection. It is estimated that stockpiles that cover 20-25% of the population would be sufficient to treat most of the clinical cases and could lead to 50-77% reductions in hospitalizations. Substantial reductions in hospitalization could be achieved with smaller antiviral stockpiles if drugs are reserved for persons at high risk.


The investigators evaluated the effect of school closure on the occurrence of respiratory infection among children ages 6-12 years and its impact on health care services. During this period, there were significant decreases in the diagnosis of respiratory infections (42%), visits to physician (28%) and emergency departments (28%) and medication purchases (35%). The present study provides quantitative data to support school closure during an influenza pandemic.


Although most influenza infections are self-limiting, few other diseases exert such a huge toll of suffering and economic loss. Despite the importance of
influenza, there had been, until recently, little advance in its control since amantadine was licensed almost 40 years ago. During the past decade, evidence has accrued on the protection afforded by inactivated vaccines and on the safety and efficacy in children of live influenza-virus vaccines. There have been many new developments in vaccine technology. Moreover, work on viral neuraminidase has led to the licensing of potent selective antiviral drugs, and economic decision-modelling provides further justification for annual vaccination and a framework for the use of neuraminidase inhibitors. Progress has also been made on developing near-patient testing for influenza that may assist individual diagnosis or the recognition of widespread virus circulation and so optimize clinical management. Despite these advances, the occurrence of avian H5N1, H9N2 and H7N7 influenza in human beings and the rapid global spread of severe acute respiratory syndrome (SARS) are reminders of our vulnerability to an emerging pandemic. The contrast between recent cases of H5N1 infection, associated with high mortality, and the typically mild, self-limiting nature of human infections with avian H7N7 and H9N2 influenza shows the gaps in our understanding of molecular correlates of pathogenicity and underlines the need for continuing international research into pandemic influenza. Improvements in animal and human surveillance, new approaches to vaccination and increasing use of vaccines and antiviral drugs to combat annual influenza outbreaks are essential to reduce the global toll of pandemic and inter-pandemic influenza.
Epidemiology


The guidance set out is general and is intended for adaptation to specific situations, in line with national health and veterinary policies. The recommendations are composed of guidance on containing the disease in poultry, general advice for coordination of services, vaccination for public health purposes, protection of persons at risk of occupational exposure, drug for treatment and prophylaxis, and initiation of surveillance.


As the epidemiological situation evolves, WHO recommends generic surveillance guideline to monitor the spread of influenza A/H5 viruses in human and animal populations, assessment of the global trend of the disease, the public health risk it poses and its pandemic potential, and to trigger public health actions. Tools to assist in the implementation of surveillance of influenza A/H5 viral infection are for clinical management and reporting within country and case definitions with a hierarchy of case categories according to the epidemiological situation. Depending on the scope of HPAI outbreaks in animal populations and the physical size of the country, the case definitions for local clinical and public health management may vary. The guideline also has case definition used in Viet Nam with a template of case report form as an example.


The ongoing outbreaks of H5N1 avian influenza in migratory waterfowl, domestic poultry and humans in Asia during the summer of 2005 present a continuing, protean pandemic threat. The acquisition of novel traits, including lethality to waterfowl, ferrets, felids and humans, indicates an expanding host range. The substantial number of documented cases in humans, associated with severe disease and several fatalities, raised concerns about a pandemic
potential of the H5N1 strain. The natural selection of non-pathogenic viruses from heterogeneous sub-populations co-circulating in ducks contributes to the spread of H5N1 in Asia. When clinical signs are used to screen for the presence of HPAIV H5N1 in the field, ducks may become the 'Trojan Horse' of this virus. The spread of H5N1 and its likely reintroduction to domestic poultry increase the need for good agricultural vaccines. The root cause of the continuing H5N1 pandemic threat may be the way the pathogenicity of the virus is masked by co-circulating influenza viruses or bad agricultural vaccines.


Thailand has had three epidemic waves of highly pathogenic avian influenza (HPAI) since 2004; virus was again detected in July 2005. This study analysed the spatial distribution of HPAI outbreaks in relation to poultry, land use and other anthropogenic variables from the start of the second epidemic wave (July 2004–May 2005). Results demonstrate a strong association between the H5N1 virus in Thailand and the abundance of free-grazing ducks and, to a lesser extent, native chickens, cocks, wetlands and humans. Wetlands used for double-crop rice production, where free-grazing duck feed round the year in rice paddies, appear to be a critical factor in HPAI persistence and spread. This finding could be important for other duck-producing regions in eastern and south-eastern Asian countries affected by HPAI.


Highly pathogenic avian virus replicates in the respiratory and intestinal tracts of infected ducks and excretes large amounts of the virus via respiratory route as well as in faeces. All infected ducks shed the virus for 11 days and some for 17 days and longer. In comparison, ducks infected with an H5N1 virus isolated in 2003 shed virus for a maximum of 10 days. No symptoms or deaths were observed in a majority of ducks and contacts infected with human and chicken H5N1 viruses from the 2004 outbreaks in Viet Nam. The amounts of H5N1 virus shed allow the transmission of the virus directly from apparently healthy ducks to chickens. The virus can survive in the environment for long periods, especially in low temperatures (i.e. in manure-contaminated water). Recent studies indicate that the H5N1 viruses isolated
in 2004 have become more stable, surviving at 37°C for 6 days -- isolates from
the 1997 outbreak survived just 2 days.

17. World Health Organization. Review of latest available evidence on risks to
human health through potential transmission of avian influenza (H5N1)
through water and sewage. Geneva, 2006. Full text available at:
http://www.who.int/water_sanitation_health/emerging/h5n1background.pdf

The purpose of this document is to summarize the latest available evidence
on avian influenza-related risks to human health associated with water
sources, water supplies and sanitation (management of human excreta). It is
intended to serve as a scientific basis to inform public health authorities, those
involved in the management of water resources and supplies and the general
public. This document will be periodically updated. Based on this review,
water supplies receiving treatment as recommended in the WHO Guidelines
for Drinking-Water Quality are unlikely to pose a significant risk of infection
even if infected waterfowl are present in source waters. In water, the virus can
survive for up to four days at 22°C, and more than 30 days at 0°C.

18. World Health Organization, Regional Office for the Western Pacific.
Public health considerations in the application of measures to contain and
control highly pathogenic avian influenza (HPAI) outbreaks in poultry.
Manila, 2004. Full text available at:
http://www.wpro.who.int/NR/rdonlyres/23C21802-AOBE-42-B9-825F-
18977C05EE58/0/Advice30042004.pdf

The document provides key points of the HPAI virus. Depending on
environmental conditions, AI viruses may remain infectious in manure, water
and soil and on contaminated equipment for at least 35 days and perhaps as
long as three months in colder climates. HPAI viruses can survive in frozen
carcasses and blood for as long as three weeks. The virus is killed by heat
(56°C for 3 hours or 60°C for 30 minutes) and common disinfectants, such as
detergents, chlorine and iodine compounds and formaldehyde.

19. Mounts AW, Kwong H, Izurieta HS, Ho Y, Au T, Lee M, Bridges CB,
Williams SW, Mak KH, Katz JM, Thompson WW, Cox NJ, and Fukuda K.
Case-control study of risk factors for avian influenza A (H5N1) disease,

In May 1997, a 3-year-old boy in Hong Kong died of a respiratory illness
related to influenza A (H5N1) virus infection, the first known human case of
disease from this virus. An additional 17 cases followed in November and
December. A case-control study of 15 of these patients hospitalized for the influenza A (H5N1) disease was conducted using controls matched by age, sex and neighbourhood to determine the risk factors for the disease. Exposure to live poultry (by visiting either a retail poultry stall or a market selling live poultry) in the week before the illness began was significantly associated with H5N1 disease (64% of cases vs 29% of controls, odds ratio 4.5). By contrast, travel, eating or preparing poultry products, recent exposure to persons with respiratory illness, including persons with known influenza A (H5N1) infection, were not associated with H5N1 disease.


Beginning in late 2003, a substantial outbreak of influenza A (H5N1) virus spread among poultry in Thailand. On January 23, 2004, the Ministry of Public Health (MOPH) detected the first confirmed human case of H5N1 infection. During February-November 2004, the MOPH's Bureau of Epidemiology and provincial health offices worked together to investigate the H5N1 outbreak in humans. Two studies were conducted: a descriptive study to describe the clinical manifestations and epidemiological characteristics of the cases and a matched case-control study to determine the risk factors for persons who might subsequently become ill with H5N1. A total of 16 patients with confirmed H5N1 were identified for the case-control study. Fever and respiratory symptoms predominated. Leucopenia and thrombocytopenia were present respectively in nine (100%) and four (44%) persons aged <15 years. Direct touching of unexpectedly dead poultry was the most significant risk factor (odds ratio = 29.0; 95% confidence interval = 2.7--308.2). The overall mortality was 75%; mortality for persons aged <15 years was 90%, compared with 57% for persons aged ≥15 years. In conclusion, avian influenza was more severe in children, who should avoid handling dead poultry during epizootics. Early avian influenza in children resembled the more common dengue fever, but the presence of cough and the absence of haemoconcentration distinguished avian influenza, which often progressed rapidly to acute respiratory distress syndrome, requiring intensive care.

This is an investigation of possible person-to-person transmission in a family cluster of the disease in Thailand. For each of the three involved patients, the investigators reviewed the circumstances and timing of exposures to poultry and to other ill persons. Field teams isolated and treated the surviving patient, instituted active surveillance for the disease and prophylaxis among exposed contacts, and culled the remaining poultry surrounding the affected village. Specimens from the family members were tested by viral culture, microneutralization serological analysis, immunohistochemical assay, reverse-transcriptase–polymerase-chain-reaction (RT-PCR) analysis and genetic sequencing. The index patient became ill three-to-four days after her last exposure to dying household chickens. Her mother came from a distant city to care for her in the hospital, had no recognized exposure to poultry, and died from pneumonia after providing 16 to 18 hours of unprotected nursing care. The aunt also provided unprotected nursing care; she had fever five days after the mother first had fever, followed by pneumonia seven days later. The autopsy tissue from the mother and nasopharyngeal and throat swabs from the aunt were positive for influenza A (H5N1) by RT-PCR. No additional chains of transmission were identified, and the sequencing of the viral genes identified no change in the receptor-binding site of haemagglutinin or other key features of the virus. The sequences of all eight viral gene segments clustered closely with other H5N1 sequences from recent avian isolates in Thailand. In conclusion, the disease in the mother and the aunt probably resulted from person-to-person transmission of this lethal avian influenza virus during the unprotected exposure to the critically-ill index patient.


Through regional contacts and public sources, the authors have monitored family clusters and other aspects of H5N1 in South-East Asia. A cluster was defined as >2 family members with laboratory-confirmed H5N1 or >2 family
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members with severe pneumonia or respiratory death, at least one of which had confirmed H5N1. From January 2004 to July 2005, 109 cases of avian influenza A (H5N1) were officially reported to the World Health Organization (WHO). During this time, 15 family clusters were identified. Of the 11 (73%) clusters that occurred in Viet Nam, 7 were in northern Viet Nam. The cluster size ranged from 2 to 5 persons, and 9 (60%) had >2 persons with laboratory-confirmed H5N1. The cluster in Thailand was well-documented and was likely the result of limited person-to-person transmission. For the other clusters, the epidemiological information was insufficient to determine whether person-to-person transmission had occurred. In at least 3 clusters in Viet Nam, >7 days had occurred between the onset of the first and the next case, suggesting that simultaneous acquisition from a common source was unlikely. In one cluster, 2 nurses assisted in the care of the index case-patient; 1 had laboratory-confirmed H5N1. The proportion of deaths dropped significantly, from 32 out of 44 (73%) during December 2003 to November 2004 to 23 out of 65 (35%) during December 2004 to July 2005 (p<0.0001). No evidence to date shows genetic reassortment between H5N1 and human influenza A viruses. The viruses isolated from case-patients need to be immediately sequenced and characterized in relation to previously circulating viruses to see whether they are evolving.


The authors, in their review of observations made to date, suggest that differences in the routes of transmission between human and avian influenza viruses exist. The multiple potential routes for the spread of avian influenza viruses, particularly H5N1, indicate that, in addition to protection for the respiratory tract and eyes, proper hand hygiene may be especially important in preventing infection. This applies also in emergency departments and clinics where patients with febrile illnesses, who are from areas with documented H5N1 virus infections in poultry or people, may be evaluated. In households in which the illness has occurred, additional specific protective measures – that is, post-exposure chemoprophylaxis with oseltamivir – would be advisable for known household contacts. In affected countries, public education regarding simple precautionary measures for food preparation, poultry handling and avoidance of contaminated water are essential until effective human vaccines for H5N1 viruses become available.

The spread of highly pathogenic avian influenza H5N1 viruses across Asia in 2003 and 2004 devastated domestic poultry populations and resulted in the largest and most lethal H5N1 virus outbreaks in humans to date. To better understand the potential of H5N1 viruses isolated during this epizootic event to cause disease in mammals, researchers used the mouse and ferret models to evaluate the relative virulence of selected 2003 and 2004 H5N1 viruses representing multiple genetic and geographical groups and compared them to earlier H5N1 strains isolated from humans. Four out of five human isolates tested were highly lethal for both mice and ferrets and exhibited a substantially greater level of virulence in ferrets than other H5N1 viruses isolated from humans since 1997. One human isolate and all four avian isolates tested were found to be of low virulence in either animal. The highly virulent viruses replicated to high titers in the mouse and ferret respiratory tracts and spread to multiple organs, including the brain. Rapid disease progression and high lethality rates in ferrets distinguished the highly virulent H5N1 viruses in 2004 from the H5N1 viruses in 1997. A pair of viruses isolated from the same patient differed by eight amino acids, including a Lys/Glu disparity at 627 of PB2, previously identified as an H5N1 virulence factor in mice. The virus possessing Glu at 627 of PB2 exhibited only a modest decrease in virulence in mice and was highly virulent in ferrets, indicating that for this virus pair, the K627E PB2 difference did not have a prevailing effect on virulence in mice or ferrets. The results demonstrate the general equivalence of mouse and ferret models for assessment of the virulence of 2003 and 2004 H5N1 viruses. However, the apparent enhancement of virulence of these viruses in humans in 2004 was better reflected in the ferret.

Preparedness for a possible influenza pandemic caused by highly pathogenic avian influenza A subtype H5N1 has become a global priority. The spread of the virus to Europe and continued human infection in South-East Asia have heightened the pandemic concern. It remains unknown from where the pandemic strain may emerge; current attention is directed at Viet Nam, Thailand and, more recently, Indonesia and China. This article reports that genetically and antigenically distinct sublineages of H5N1 virus have become established in poultry in different geographical regions of South-East Asia, indicating the long-term endemicity of the virus, and the isolation of H5N1 virus from apparently healthy migratory birds in southern China. The data show that the H5N1 influenza virus has continued to spread from its established source in southern China to other regions through transport of poultry and bird migration. The identification of regionally distinct sublineages contributes to the understanding of the mechanism for the perpetuation and spread of H5N1, providing information that is directly relevant to the control of the source of infection in poultry. It points to the necessity of surveillance that is geographically broader than previously supposed and that includes H5N1 viruses of greater genetic and antigenic diversity.


The first documented outbreak of human respiratory disease caused by avian influenza A (H5N1) viruses occurred in Hong Kong 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, >14 days after symptom onset. 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.


The first outbreak of avian influenza A (H5N1) occurred among humans in Hong Kong in 1997. To estimate the risk of person-to-person transmission, a retrospective cohort study was conducted to compare the prevalence of H5N1 antibody among health care workers (HCWs) exposed to H5N1 case-patients with the prevalence among non-exposed HCWs. Information on H5N1 case-patient and poultry exposures and blood samples for H5N1-specific antibody testing were collected. Eight (3.7%) of 217 exposed and 2 (0.7%) of 309 non-exposed HCWs were H5N1 seropositive (\( P = .01 \)). The difference remained significant after controlling for poultry exposure (\( P = .01 \)). This study presents the first epidemiological evidence that H5N1 viruses were transmitted from patients to HCWs. Human-to-human transmission of avian influenza may increase the chances for the emergence of a novel influenza virus with pandemic potential.


To determine whether avian H5N1 influenza viruses associated with human infections in Vietnam had transmitted to pigs, the serological evidence of exposure to H5N1 influenza virus in Vietnamese pigs was investigated in 2004. Of the 3175 pig sera tested, 8 (0.25%) were positive for avian H5N1
influenza viruses isolated in 2004 by virus neutralization assay and Western blot analysis. Experimental studies of replication and transmissibility of the 2004 Asian H5N1 viruses in pigs revealed that all the viruses tested replicated in the swine respiratory tract but none were transmitted to contact pigs. Virus titers from nasal swabs peaked on day 2, and low titers were detected in the liver of two of the four pigs tested. The findings indicated that pigs could be infected with highly lethal Asian H5N1 viruses but that these viruses were not readily transmitted between pigs under experimental conditions.
Clinical Presentation


An unprecedented epizootic avian influenza A (H5N1) virus that is highly pathogenic has crossed the species barrier in Asia to cause many human fatalities and poses an increasing pandemic threat. This summary describes the features of human infection with influenza A (H5N1) virus and reviews recommendations for prevention and clinical management presented in part at the WHO Meeting on Case Management and Research on Human Influenza A/H5, which was held in Hanoi, 10-12 May 2005. Because many critical questions remain, modifications of these recommendations are likely.


Since 1959, human infections with avian influenza viruses have only rarely occurred. Of the hundreds of strains of avian influenza A viruses, only four are known to have caused human infection: H5N1, H7N3, H7N7 and H9N2. For the H5N1 virus, close contact with dead or sick birds (i.e. slaughtering, plucking, butchering and preparation) or exposure to chicken faeces on playgrounds seem to be the principal sources of human infection. Apart from H5N1, human infection generally resulted in mild symptoms and rarely in severe illness. In patients infected with the H5N1 virus, clinical deterioration is rapid. In Thailand, the time between the onset of illness to the development of acute respiratory distress was around 6 days, with a range of 4 to 13 days. In severe cases in Turkey, clinicians have observed respiratory failure 3 to 5 days after symptom onset. Another common feature is multi-organ dysfunction, notably involving the kidney and the heart. Common laboratory abnormalities include lymphopenia, leukopenia, elevated aminotransferases and mild-to-moderate thrombocytopenia with some instances of disseminated intravascular coagulation.

Influenza can spread rapidly to patients and health care personnel in health care settings after influenza is introduced by visitors, staff or patients. Influenza outbreaks in health care facilities can have potentially devastating consequences, particularly for immunocompromised persons. Although vaccination of health care personnel and patients is the primary means to prevent and control the outbreaks of influenza in health care settings, antiviral influenza medications and isolation precautions are important adjuncts. Although droplet transmission is thought to be the primary mode of influenza transmission, limited evidence is available to support the relative clinical importance of contact, droplet and droplet nuclei (airborne) transmission of influenza. In this article, the results of studies on the modes of influenza transmission and their relevant isolation precautions are reviewed.


The aim of this study was to make an inventory of the clinical signs of high-pathogenicity avian influenza (HPAI), to facilitate the development of an operational syndrome-reporting system (SRS) in the Netherlands as an early warning system for HPAI outbreaks. A total of 537 poultry flocks (240 infected and 297 non-infected) with a clinical suspicion of an infection with HPAI virus were investigated with respect to the clinical signs observed. Standardized reports were analysed with respect to observed clinical signs in the flocks. Various poultry types were distinguished. In infected commercial flocks with egg-producing chickens, the presence of increased mortality, apathy, coughing, reduction in normal vocalization, or pale eggs appeared to be overall the most sensitive indicators to detect an HPAI outbreak, matching a sensitivity of 99% with a specificity of 23%. In infected turkey flocks, the presence of apathy, decreased growth performance, reduction of normal vocalization, swollen sinuses, yawning, huddling, mucosal production from the beak, or lying down with an extended neck appeared to be overall the most sensitive indicators to detect an HPAI outbreak, matching a sensitivity of 100% with a specificity of 79%. In infected backyard/hobby flocks, increased mortality or swollen head appeared to be overall the most sensitive indicators of an HPAI outbreak, matching a sensitivity of 100% with a specificity of 26%. These results indicate that there is a solid basis for the choice of using increased mortality in the operational SRS in the Netherlands as an early warning system for HPAI outbreaks. The presence of apathy, specifically for
turkeys, should be added to the SRS as an indicator. In layers, soft-shelled eggs are seen initially, but any laying activities cease rapidly with the progression of the disease. Less severe forms of HPAI can be clinically even more confusing. Rapid laboratory diagnostic aid, therefore, is pivotal to all further measures.


The paper described the clinical presentation of the first 12 patients and options for rapid viral diagnosis. Case notes of 12 patients with virus-culture-confirmed influenza A H5N1 infection were analysed. The clinical presentation and risk factors associated with severe disease were defined and the results of methods for rapid virus diagnosis were compared. Findings: The patients ranged from 1 to 60 years of age; the clinical presentation was that of an influenza-like illness with evidence of pneumonia in seven patients; all seven patients older than 13 years had severe disease (four deaths), whereas children 5 years or younger had mild symptoms with the exception of one who died with Reye’s syndrome associated with intake of aspirin. Gastrointestinal manifestations, raised liver enzymes, renal failure unrelated to rhabdomyolysis, and pancytopenia were unusually prominent. Factors associated with severe disease included older age, delay in hospitalization, lower respiratory-tract involvement, and a low total peripheral white blood cell count or lymphopenia at admission. An H5-specific reverse-transcription PCR assay (RT-PCR) was useful for rapid detection of the virus directly in respiratory specimens. A commercially available enzyme immunoassay was more sensitive than direct immunofluorescence for rapid viral diagnosis. Direct immunofluorescence with an H5-specific monoclonal antibody pool was useful for rapid exclusion of H5-subtype infection. Interpretation Avian Influenza A H5N1 virus causes human influenza-like illness with a high rate of complications in adults admitted to hospital. Rapid H5-subtype-specific laboratory diagnosis can be made by RT-PCR applied directly to clinical specimens.


Prompt testing for influenza can help guide clinical management of patients with suspected influenza. Three antiviral medications – amantadine,
oseltamivir and zanamivir – are approved for the treatment of influenza in children. Rimantadine and ribavirin have also been used. The author reviewed the published evidence on clinically useful diagnostic tests and antiviral treatment for influenza virus infections in children. Studies published from 1966 through September 2002 were reviewed on clinical diagnosis, immunofluorescence and rapid influenza tests and on antiviral treatment of influenza virus infections among paediatric populations. The results revealed that no studies assessed the accuracy of the clinical diagnosis of influenza in children compared with viral culture. Compared with viral culture, direct immunofluorescence antibody and indirect immunofluorescence antibody tests for influenza had fair-to-moderate median sensitivities and high median specificities, whereas rapid influenza diagnostic tests had moderate median sensitivities and moderately high median specificities. No randomized, placebo-controlled studies were found of amantadine or rimantadine for the treatment of influenza A. In a few separate controlled studies, oseltamivir, zanamivir and ribavirin each reduced symptom duration of influenza compared with placebo. In conclusion, additional data are needed about the accuracy of the clinical diagnosis of influenza in children. Although direct immunofluorescence antibody staining, indirect immunofluorescence antibody staining and rapid tests are moderately-to-reasonably accurate in detecting influenza virus infections in children, physicians should use clinical judgement and local surveillance data about circulating influenza viruses when interpreting test results. Further controlled studies of the efficacy, adverse effects and emergence of antiviral resistance during the treatment of influenza are needed for all the antiviral drugs.


To establish whether human-to-human transmission of influenza A H5N1 occurred in the health care settings in Viet Nam, the investigators conducted a cross-sectional seroprevalence survey among hospital employees exposed to 4 confirmed and 1 probable H5N1 case-patients or their clinical specimens. Eighty-three (95.4%) of 87 eligible employees completed a questionnaire and provided a serum sample, which was tested for antibodies to influenza A H5N1. Ninety-five per cent reported exposure to >1 H5N1 case patients; 59 (72.0%) reported symptoms, and 2 (2.4%) fulfilled the definition for a possible
H5N1 secondary case-patient. No study participants had detectable antibodies to influenza A H5N1. The data suggest that the H5N1 viruses responsible for human cases in Viet Nam in January 2004 were not readily transmitted from person to person. However, influenza viruses are genetically variable and their transmissibility is difficult to predict. Therefore, persons providing care for H5N1 patients should continue to take measures to protect themselves.
Antiviral Medicines and Vaccines


Influenza vaccines and antiviral drugs for influenza are essential components of a comprehensive pandemic response, which also includes planning for antibiotic supplies and other health care resources. However, the current reality is that most countries have no or very limited supplies. Such a situation would force national authorities to make difficult decisions concerning which citizens should receive the first call on limited vaccines and drugs. This document provides guidance to health policy-makers and national authorities on planning principles and options for the prioritization of vaccine and antiviral drug use during an influenza pandemic. It includes recommendations on actions that can improve future supply for the many countries that currently have no national vaccine or antiviral drug production. The document was drafted during the WHO Consultation on Guidelines for the Use of Vaccines and Antivirals during Influenza Pandemics, held from 2-4 October 2002 in Geneva, Switzerland.


Physicians have several treatment options for influenza, including vaccination and various antiviral therapies. However, the optimal influenza prevention and treatment strategy is unknown. This study compares the relative health values of contemporary treatment strategies for influenza in a healthy sample of working adults. A cost–benefit analysis using a decision model was conducted by using previously published data among healthy employed adults 18 to 50 years of age during a complete influenza season. The study looked at eight treatment options (yes or no) based on the possible combinations of vaccination and antiviral therapy (rimantadine, oseltamivir or zanamivir or no treatment) should infection develop. The outcome was measured in U.S. dollars, including the value of symptom relief and medication side-effects, which was assigned a monetary value through a conjoint analysis that used a “willingness-to-pay” approach. In the base-case
analysis, all strategies for influenza vaccination had a higher net benefit than the non-vaccination strategies. Vaccination and use of rimantadine, the most cost-beneficial strategy, was $30.97 more cost-beneficial than non-vaccination and no use of antiviral medication. The health benefits of most antiviral treatments equalled or exceeded their costs for most scenarios. The choice of the most cost-beneficial antiviral strategy was sensitive to the prevalence of influenza B and to the comparative workdays gained by each antiviral therapy. The study concluded that vaccination was cost-beneficial in most influenza seasons in healthy working adults. Although the benefits of antiviral therapy for persons with influenza infection appear to justify its cost, head-to-head trials of the various antiviral therapies are needed to determine the optimal treatment strategy.


The protocol has three main parts. The first describes the steps needed to recognize the signal or “triggering” event. The second part describes the immediate actions that should follow the recognition of the signal. The third part describes the actions that should be undertaken once the event has been verified, the overall situation has been assessed, and a decision has been made to launch the rapid containment operation with oseltamivir. The success of a strategy for containing an emerging pandemic virus is strictly time-dependent: modelling studies suggest that mass administration of antiviral drugs must begin within 21 days following detection of the first case representing improved human-to-human transmission of the virus. The detection of clusters of cases, closely related in time and place, is likely to be the most important epidemiological signal of such transition. Routine control measures aimed at reducing opportunities for further transmission to occur should be initiated as soon as clusters of cases are detected. Immediately following signal detection, local authorities, supported by national resources if needed, should apply the measures, aimed at reducing the transmission. The decision to initiate activities aimed at rapid containment and use of antiviral drugs should be triggered by compelling evidence that the situation represents a transition in the behaviour of the virus likely to result in efficient and sustained human-to-human transmission. Such evidence will derive from a combination of clinical, epidemiological and virological findings.

Over the past few years a novel class of antiviral agents, the neuraminidase inhibitors, has been found to be safe and effective in the prevention and treatment of influenza. The previously available agents, the M2 inhibitors amantadine and rimantadine, could only be used to treat influenza A infections and resistance developed rapidly. Zanamivir (Relenza®) and oseltamivir (Tamiflu™), the two clinically available neuraminidase inhibitors, are effective for treating both influenza A and B infections in adults and children and have also been shown to reduce the frequency of antibiotic-requiring complications of influenza infections. Inhaled zanamivir has shown benefit in treating acute influenza with mild-to-moderate underlying asthma or chronic obstructive pulmonary disease. Studies are needed to examine the use of these agents, alone or in combination with M2 inhibitors or ribavirin, in the management of severe infections in hospitalized patients and immunocompromised hosts. Studies are also needed to address other groups at increased risk for influenza complications, such as pregnant women and children below one year of age.


Influenza vaccination with current inactivated vaccines homologous to the prevalent wild-type virus can reduce influenza illness in 75%–80% of healthy adults. Vaccine is recommended for all individuals with chronic underlying diseases and for those aged 65 years or older. Although influenza vaccination is still advocated for patients with blunted immunity, protection rates are not as high, running at 40% for frail institutionalized elderly people. The influenza antiviral agents, amantadine or rimantadine, zanamivir and oseltamivir, can modify the severity of illness and reduce the duration of illness by about 1.5–2.5 days. Amantadine inhibits only influenza A. Resistant virus may emerge in up to 33% of amantadine-treated patients in the first 5 days of treatment and be transmitted to susceptible close contacts. Side-effects are usually mild in short courses of treatment. The neuraminidase inhibitor drugs, zanamivir and oseltamivir, act on both influenza A and B. Treatment is most effective when given within 30–36 hours after the onset of illness, and the earlier the better. Influenza should be treated with antiviral drugs in unvaccinated and vaccinated high-risk patients, as well as immunosuppressed patients with influenza-like illness, in periods of confirmed influenza prevalence. These
drugs may be of great value in the event of a major viral antigenic shift that causes pandemic influenza, if an adequate supply can be sustained.


The impact of influenza infection is felt globally each year when the disease develops in approximately 20% of the world’s population. Recent events, including human cases of avian influenza, have heightened awareness of the threat of a pandemic and have spurred efforts to develop plans for its control. Although vaccination is the primary strategy for the prevention of influenza, there are a number of likely scenarios for which vaccination is inadequate and effective antiviral agents would be of the utmost importance. During any influenza season, antigenic drift in the virus may occur after formulation of the year’s vaccine has taken place, rendering the vaccine less protective, and outbreaks can more easily occur among high-risk populations. In the course of a pandemic, vaccine supplies would be inadequate. Vaccine production by current methods cannot be carried out with the speed required to halt the progress of a new strain of influenza virus; therefore, it is likely that vaccine would not be available for the first wave of the spread of the virus. Antiviral agents thus form an important part of a rational approach to the control of epidemic influenza and are critical to planning for a pandemic. The article reviewed the application of antiviral in treatment and prophylaxis through several clinical trials.


Influenza A (H5N1) virus with an amino acid substitution in neuraminidase conferring high-level resistance to oseltamivir was isolated from two of eight Vietnamese patients during oseltamivir treatment. Both patients died of influenza A (H5N1) virus infection, despite early initiation of treatment in one patient. Surviving patients had rapid declines in the viral load to undetectable levels during treatment. These observations suggest that resistance can emerge during the currently recommended regimen of oseltamivir therapy and may be associated with clinical deterioration and that the strategy for the treatment of influenza A (H5N1) virus infection should include additional antiviral agents.

In the United States, 109/120 (91%) influenza A (H3N2) viruses isolated in the 2005-06 season until 12 January 2006, contained an amino acid change at position 31 of the M2 protein, which confers resistance to amantadine and rimantadine. On the basis of these results, the CDC issued an interim recommendation that neither amantadine nor rimantadine be used for the treatment or prophylaxis of influenza A in the United States for the remainder of the 2005-06 influenza season. During this period, oseltamivir or zanamivir should be selected if an antiviral medication is used for the treatment and prophylaxis of influenza.


Vaccination against influenza viruses is the second cornerstone in preventing influenza. Vaccination in the northern hemisphere is recommended to start in October. Recommendations regarding the composition of the vaccine are issued yearly on the basis of detailed investigations of the circulating strains. Vaccination against the prevalent wild-type influenza virus is recommended for all individuals in high-risk groups, including those aged 65 years or older (CDC 2005), and those with chronic illness, particularly diabetes, chronic respiratory and cardiac disease, and persons immunocompromised from disease or concomitant therapy. In addition, a specific vaccination against influenza among health care personnel was recommended (CDC 2006).


The use of influenza vaccine is increasing, especially in developing countries. Yet most of the world’s influenza vaccine is produced by companies located
in nine developed countries. When the threat of an influenza pandemic appears, the traditional approach to providing inter-pandemic vaccines will not be able to meet the global demand for pandemic vaccine. Several steps must be taken to address this problem, including the use of reverse genetics to prepare seed strains for vaccine production, the undertaking of clinical studies to define the characteristics of candidate “pandemic-like” vaccines and vaccination schedules, the development of procedures for global vaccine registration, the expansion of recommendations and reimbursement for inter-pandemic vaccination, the country-specific reporting of vaccine use and forecasts of future vaccine needs, and the negotiation of political agreements that will ensure adequate production and equitable distribution of pandemic vaccine throughout the world.


Influenza epidemics lead to increased mortality, principally among elderly persons and others at high risk, and in most developed countries, influenza-control efforts focus on the vaccination of this group. Japan, however, once based its policy for the control of influenza on the vaccination of schoolchildren. From 1962 to 1987, most Japanese schoolchildren were vaccinated against influenza. For more than a decade, vaccination was mandatory, but the laws were relaxed in 1987 and repealed in 1994; subsequently, the vaccination rates dropped to low levels. When most schoolchildren were vaccinated, it is possible that herd immunity against influenza was achieved in Japan. If this was the case, both the incidence of influenza and mortality attributed to influenza should have been reduced among older persons. The study analysed the monthly rates of death from all causes and death attributed to pneumonia and influenza, as well as census data and statistics on the rates of vaccination for both Japan and the United States from 1949 through 1998. For each winter, the number of deaths per month in excess of a baseline level, defined as the average death rate in November, was estimated. The excess mortality from pneumonia and influenza and that from all causes were highly correlated in each country. In the United States, these rates were nearly constant over time. With the initiation of the vaccination programme for schoolchildren in Japan, excess mortality rates dropped from values three to four times those in the United States to values similar to those in that country. The vaccination of Japanese children prevented about 37 000 to 49 000 deaths per year, or about 1 death for every 420 children vaccinated. As the vaccination of schoolchildren was
discontinued, the excess mortality rates in Japan increased. In conclusion, the
effect of influenza on mortality is much greater in Japan than in the United
States and can be measured about equally well in terms of deaths from all
causes and deaths attributed to pneumonia or influenza. Vaccinating
schoolchildren against influenza provides protection and reduces mortality
from influenza among older persons.

47. **Treonor JJ, Campbell JD, Zangwill KM, Rowe T, and Wolff M. Safety and
immunogenicity of an inactivated subvirion influenza A (H5N1) vaccine. N

A multicentre, double-blind two-stage study was conducted involving 451
healthy adults 18 to 64 years of age who were randomly assigned in a
2:2:2:2:2:2:2:1 ratio to receive two intramuscular doses of a subvirion influenza A
(H5N1) vaccine of 90, 45, 15 or 7.5 µg of haemagglutinin antigen or placebo.
The subjects were followed for safety analysis for 56 days. Serum samples
obtained before each vaccination and again 28 days after the second
vaccination were tested for H5 antibody by microneutralization and
haemagglutination inhibition. Mild pain at the injection site was the most
common adverse event for all doses of vaccine. The frequency of a serum
antibody response was the highest among subjects receiving doses of 45 µg or
90 µg. Among those who received two doses of 90 µg, neutralization
antibody titers reached 1:40 or greater in 54% and haemagglutination-inhibition titers reached 1:40 or greater in 58%. Neutralization titers of 1:40
or greater were seen in 43%, 22% and 9% of the subjects receiving two doses of
45, 15 and 7.5 µg, respectively. No responses were seen in placebo
recipients. The researchers concluded that a two-dose regimen of 90 µg of
subvirion influenza A (H5N1) vaccine does not cause severe side-effects and,
in the majority of recipients, generates neutralizing antibody responses
typically associated with protection against influenza. A conventional
subvirion H5 influenza vaccine may be effective in preventing influenza A
(H5N1) disease in humans. (ClinicalTrials.gov number, NCT00115986.)

http://content.nejm.org/cgi/reprint/354/13/1411.pdf**

In editorial comment stated that the immunogenicity was only poor-to-
moderate at best. In fact, in only one group did more than 50% of the
subjects reach the immunogenicity threshold (defined a priori) of an antibody
titer of 1:40 or greater (typically thought of as seroprotective) – the subjects
who received two doses of 90 µg each 28 days apart – a total dose 12 times that of seasonal influenza vaccines. Notably, the current worldwide manufacturing capacity for influenza vaccine is estimated at only 900 million doses (at the dose level of 15 µg). The requirement of two doses of 90 µg per person means that only 75 million persons (1.25% of the world’s population) could be fully immunized, and of those, only half would achieve seroprotection. Thus, vaccines must contain much less influenza haemagglutinin to be widely useful as a global public health measure.


Vaccination of poultry with inactivated influenza vaccine can be an effective tool in the control of avian influenza (AI). One major concern of using inactivated vaccine is vaccine-induced antibody interference with serological surveillance and epidemiology. In the United States, low pathogenicity H5 and H7 subtype AI viruses have caused serious economic losses in the poultry industry. Most of these viruses also have the accompanying N2 subtype and no H5N1 or H7N8 subtype AI viruses have been identified in poultry in the US. In order to allow the Differentiation of Infected from Vaccinated Animals (DIVA) while maintaining maximum efficacy of the vaccine, the authors generated reassortant viruses by reverse genetics that contained the same H5 and H7 haemagglutinin (HA) gene as the challenge virus, but a heterologous N1 or N8 neuraminidase (NA) gene. In vaccination-challenge experiments in 2-week-old specific pathogen-free chickens, reassortant influenza vaccines (rH5N1 and rH7N8) demonstrated similar antibody profiles and comparable protection rates as vaccines prepared with parent H5N2 and H7N2 viruses. Furthermore, the authors were able to differentiate the sera from the infected and the vaccinated birds by neuraminidase inhibition test and indirect immunofluorescent antibody assay on the basis of different antibodies elicited by their NA proteins. These results demonstrate the usefulness of a reverse genetics system for the rapid generation of reassortant AI virus that allows for the utilization of the DIVA strategy for the control of AI infections in poultry.
Non-pharmaceutical Interventions


Since the global availability of vaccines and antiviral agents against influenza caused by novel human subtypes is insufficient, WHO recommends non-pharmaceutical public health interventions to contain infection, delay spread, and reduce the impact of pandemic disease. Virus transmission characteristics will not be completely known in advance, but difficulties in influenza control typically include peak infectivity early in illness, a short interval between cases and, to a lesser extent, transmission from persons with incubating or asymptomatic infection. Screening and quarantining entering travellers at international borders did not substantially delay virus introduction in past pandemics, except in some island countries, and will likely be even less effective in the modern era. Instead, WHO recommends providing information to international travellers and possibly screening travellers departing from countries with transmissible human infection. The principal focus of interventions against pandemic influenza spread should be at national and community levels rather than international borders.


The World Health Organization recommended pandemic influenza interventions based on transmission pattern, pandemic phase, illness severity and extent. In the pandemic alert period, the recommendations include isolation of patients and quarantine of contacts, accompanied by antiviral therapy. During the pandemic period, the focus shifts to delaying the spread and reducing the effects through population-based measures. Ill persons should remain at home when they first become symptomatic; forced isolation and quarantine are thought to be ineffective and impractical. If the pandemic is severe, social distancing measures such as school closures should be considered. Non-essential domestic travel to affected areas should be deferred. Physicians should encourage regular hand-washing among family members of patients. In general, people should be discouraged to touch their eyes, nose or mouth. Minimize the impact of sneezes and coughs by all
possible means. Hand and respiratory hygiene should be routine; mask use should be based on setting and risk, and contaminated household surfaces should be disinfected. Additional research and field assessments during pandemics are essential to update recommendations. Legal authority and procedures for implementing interventions should be understood in advance and should respect cultural differences and human rights.


In addition to causing 12 human deaths and 17 cases of human infection, the 2004 outbreak of H5N1 influenza virus in Thailand resulted in the death or slaughter of 60 million domestic fowl and the disruption of poultry production and trade. After domestic ducks were recognized as silent carriers of H5N1 influenza virus, government teams went into every village to cull flocks in which the virus was detected; these team efforts markedly reduced the H5N1 infection. The investigators examine the pathobiology and epidemiology of the H5N1 influenza virus in the four systems of duck raising used in Thailand in 2004. No influenza viruses were detected in ducks raised in “closed” houses with high biosecurity. However, the H5N1 influenza virus was prevalent among ducks raised in “open” houses, free-ranging (grazing) ducks and backyard ducks.


In response to increasing concerns about respiratory illness in military recruits, a simple hand-washing programme was developed and evaluated at a large navy training centre. Clinical records from 1996 to 1998 were reviewed to determine weekly rates of respiratory illness before and after programme implementation (1 089 800 person-weeks reviewed). A supplemental survey was given to a sample of recruits to assess self-reported respiratory illness and compliance with the hand-washing programme. A 45% reduction in total outpatient visits for respiratory illness was observed after implementation of the hand-washing programme. No change was noted in the hospitalization rates for respiratory illness, which remained low during the observation period. Survey data supported clinical observations as frequent hand-washers self-reported fewer respiratory illness episodes when compared to infrequent
hand-washers. Surveys also revealed challenges with hand-washing compliance. In summary, the implementation of a hand-washing programme in this population of healthy young adults was associated with a marked reduction in outpatient visits for respiratory illness. Despite its success, maintenance of the hand-washing programme has been challenging in the time-constrained setting of military training.


The H5N1 strain of avian influenza was first reported in China’s mainland in January 2004 and rapidly spread throughout the country. As of February 2006, China had reported 12 laboratory-confirmed human cases with eight fatalities. The situation was classified as pandemic phase 3 by WHO definition. The article summarized progress to achieve phase 3 national objectives of preparedness plan. China established a national command headquarter in January 2004 chaired by the Vice Prime Minister, in order for several ministries to oversee the response to AI. At the same time, the country has improved the case detection with enhanced surveillance. A comprehensive surveillance system for pneumonia of unknown cause was established after the SARS outbreak. Surveillance for animal diseases was conducted in the poultry-affected area. China CDC has developed laboratory capacity for diagnosing and studying the AI virus. In addition, the Ministry of Health has trained more than 1000 staff for field investigation and laboratory to strengthen the epidemiology team. Collaboration between ministries and international organizations has been strengthened with improved information dissemination.
Risk Communication


The report has two parts. The first, devoted to outbreak experience, describes the special case of outbreaks and the many difficult challenges they present for communicators. It also summarizes presentations during the consultation that looked at recent outbreaks in terms of what they have to say about effective communication and the consequences of certain errors. The second part translates these experiences into best practices for communication during an outbreak. Contents are organized around five essential practices for effective outbreak communication identified during the consultation: build trust, announce early, be transparent, respect public concerns, and plan in advance.


With poultry outbreaks of avian influenza H5N1 continuing in Thailand, preventing human infection remains a priority. The investigators surveyed residents of rural Thailand regarding avian influenza knowledge, attitudes and practices. Results suggest that public education campaigns have been effective in reaching those at greatest risk, although some high-risk behaviour continues.


A telephone survey of 986 Hong Kong households determined exposure and risk perception of avian influenza from live chicken sales. Householders bought 38,370,000 live chickens; 11% touched them when buying, generating 4,220,000 exposures annually; 36% (95% confidence interval [CI] 33%–39%) perceived this as risky, 9% (7%–11%) estimated >50% likelihood
of resultant sickness, whereas 46% (43%–49%) said friends worried about such sickness. Recent China travel (adjusted odds ratio 0.35; CI 0.13–0.91), traditional beliefs (1.20, 1.06–1.13), willingness to change (0.29, 0.11–0.81) and believing cooking protects against avian influenza (8.66, 1.61–46.68) predicted buying. Birth in China (2.79, 1.43–5.44) or overseas (4.23, 1.43–12.53) and unemployment (3.87, 1.24–12.07) predicted touching. Age, avian influenza contagion worries, husbandry threat, avian influenza threat, and avian influenza anxiety predicted perceived sickness risk. High population exposures to live chickens and low perceived risk are potentially important health threats in avian influenza.

58. Investigation of Avian Influenza (H5N1) Outbreak in Humans – Thailand, 2004

Introduction: Beginning in late 2003, a substantial outbreak of influenza A (H5N1) virus spread among poultry in Thailand. On 23 January 2004, the Ministry of Public Health detected the first confirmed human case of H5N1 infection.

Methods: During February-November 2004, the MOPH's Bureau of Epidemiology and provincial health offices worked together to investigate the H5N1 outbreak in humans. Two studies were conducted: a descriptive study to describe clinical manifestations and epidemiological characteristics of the cases and a matched case-control study to determine risk factors for persons who might subsequently become ill with H5N1.

Results: A total of 16 patients with confirmed H5N1 were identified for the case-control study. Fever and respiratory symptoms predominated. Leucopenia and thrombocytopenia were present, respectively, in nine (100%) and four (44%) cases aged <15 years. Direct touching of unexpectedly dead poultry was the most significant risk factor (odds ratio = 29.0; 95% confidence interval = 2.7–308.2). The overall mortality was 75%; mortality for persons aged <15 years was 90%, compared with 57% for persons aged ≥15 years.

Conclusion: Avian influenza was more severe in children, who should avoid handling dead poultry during epizootics. Early avian influenza in children resembled the more common dengue fever, but the presence of cough and the absence of haemoconcentration distinguished avian influenza, which often progressed rapidly to acute respiratory distress syndrome, requiring intensive care.
59. Cases of Influenza A (H5N1) – Thailand, 2004 - 2005

Since mid-December 2003, eight Asian countries (Cambodia, China, Indonesia, Japan, Laos, South Korea, Thailand and Viet Nam) have reported an epizootic of highly pathogenic avian influenza in poultry and various other birds caused by influenza A (H5N1). As of 9 February 2004, a total of 23 laboratory-confirmed human cases of influenza A (H5N1) had been reported in Thailand and Viet Nam. In 18 (78%) of these cases, the patients died. Clinical experience with avian H5N1 disease in humans is limited. The human H5N1 viruses identified in Asia in 2004 are antigenically and genetically distinguishable from the 1997 and February 2003 viruses. To aid surveillance and clinical activities, this report provides a preliminary clinical description of the initial five confirmed cases in Thailand.

Of the 17 laboratory-confirmed cases in Thailand, nine were in male, the median age was 14 years, and all patients were previously healthy. Fourteen patients reported exposure to ill poultry. The symptoms included: fever (17), cough (16), sore throat (12), rhinorrhea (9), myalgia (9), and diarrhoea (7). Shortness of breath was reported in 13 patients; clinically apparent pneumonia with chest radiograph changes with pulmonary infiltrations was observed in all patients. Peripheral leukocytes were normal or decreased, 7 out of 12 patients had lymphopenia (<1,000/µL) and 4 out of 12 had thrombocytopenia. Mild-to-moderate elevations in hepatic transaminases were found in 8 out of 12 patients tested.