



Avian Influenza

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Since December 2003, highly pathogenic A/H5N1 avian influenza viruses have swept through poultry populations across Asia, Europe and Middle-East, and have now reached Sub-Saharan Africa. The avian outbreaks are historically unprecedented in scale and geographical spread. In addition, and as of 16 June 2006, 225 cases of human H5N1 infections, including 129 deaths, have been reported in 10 countries. Human cases often occur in small family clusters with, in the large majority of cases, a clear history of exposure to infected birds, primarily backyard poultry and, less frequently, wild birds. Seasonal patterns have been noted with most human cases reported in winter and early spring. Although genetic analysis of the human viral isolates have not shown any recombination with human influenza virus genome, there is evidence of genetic variations and the constitution of two major groups, or clades, of H5N1 viruses.

Although direct support and clear guidelines are provided by FAO and OIE, the control of the epizooty has proven to be difficult in countries with limited veterinary services and a large proportion of backyard poultry. Although there is no doubt that migratory birds have contributed to the international spread of the virus, the role of informal and/or illegal trade of poultry is thought to be important in the spread of the disease.

Significant scientific knowledge has been assembled on H5N1 virus infection in animals and humans; however, a number of elements remain poorly understood and more research is needed particularly in epidemiology, transmission patterns, human case management, and even communication to the public.

The threat of a pandemic of influenza is of concern since we now know for certain that a pandemic like the one in 1918-19 was caused by a mutated avian influenza virus. WHO is spearheading global and national efforts to improve pandemic preparedness all over the world. However major challenges remain including global control of the epizooty, surveillance in animals and humans, human vaccine development, vaccine mass production, access to antivirals, case-management, non-pharmaceutical interventions, communication, inter-sectoral and international coordination.

As of today, WHO pandemic phase 3 reflects the absence of sustained human to human transmission. WHO, with support from various partners, including industry, is planning for a rapid intervention at the site of emergence of a pandemic strain while a number of pandemic exercises are conducted at national and regional level. The recent resolution of the World Health Assembly for immediate voluntary implementation of related articles of the 2005 revised International Health Regulations reflects the concern of the international community. Should a pandemic start, this new global framework for the management of public health emergencies of international concern should allow for better and faster international coordination...

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The need of a global task force for influenza

Pr Albert Osterhaus

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Influenza A-viruses are divided in two distinct groups based on their ability to cause disease in birds: low pathogenic and highly pathogenic avian influenza (LPAI and HPAI). Only viruses of the H5 and H7 subtype have been shown to cause HPAI. Migratory birds are the reservoir of influenza A-viruses and are the source of LPAI viruses that may mutate into HPAI viruses in domestic poultry, causing severe disease outbreaks with high mortality in these animals. Since 1997, it has become clear that avian influenza viruses may infect humans: in Hong Kong 18 people became infected with HPAI H5N1 virus and 6 of them died. In 2003, a massive outbreak of HPAI amongst poultry in The Netherlands caused by a H7N7 virus resulted in 89 clinical cases among farmers and poultry workers, one of which was fatal. The ancestors of this H7N7 virus had been found in migratory ducks prior to the outbreak. The virus had probably spilled over as a LPAI H7N7 virus to free range chickens, in which it mutated to a HPAI virus.

In the past three years, outbreaks of HPAI in domestic poultry in Asia, caused by HPAI H5N1 viruses were associated with about 200 severe human infections, more than half of which were fatal. From Asia HPAI H5N1 virus infections spread to the Middle East, Europe and Africa, affecting domestic poultry, wild birds and a number of mammalian species. Also from Turkey and the Middle East human cases, some with fatal outcome, were reported. The pattern of spread largely coincided with the flyways of migratory birds...

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Influenza h5n1: diagnosis and disease

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Human infections with avian influenza A (H5N1) virus continue to occur in Asia and Europe, igniting fears of an imminent influenza pandemic. Early recognition of influenza H5N1 is important for clinical management, and infection- and outbreak control, but is hampered by the non-specific nature of symptoms and infrastructural limitations in most affected countries. In regions where human and avian influenza strains are cocirculating, rapid laboratory methods which distinguish human and avian subtypes are essential for timely confirmation of disease, but these require good laboratory facilities.

The pathogenesis underlying the high mortality of influenza H5N1 remains unclear, although laboratory studies have implicated cytokine dysregulation in H5N1 pathogenicity. We studied seventeen H5N1-infected patients and show that H5N1 influenza is often associated with disseminated infection with detectable viral RNA in blood and faeces, and with higher levels of viral replication in the nasopharynx compared to contemporary Vietnamese cases of H1N1 or H3N2 influenza. Fatal outcome of H5N1 influenza was associated with the presence of viraemia, high nasopharyngeal viral load and high serum concentrations of cytokines and chemokines...

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Risk of H5N1 mutations and mammalian adaptation

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Highly pathogenic avian H5N1 influenza viruses that emerged from Southeast Asia continue to spread worldwide. Although still very much an avian disease, there have been a number of reports of natural infection of mammals including humans. H5N1 viruses causing lethal disease in chickens show dramatic differences in their ability to cause severe disease and death in experimentally infected ferrets. What genetic changes cause high lethality and possible adaptation to the mammalian host? Sequence analysis of lethal A/Vietnam/1203/04 (VN1203), a fatal human case isolate, and non-lethal A/chicken/Vietnam/C58/04 (CH58) virus's complete genome revealed 1 to 9 amino acid differences encoded by seven genes. We applied reverse genetics to generate H5N1 reassortants combining genes of VN1203 and CH58 and tested their pathogenicity in ferrets and mice. Both viruses had multiple basic amino acid at the cleavage site and $\alpha 2,3$ receptor binding specificity. Surprisingly, exchanging hemagglutinin and neuraminidase genes did not alter pathogenicity, but substituting CH58 polymerase genes completely attenuated VN1203 virulence. This study highlights that multibasic amino acids in the cleavage site of the HA are necessary but not sufficient for high lethality in mammalian species. To cause severe disease and death in the mammalian host, H5N1 viruses must have polymerase complex proteins with high replication/transcription activity...

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Role of Mathematical Modelling in Pandemic Preparedness

Dr Simon Cauchemez

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I will discuss the role mathematical modelling in pandemic planning and response. Recent research examining the whether antiviral prophylaxis and social distance measures could be used to contain a nascent pandemic at its point of origin will then be reviewed. Containment is potentially feasible, but requires rapid detection of the initial transmissible case cluster and a rapid and organised response to each new case. These may be demanding criteria for much of SE Asia. If containment fails, slowing spread becomes a policy priority and in that context I will discuss the potential impact of restrictions on international travel. To conclude, I will provide a brief updated of ongoing work examining pandemic mitigation strategies which make best use of limited vaccine and antiviral supplies....

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Avian influenza in humans: existing treatments, their limits, and new perspectives

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In the wake of a pandemic with avian influenza H5N1 virus, neuraminidase inhibitors such as oseltamivir (Tamiflu®) and zanamivir (Relenza®) could be recommended for both therapeutic and preventive use. Other drugs that could be advocated to contain such pandemic are amantadine/rimantadine, ribavirin, and interferon (in its pegylated form). Yet, other compounds are under investigation. Moreover, when combined, the available compounds may be expected to achieve a synergistic action, while reducing the likelihood of resistance development ...

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Multivalent lectins as inhibitors of viral fusion and entry in cells: new antiviral mechanism

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Natural antiviral defenses mediated by the innate immune systems involve defensins, antimicrobial peptides expressed by leukocytes and by epithelial cells. We explored an antiviral activity of a theta-defensin retrocyclin-2, RC2 1. We found RC2 to inhibit influenza virus infection by blocking viral entry into host cells at a stage of fusion between viral envelope and cell membrane. Binding of RC2, a multivalent lectin, to cell and viral surface carbohydrates prevented fusion by erecting a network of crosslinked and immobilized surface glycoproteins. RC2 also inhibited fusion mediated by Sindbis virus and baculovirus. Two other multivalent lectins in innate immunity, human beta defensin-3 and mannan-binding lectin, blocked viral fusion by the same mechanism ...

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The need of a global task force for influenza

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Electrochemical Influenza Surveillance System

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In the face of concerns over an influenza pandemic, identification of virulent influenza A isolates must be obtained quickly for effective responses. Rapid subtype identification however is difficult even in well-equipped virology laboratories or currently unobtainable in the field under more austere conditions. Here we describe a sensitive genome assay and microarray design that can be used to rapidly identify influenza A hemagglutinin subtypes 1 through 16 and neuraminidase subtypes 1 through 9. The system is based on an electrochemical microarray technology that is simple enough to use in field studies. Assay time is around 4 hours and produces data on the strain, likely origin of the infectious agent and in some cases relative pathogenicity...

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Development of an adenoviral-vector-based pandemic influenza vaccine against antigenically distinct human H5N1 strains in mice

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In the 20th century, the world has experienced three influenza pandemics including the worst pandemic of all time in 1918-19 in which approximately 40-50 millions people died. Now we are facing a substantial risk of the first pandemic of 21st century mainly due to the emergence of highly pathogenic avian H5N1 influenza viruses. These H5N1 viruses have expanded their geographical distribution from Southeast Asia to several countries in Asia, Middle East, Africa, and Europe causing widespread deaths in domestic and migratory birds. In addition, as of April 21, 2006, 204 laboratory-confirmed cases of human infections with 113 fatalities were reported to the World Health Organization. The Majority of the human fatalities are due to direct virus transmission from infected birds to humans, although probable human-to-human transmission has also been reported. Vaccines developed in response to pandemic threat by H5N1 viruses using either surrogate inactivated virus, baculovirus-expressed hemagglutinin (HA), or egg-derived vaccines using A/PR/8-based reassortants by reverse genetics so far performed below expectations, even at higher doses. Since H5N1 viruses are highly lethal to chickens and the maintenance of a constant supply of embryonated eggs to make conventional egg-derived vaccine would be difficult in a pandemic, we developed an egg-independent vaccine strategy to combat the avian influenza virus ...

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Antiviral effect of catechins in green tea on influenza virus

Baik Lin Seong

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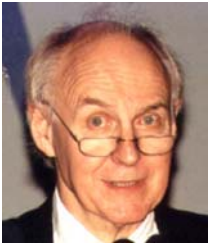
Polyphenolic compound catechins (EGCG, ECG and EGC) from green tea exert strong antiviral effects on influenza viruses. The antiviral effect is observed in all influenza virus subtypes tested, including three major subtypes of human influenza, A/H1N1, A/H3N2 and B strain, and H9N2 avian virus. Structure-function relationships observed among natural and chemical derivatives usefully guide effective use of catechins as alternative means for controlling influenza and avian flu pandemics....

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Pandemic influenza: a potential role for statins in treatment and prophylaxis

Pr David Fedson

Former Professor of Medicine, University of Virginia School of Medicine, Sergy Haut, France

The next influenza pandemic may be imminent. Because antiviral agents and vaccines will be unavailable to people in most countries, we need to determine whether other agents could offer clinical benefits. Influenza is associated with an increase in acute cardiovascular diseases and influenza viruses induce pro-inflammatory cytokines. Statins are cardioprotective, have anti-inflammatory and immunomodulatory effects and thus might benefit patients with influenza. Observational studies have already shown they reduce mortality in patients with bacteremia, sepsis and pneumonia. The statin/influenza hypothesis should be evaluated by using administrative databases to look for reduced rates of hospitalization and death due to influenza-related conditions in people taking statins. These studies should be followed by laboratory studies of statins in animal and cell-based models of influenza virus infection, and later by clinical trials...

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Ethical Challenges in Pandemic Planning

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Plans to deal with an influenza pandemic need to be founded on widely held ethical values, so that people understand in advance the kinds of choices that will have to be made. Decision makers and the public need to be engaged in the discussions about ethical choices, so plans reflect what most people will accept as fair, and good for public health. The Pandemic Influenza Working Group at the University of Toronto Joint Centre for Bioethics (JCB) has developed a 15-point ethical guide for planning and decision-making for a pandemic. This presentation will discuss the 15 point guide. The utility of the guide will be discussed using four key ethical issues that need to be addressed in pandemic planning...

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