

# Pandemic flu: facts, feathers and forecast

<sup>1</sup>N Meyer, <sup>2</sup>G Hawkins

<sup>1</sup>Fellow, European Programme for Intervention Epidemiology Training, <sup>2</sup>Specialist Registrar in Public Health Medicine, Health Protection Scotland, Glasgow, Scotland

**ABSTRACT** The Royal College of Physicians of Edinburgh organises ‘hot topic’ meetings in response to medical matters attracting major public and media interest. This report of the implications of a future influenza pandemic complements a previous report in the *Journal* on Asian flu.<sup>1a</sup>

**KEYWORDS** Avian influenza, communicable disease control, epidemics, human influenza, outbreaks, pandemics

**LIST OF ABBREVIATIONS** Critical Care Contingency Planning Group (CCCCPG), Department of Health (DoH), Emergency Preparedness Clinical Leadership Advisory Group (EPCLAG), Health Protection Agency (HPA), intensive care unit (ICU), severe acute respiratory syndrome (SARS)

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Correspondence to N Meyer, Health Protection Scotland, Clifton House, Clifton Place, Glasgow, G7 0YN

tel. +44 (0)141 300 1100

e-mail [nadia.meyer@hps.scot.nhs.uk](mailto:nadia.meyer@hps.scot.nhs.uk)

## INTRODUCTION

Influenza pandemics have historically taken the world by surprise. The present situation is different, as the world has been warned in advance. For more than two years, conditions favouring another pandemic have been unfolding in different parts of the world. Warnings that a pandemic may be imminent have come from both changes in the epidemiology of human and animal disease, and an expanding geographical presence of the virus, creating further opportunities for human exposure. The advanced warning has brought an unprecedented opportunity to prepare for a pandemic and develop ways to mitigate its effects.<sup>1</sup> The one-day ‘Hot Topic Symposium,’ organised by The Royal College of Physicians of Edinburgh and Health Protection Scotland, provided a great opportunity to strengthen national and international collaboration on interventions aimed at delaying the emergence of a pandemic virus or forestalling its international spread. The symposium was aimed at the widest audience in the NHS and throughout the UK. Speakers were chosen for their expertise and are currently involved in influenza contingency planning, either in the UK or abroad.

## SESSION I HUMAN AND AVIAN INFLUENZA

### *Influenza, the basic facts*

Professor J Oxford, Professor of virology at Queen Mary’s School of Medicine, London, highlighted the history of pandemic influenza, with particular reference to the 1918 pandemic and its origins. In 1917, outbreaks of purulent bronchitis were reported in army camps in France and England. These had a 40% mortality rate, and a key clinical

feature was the development of heliotrope cyanosis: a dusky blue discoloration of the skin also seen during the 1918 pandemic. This feature, coupled with soldiers living in crowded conditions in close proximity to poultry and pigs, provides a convincing argument that the 1918 pandemic may have originated in Europe.<sup>2</sup> Professor Oxford also spoke of his work examining pathology samples taken from those who died during the 1918 pandemic, which has identified similarities between today’s H5N1 virus and the H1N1 virus of 1918. He suggested that efforts to control the threat posed by the H5N1 virus should focus on preventing the spread of the virus from the ‘silent carriers’ (e.g. wild ducks and geese) to domestic poultry flocks.

### *Scottish virology arrangements for avian and pandemic influenza*

Dr B Carmen, Chairman of the UK Clinical Virology Network, reported on the current provision for the testing of samples from isolated cases of suspected avian influenza in humans. He stressed that swabs should ideally be transported in lysis buffer, as this kills the virus. Plans for the Scottish laboratory response to pandemic influenza have been developed by the Scottish Clinical Virology Consultants Group.<sup>3</sup> It is anticipated that, once a pandemic has reached UK shores, demands for testing will be highest during the first few weeks while a clinical case definition is being established. Thereafter, it is expected that diagnosis will be made largely on clinical grounds with testing becoming more selective, limited to cases where results will influence clinical management. The development of a sampling strategy for use during a pandemic will require a clear lead from Public Health and the Scottish Executive. Laboratories will operate a restricted service for non-flu testing and will stay open for as many hours as workload demands and staffing permits.

### Avian influenza as it affects humans

Dr M Koopman, of the National Institute of Public Health and the Environment in the Netherlands, reported that prior to 1997, when 18 human cases of H5N1 infection occurred in Hong Kong, only four human cases of avian influenza had been reported in the world literature. Since 1997, there have been a further 346 human cases of avian influenza worldwide and 139 deaths.<sup>4</sup> In 2003, an outbreak of H7N7 avian influenza in the Netherlands resulted in 89 confirmed human cases and one death.<sup>5</sup> This outbreak featured higher rates of transmission from birds to humans than had been previously observed, and there was also evidence of secondary transmission. Conjunctivitis was a common clinical presentation, and it has been hypothesised that H7N7 may enter the human host via receptors in the conjunctiva.<sup>6</sup> Dr Koopman recommended the inclusion of eye swabs in any sampling strategy developed for H5N1 infection. Human infection with H5N1 has commonly presented with high fever, shortness of breath and cough. However, the presence of other symptoms such as diarrhoea (a prominent feature of infection in Vietnam) has been more variable. An alarming feature of infection with the H5N1 virus has been the presence of cytokine resistance<sup>7,8</sup> where infection leads to massive cytokine induction – the cytokine storm – that has no impact on the replicating virus. Dr Koopman closed by cautioning that, while protocols and case definitions are important, awareness of clinicians is crucial.

#### KEYPOINTS SESSION 1

- Similarities have been found between the H5N1 virus of today and the H1N1 virus of the 1918 pandemic.
- Prevention should aim to stop the H5N1 virus spreading from birds to domestic poultry.
- From 1997, there have been 346 human cases of H5N1 avian influenza, with 139 deaths giving a mortality of 40%.
- H5N1 infection has been associated with 'cytokine resistance' in which massive cytokine induction does not reduce viral replication.

## SESSION 2 PANDEMICS: PAST AND FUTURE

### *The threat posed by highly pathogenic H5N1 avian influenza*

Dr J de Jong, of the Erasmus Medical Centre in Rotterdam, cited some worrying facts relating to the pandemic potential of H5N1: all three pandemic influenza strains in the twentieth century developed from avian influenza. Since the last pandemic, poultry farming has increased worldwide and HP H5N1 infection in birds is now endemic in many areas. There is also evidence of genetic drift in the H5N1 virus. The resulting marked antigenic drift displayed by HP H5N1 viruses requires constant updating of candidate vaccine strains. However, Dr de Jong countered these worrying facts with some

reassuring ones. Despite decades of infection, H5 and H7 epidemics in birds have not caused pandemics in humans. There is no evidence for increasing efficiency of transmission from bird-to-human, human-to-human transmission is rare, and no re-assortment has been detected. Dr de Jong outlined options for the control of avian influenza in poultry. He highlighted the fact that stamping out – the practice of culling affected flocks – is cheap and effective, but it can result in the loss of an important source of income and food. Vaccination is a more economical option than stamping out, but carries the risk of continuing (undetected) virus transmission in flocks and accelerated antigenic drift. High costs and the risk of resistance make the use of antivirals in birds unviable. Dr de Jong proposed that one approach to control might be the combination of general vaccination, intensive surveillance and local stamping out.

### *What does modelling tell us about how to respond to a pandemic?*

Professor N Fergusson, Professor of Mathematical Biology, Imperial College, London, explained how some models predict that a pandemic could be contained at source. However, this would require a stockpile of at least three million courses of antiviral, the initial outbreak would need to be detected very early (fewer than 50 cases), and new cases would need to be isolated and treated within 48 hours. Unless truly draconian, border controls will have a limited impact on the spread of a pandemic: a 99.9% reduction in travel will only delay the spread by around six weeks. Local mitigation measures aimed at reducing morbidity and mortality have been modelled for the UK. A reactive school closure policy (where a school closes following its first case) will not reduce the number of people infected, but will reduce the height of the epidemic peak by up to 40%, spreading cases out over a longer period of time, and reducing demands made on services at any one time. Treatment of cases with antivirals can reduce transmission, but it needs to be administered within 24 hours. Household prophylaxis and quarantine, combined with school closures, could halve the clinical case numbers. However, this would require stockpiling sufficient antivirals for 50% of the population. Vaccination will have little impact unless it is available in the UK within two months of the onset of a global epidemic. Professor Fergusson closed by stating that intensive combination policies could dramatically reduce case numbers during a pandemic, but would require big stockpiles of antivirals and would be difficult to deliver.

### *The experience of pandemic flu in 1969 and lessons for the next pandemic*

Dr D Fleming, Director of the Royal College of General Practitioners Research Unit, drew on data from the annual UK influenza epidemics and his personal experience of working during the 1969 pandemic, to

speak on the potential impact on the community of another pandemic. He commented that the incidence of illness in 1969 was high, but the country did not grind to a halt. He highlighted several changes in the provision of General Practice services since 1969, and suggested that planning for an influenza pandemic had not taken account of these changes. In particular, the organisation of out of hours care has changed dramatically, and house visits, which constituted 25% of consultations in 1969, now only account for 2%. He also argued that annual flu vaccination is not protecting the over 75s, and speculated that vaccination would confer little benefit to this age group in a pandemic. He closed by stressing that reinforcement of primary healthcare services will be needed, and that one of the main challenges will be getting antivirals into households promptly.

## PANEL DISCUSSIONS AND QUESTIONS

The relative contributions made to the spread of avian influenza by trade routes and the migration of birds was discussed. Dr de Jong said that both had a role in the spread, and legal trade routes for poultry were the most likely source of the avian influenza now seen in Nigeria.

The panel also discussed strategies that might be adopted to make oseltamivir available quickly when needed. Dr Koopman stressed that this would require great planning, and Professor Oxford suggested that pharmacists might have a role in prescribing antivirals. Dr Fleming commented that those in most need would not be able to get out of the house and that there would be a need for good home visiting services. The role of near-patient influenza testing was raised. This is expensive and, if adopted, its application would be limited, for example to the screening of healthcare workers.

The question of why avian influenza is not easily transmitted between humans was considered. Dr Oxford stated that the virus has a predilection for the lower respiratory tract and therefore cases will not be excreting much virus. A recent paper in *Nature* has examined this phenomenon.<sup>9</sup> Human influenza viruses preferentially recognise binding molecules SA $\alpha$ 2,6Gal, which are present in epithelial cells in the nasal mucosa, pharynx, trachea and bronchi. In contrast, avian influenza viruses preferentially recognise, and bind extensively to, SA $\alpha$ 2,3Gal binding molecules found in alveolar cells. A similar pattern of virus attachment has been observed for H5N1 infections in the domestic cat.<sup>10</sup> Dr de Jong added that exudation in the lower respiratory tract inhibits movement of the virus and therefore reduces its transmissibility.

Finally, the role of antibiotics during a pandemic was discussed. Dr Fleming stated that pandemic flu plans include advice on the use of antibiotics, but data from seasonal flu epidemics in the UK suggests that people die from the flu rather than secondary bacterial infections.

Professor Oxford countered by saying that around a third of deaths in the 1918 pandemic were caused by pneumococcal and other bacterial infections, and speculated that this was reassuring.

## KEYPOINTS SESSION 2

- H5N1 virus infection in poultry is endemic in many areas and the virus has shown genetic drift, but there is not yet evidence of more efficient bird-to-human or human-to-human transmission.
- General vaccination, intensive surveillance and local culling might be most effective in controlling the virus.
- Control of pandemic infection reaching the UK would require large stockpiles of antivirals and strict population controls. Border controls would not be likely to succeed.
- Bird migration routes and legal poultry trade routes probably both contribute to spread of H5N1 virus.
- Rapid availability of antiviral for patients will need planning of domiciliary medical services.
- The importance of bacterial infection, and hence of antibiotics, in influenza deaths is uncertain.

## SESSION 3 PATIENTS AND SERVICE CARE

The Scottish Minister for Health and Community Care, Andy Kerr opened the session by making the point that Scotland has been working with health departments across the UK and is fully prepared for a flu pandemic.

### Clinical features

Dr A Todd, Consultant Physician, Monklands Hospital, Airdrie, explained that the 'Spanish Flu' in 1918 had three main clinical courses:

- 1 'Simple influenza' with a natural course to recovery in 7–10 days;
- 2 'Simple influenza' with sudden acute and fulminating complications with death due to heart failure;
- 3 'Simple influenza' with return of pyrexia after several days and pneumonitis.

Pandemic flu had higher mortality and morbidity rates compared to seasonal flu. There was a loss of normal seasonality and different age groups were affected. Dr Todd described briefly the 'Clinical guidelines for patients with an influenza-like illness during an influenza pandemic' published by the British Thoracic Society, the British Infection Society, and the Health Protection Agency and available from the Department of Health website.<sup>11</sup> He concluded that in the next pandemic a new virus with new clinical features might emerge. Core features might be those of influenza A, but if H5N1 is involved, there may be additional specific clinical presentations. We should expect large numbers of the population to be affected and

be ready for a variable epidemiology and clinical presentations of the disease.

### *Life-threatening complications.*

Dr S Ramsay, Consultant Anaesthetist, Western Infirmary, Glasgow, reported on modelling work which predicted that during the peak of the flu pandemic the bed occupancy rate in ICUs would be overwhelmed by 120%. Reports from patients with avian flu showed that most patients required ventilation and/or other organ support within 48 hours of admission to hospital. Despite the evidence of high workloads for ICUs, the UK Influenza Pandemic Contingency Plan did not consider the resources needed by ICUs for the care of patients.<sup>12</sup> The Department of Health recognised this shortcoming and set up CCCPG to consider more specifically preparedness and contingency issues, and also personal protective equipment and infection control guidelines for ICUs. Referring to lessons learned from the SARS epidemic in Hong Kong, she highlighted the importance of identifying current and additional ICU capacity (equipment/space and staff), and considering indemnity coverage for unit and reserve staff and other types of support for staff.<sup>13</sup> Patient triage decisions might be very difficult to take and the DoH has set up the EPCLAG to support clinicians in making difficult decisions. She concluded that the spectrum of illness of the next pandemic is unknown and during the next pandemic real-time research needs to be conducted to identify best treatment options for patients.

### *Therapy and management*

Professor K Nicholson, Professor of Infectious Diseases, Leicester Royal Infirmary, said that a clinical diagnosis might be difficult to make at the early stage of the pandemic. Clinicians must think 'travel/exposure history' – this will be critically important to identify cases. He described the readily accessible HPA algorithm for 'The management of returning travellers from countries affected by avian influenza and presenting with febrile respiratory illness',<sup>14</sup> the guidelines for 'Microbiological guidance for taking and handling specimens from individuals at risk of avian influenza',<sup>15</sup> and the WHO/HPA draft algorithm for 'Post-exposure prophylaxis for contact of confirmed human cases of avian influenza (H5N1) in the UK'.<sup>16</sup> He concluded that the expectations on the efficacy of neuraminidase inhibitors in cutting pneumonia, hospitalisations and deaths might not be met in a pandemic because of the evidence of resistance to neuraminidase inhibitors from several studies, and because the supply and timely distributions of antivirals will be a real challenge during the pandemic.<sup>17, 18, 19, 20</sup>

### *The logistics*

Dr B Cowan, Medical Director, Greater Glasgow Health Board, Glasgow, reported that figures from the 1918

pandemic flu showed that around 14.6% of staff working hours were lost because of disease, death, and bereavement among staff and/or their family. A predicted 20% staff absence rate will badly affect the critical care of patients. Possible solutions could be to recruit retired healthcare personnel, volunteers, medical and nursing students. A reassignment of personnel from surgical operating theatres to provide support for essential patient-care areas could also be considered. However, insurance, liability, and training of staff will need to be addressed beforehand. One way to deal with the demand for extra hospital beds during a pandemic would be to cancel elective surgery, use mothballed beds, if extra staff can be found to man these beds, ensure surge capacity in the private health sector, and plan for the provision of care in non-hospital settings. It is important to consider how to extend the availability of ICU care. Excessive workloads in primary care and any failure to cope with the increased demand will rebound on hospital care services. Also, pharmacy staff will be challenged to ensure adequate and continuous supplies of many types of drugs, not only antivirals.

### KEYPOINTS SESSION 3

- Experience with SARS in Hong Kong<sup>21a</sup> suggests that current and additional ICU capacity needs to be identified.
- Indemnity for ICU staff needs to be arranged.
- Diagnosis, especially a history of travel or exposure, will be vital in facilitating early antiviral therapy.<sup>1a</sup>

## SESSION 4 PROTECTING THE PUBLIC'S HEALTH

### *Preventing and controlling the pandemic flu*

Dr J Van Tam, Epidemiologist, Health Protection Agency, London, reported that antiviral drugs will be available for some countries when the next pandemic virus emerges. However, a specific pandemic vaccine will take at least four to six months. The UK has stockpiled oseltamivir in sufficient quantity to support a treatment strategy (limit impact), but not to support a preventive strategy (prophylaxis). There is a need to consider additional non-pharmaceutical control strategies, such as school closures, cancellation of mass gatherings, personal hygiene measures and use of masks, international travel restrictions, entry and/or exit screening, and other measures. True prevention will only be implemented later, when the first pandemic vaccines become available.

### *Prepared to respond: pandemic influenza and Scotland*

Dr M Donaghy, Medical Director, Health Protection Scotland concluded that preparedness and response to pandemic influenza in Scotland will depend on a number of factors. These include; the effectiveness of an international public health effort in developing enhanced



surveillance systems for influenza, planning in advance for the availability of a workforce and for the prioritisation of health services, and the stockpiling of antivirals.

#### KEYPOINTS SESSION 4

- Oseltamivir stocks in the UK would allow a treatment but not a prophylaxis strategy.
- A specific pandemic vaccine would take at least 4–6 months to produce.

### PANEL DISCUSSIONS AND QUESTIONS

During the panel discussions, an article in *Science* was mentioned, which reports on an epidemiological study from the Netherlands, in which the researchers examined a database of 60,000 primary care patients.<sup>21</sup> They found that during influenza seasons between 1996 and 2003, patients who had at least two statin prescriptions in the previous year had a 26% lower risk of developing pneumonia. Professor Nicholson said that this study represented extremely interesting work, but it was too early to say that prophylactic statin use in a pandemic is a reasonable strategy.

Worries about the over prescription of antivirals and their stock piling at home by physicians in the Netherlands and other countries were discussed. Actions that may contribute to drug shortages and their misuse will lead to the development of resistance. Dr Van Tam mentioned that Roche has deliberately held Tamiflu back from the supply chain, as otherwise it would disappear regardless of whether or not there is flu in the community.

Professor Oxford mentioned that there was no outburst of public panic during the last flu pandemics, and just the opposite happened: the public pulled together to help and assist each other. Dr Donaghy said that maintaining

appropriate communication channels between the public, the media, and health professionals will be key in maintaining public order and wellbeing during a pandemic.

It was also said that the 15 NHS Boards in Scotland need to lead a consistent approach to tackling pandemic flu, so that patients all over Scotland have access to the same high quality of care and prevention.

Some were worried that the primary care community in Scotland was not sufficiently involved in pandemic planning and preparedness. Further modelling on the expected demand on 'NHS 24' services during a pandemic is needed to anticipate and prepare properly for additional service requests during a pandemic.

### CLOSING REMARKS BY DR HARRY BURNS, CHIEF MEDICAL OFFICER FOR SCOTLAND

Never before in human history have we had prior warning of a pandemic. We now have ample opportunity to strengthen our response capacity. We have antivirals and hopefully we will have a vaccine at our disposal to reduce disease attack rates and improve the clinical management of cases during a pandemic. Although a flu pandemic vaccine cannot be created in advance of the virus appearing, we are already stockpiling 1.3 million doses of antivirals, enough to treat the one in four Scots who might be exposed to the virus during a flu pandemic. Updated versions of the Scottish contingency plan and advice for healthcare staff and new public information leaflets have been published.<sup>22</sup> Preparing for pandemic flu is a major priority for Scotland. Dr Burns also announced that an intensive care physician was joining the Scottish Executive team to improve the component related to ICUs in the pandemic plan.

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## Forthcoming symposia for 2006–2007

All symposia are held at the Royal College of Physicians of Edinburgh unless otherwise stated. Further symposia may be added at a later date.

### 2006

- Renal Medicine 19 October
- Updates in Internal Medicine (Annual Collegiate Members' Symposium) 27 October
- Cardiovascular Medicine:  
turning people into patients – has modern medicine gone too far? 31 October
- Preston Symposium 1 November
- Moving Points in Medicine (Dundee Symposium) 8 November
- Neurology 9 November
- Palliative Care 17 November
- 46th St Andrew's Day Festival Symposium:  
Updates in Acute and Internal Medicine 30 November, 1 December

### 2007

- Therapeutics 2007: Improving clinical effectiveness and patient safety 23 February
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