Pandemic influenza: report of follow-up symposium

Summary

The report *Pandemic influenza: science to policy,* which we published in November 2006, highlighted opportunities for incorporating scientific advice into policy making in this area. This symposium, which took place 12 months later, brought together key academics, stakeholders and policy makers (Annex A) for discussion of the latest developments in the field. This report summarises the key issues raised in presentations and discussions in areas including international avian influenza surveillance and vaccination, antiviral drugs and resistance, human vaccines, epidemiology, social science, communication and policy. The content of this report represents views expressed at the symposium and does not necessarily represent the views of the Royal Society or Academy of Medical Sciences.

The key points arising from the symposium were as follows:

- There is need for research funding agencies to support further research and development (R&D) on avian vaccines. There is also a need for international agencies to enhance avian vaccine standardisation.
- It is critically important to provide sustained support for basic and applied research in this area. Co-ordination, for example between research funders, in the development of the human influenza research agenda is valuable. Duplication of research in this area may be necessary, for example, in confirmation of results.
- It is important to maintain the tradition of sharing samples and data in influenza virology to ensure progress is made with H5N1.
- There is considerable concern about the spread of influenza in some African countries. There is a need to strengthen the weak infrastructure for surveillance and reporting systems in order to control this spread.
- The UK plans to increase the stockpile of antivirals. When choosing which agents to stockpile it must take into account the possible development of antiviral resistance.
- The usefulness of pre-pandemic vaccines depends on their high cross-reactivity but the experimental data do not always seem substantial and this area requires more research. For instance, controlled trials of pre-pandemic vaccines in humans are needed to determine whether immunological priming with a novel subtype is possible and whether latent infection with a variant of that subtype would result in a hyperimmune response. In addition, there is need to explore further some of the practical issues for manufacturing pre-pandemic vaccines, for example how frequently would new stocks have to be made and what are the cost implications?
- The Department of Health has identified requirements for primary care preparedness. However, doubts were expressed on whether these needs can be readily satisfied in a NHS culture increasingly dependent on "just-in-time" provision.
- The recommendation in the Academies' 2006 report for the government to appoint a non-governmental scientist as subject-specific adviser for preparedness planning has not yet been heeded. This independent, expert contribution would still be very valuable in ensuring informed

policy making and coherent strategy. Nonetheless the Department of Health's commitment to informing and evolving the preparedness plans is highly welcome and the discussions today provide a valuable basis for continuing dialogue.

1 Introduction

1.1 Lord Rees PRS and Sir John Skehel FRS FMedSci

In opening the meeting, Lord Rees PRS welcomed delegates and observed that collaboration between the Academies was important to clarify the broad range of priority issues to inform policy-making both in the UK and at the international level. Pandemic influenza typified a new problem but one that would become increasingly common, where the consequences are exacerbated by global interconnectedness. Sir John Skehel FRS FMedSci, Chair of the Royal Society and Academy of Medical Sciences pandemic influenza working group, introduced the meeting, highlighting that the symposium was designed to review recent advances in our understanding of avian influenza, antiviral drug resistance, vaccine development and epidemiology and to explore how scientific evidence has development of the UK pandemic response framework.

2 International avian surveillance and avian vaccines

2.1 Dr Ilaria Capua, Istituto Zooprofilattico Sperimentale delle Venezie, Italy

Dr Capua described the challenges and opportunities for managing avian influenza in the animal reservoir. Controlling H5N1 avian influenza has become an enormous challenge for the veterinary community and for local administrations because of its atypical characteristics: in infecting water fowl, spill over to the wild bird population (50 species of birds are infected) and mammals (10 species) and in the unprecedented scale of infection (endemic in poultry in three continents). For every human infected, there are, over one million animals infected, threatening food security in developing countries. Currently, avian influenza is substantially a disease of animals and control of the animal reservoir is a prerequisite for management of the pandemic potential.

From the veterinary perspective, the main issues are:

Ecology and epidemiology. There is need to understand how the virus moves between different populations, birds in agriculture, pet birds, wild birds, other animals. Historically, avian influenza has been assumed to be spread by people (transporting and trading birds in addition to movements of staff and vehicles) but for H5N1 in Eurasia and Africa, for the first time there was some evidence for westward spread by spillover into the wild bird population, in particular, mute swans. However, following intensive surveillance efforts, it is judged that persistence of H5N1 in the wild bird population in Europe is negligible; reinforcing the view that human activity is the prime instigator for the spread of infection in domestic birds.

Control. The bird rearing and husbandry systems in developing countries represent a difficult logistical challenge to the management and prevention of avian influenza. There are three principal tools in control efforts:

- investment in training and knowledge – interventions tailored in developing countries, appropriate to their infrastructure but also aiming to build capacity (for example, laboratory skills);
- improving biosecurity – in particular through bioexclusion and biocontainment; and
- appropriate use of vaccination, according to the DIVA (Differentiating Vaccinated from Infected Animals) strategy, notwithstanding difficult conditions in the field.

Increasing knowledge on virology and pathobiology. There is need to fill knowledge gaps to identify markers of transmission between avian species (not generalising birds as one species) and to mammalian species; to collect data on prevalence of infection in mammals, perhaps particularly in pigs; and to determine the extent of infection in Africa, with particular regard to the extent of food borne infection. Sharing of animal virus sequences is vital and can be expected to facilitate progress in molecular studies of virulence markers and reassortment dynamics within H5N1 and other avian influenza viruses. To date, there has not been the comparable difficulty in sharing animal virus sequences experienced in sharing human virus sequences.

2.2 Professor Malik Peiris FRS, University of Hong Kong

Professor Peiris further discussed the ecology with regard to the origins and maintenance of highly pathogenic avian influenza H5N1 and evaluated the criteria for pandemic potential. Phylogenetic analysis of the spread of virus clades shows that although some virus groups have crossed over to humans, the diversity in avian populations is much wider and this greater breadth of genetic diversity must be taken into account when developing pre-pandemic vaccines for preparedness purposes. Furthermore, highly pathogenic viruses can be genetically relatively similar but antigenically diverse – the causes of this diversity are not well understood but there is concern that it might be partly driven by suboptimal vaccine use.

Evidence from Indonesia and Vietnam supports the conclusion that humans are more important than wild birds for animal virus movement – and a particular role was identified for live poultry markets in amplifying and disseminating H5N1 as well as in providing the risk to human health.

In addressing the question "will the next pandemic be caused by H5N1?" it was noted that the 1957 and 1968 pandemics did not arise from highly pathogenic avian influenza viruses. In quantifying the potential of H5N1, four main criteria were proposed:

- evidence of transmission to humans or other mammals;
- opportunity for human exposure via poultry/pigs;
- evidence for binding of virus to human receptors; and
- virus capability to undergo rapid reassortment or evolution.

H5N1 fulfils these criteria (the binding to the human form of the receptor is not especially potent) but so do other poultry viruses, in particular H9N2. In terms of communicating the pandemic risk, H5N1 remains the top priority, not because of its inevitability but because of its severity.

The presentations on avian surveillance stimulated wide-ranging discussion:

Prospects for cultural change in developing countries. While education is a key part of the necessary control measures, it is proving difficult to change human behaviour about proximity to farm animals because the low risk of infection at the local level is not perceived as clearly and directly related to such exposure.

Value of animal vaccines. Using a high quality vaccine in a concerted programme in a developing country is a valuable control measure but requires infrastructure and investment of resources. Compliance is often poor and different vaccine products of variable quality are in use. One major problem is the lack of an internationally recognised standard of antigen content for vaccines in agriculture, unlike human vaccines; although the European Medicines Agency (EMEA) in the European Union has guidelines for veterinary vaccines the costs involved in standardisation and use are high for developing countries. There may be a role for the research funding agencies to support more research and development (R&D) for animal vaccine production.

Wild bird surveillance. A significant surveillance effort was initiated early in the history of H5N1 because so little was known about its ecology. Arguably, passive surveillance (collecting dead birds) has been more informative than live bird monitoring, but collecting these data represents a useful opportunity to learn about other avian influenza viruses and species differences. There may be opportunities for new initiatives in surveillance, for example in the northern flyways, such as in Siberia.

Understanding susceptibility to disease. Identifying molecular factors to account for species differences requires systematic comparison of sequences but also understanding of the significance of differences detected in terms of mechanism – and this requires increased effort in, and support of, basic research.

3 Antiviral drugs and resistance

3.1 Professor Frederick Hayden, Epidemic and Pandemic Alert and Response Programme, World Health Organisation

Professor Hayden provided an update on information obtained since the Academies' 2006 report on treatment efficacy, emergence of resistance and the development of new agents.

Treatment efficacy. Pivotal mortality data on seasonal influenza from the Toronto prospective cohort study of 327 hospitalised adults provides a reference point for determining the options for H5N1 management. One third of the seasonal influenza cohort were treated with the neuraminidase (NA) inhibitor oseltamivir, demonstrating substantial reduction in 15-day mortality, even when treatment started relatively late after onset of infection. Observational data from H5N1 patients also indicate a significant reduction in mortality with oseltamivir treatment compared to no antiviral treatment.

The World Health Organisation (WHO) has published (August 2007) an update on H5N1 clinical management with oseltamivir as the primary recommended antiviral agent. Modified drug regimens (higher dose, longer treatment, and combined treatment with amantadine in areas where the virus is likely to be susceptible) should be considered in patients with pneumonia or progressive disease and this may have implications for the sufficiency of drug stocks. One other uncertainty is the clinical relevance of observed variability in sensitivity of H5N1 isolates to oseltamivir, while it is clear that time from illness onset to starting antiviral therapy is an important variable in outcome.

Antiviral resistance. Data from seasonal influenza infections indicate that resistance to membrane proton channel (M2) inhibitors emerges rapidly and frequently during therapy, that resistant variants are fully virulent and transmissible, and that resistance confers cross-resistance to the entire class of M2 inhibitors. At present M2 inhibitor resistance is present in most H3N2 and many H1N1 and H5N1 viruses. Consequently, M2 inhibitor resistance in a pandemic virus is possible.

No equivalent frequency of H5N1 resistance has been recognised to date for the NA inhibitor oseltamivir in seasonal or H5N1 viruses. Initial experimental data from animal models and cell culture indicated that when oseltamivir resistance emerged it was usually accompanied by altered neuraminidase and decreased virulence. Emergence of resistance in H5N1 patients during oseltamivir therapy has been associated with fatal outcomes. Most neuraminidases with mutations conferring oseltamivir resistance are still susceptible to the NA inhibitor zanamivir. However, emerging surveillance data from Japan (where there is the greatest experience in using oseltamivir) shows that while the number of resistant virus variants is still quite low in seasonal influenza, there may be the possibility of low-level transmission (person to person) at the household and community level. Corresponding development and transmission of resistance for the H5N1 virus would then compromise oseltamivir use (a point developed by the next speaker).

Future directions in drug development. In addition to new NA inhibitors in development (both long-acting inhaled and parenterally administered to circumvent low oral bioavailability), there are new viral targets at an early stage of evaluation, for example the viral polymerase (lead compound in Phase 1 of clinical development) and haemagglutinin receptor (lead compound entering Phase 1), and there are opportunities for combination therapy between antiviral drugs and immunomodulators.

3.2 Professor Robert Webster FRS, St Jude Children's Research Hospital, USA

Professor Webster discussed animal model data for H5N1 resistance to antivirals that complement and help to interpret the clinical data. Use of the BALB/c mouse model, even when administering the drug before the infection challenge with H5N1 Vietnam strain virus required relatively extended dosing of oseltamivir (8 days) at the dose equivalent to the usual human dose (10mg/kg/day) to achieve 80% survival. In the ferret model, considered to resemble humans more closely with respect to respiratory tract receptors, a higher dose of oseltamivir (25mg/kg/day) was required for efficacy. If higher doses or longer treatment periods were also needed for H5N1 infections in humans then there would, again, be implications for antiviral stocks but, perhaps of even greater clinical implications, the animal studies also detected appearance of an oseltamivir-resistant variant using total cloning methods (and by direct sequencing in the ferret model).

Other studies in BALB/c mice demonstrated that oseltamivir combined with the M2 inhibitor amantadine was more efficacious against the H5N1 Vietnam strain (genetically engineered to regain sensitivity to amantadine) than the individual drugs. This synergy measured as survival and as virus spread to other organs was achieved without the appearance of antiviral resistance as measured by total cloning. Oseltamivir synergy was also obtained in combination with ribavarin (acting on RNA polymerases).

Animal studies have also been very informative in studying the fitness of H5N1 viruses carrying NA drug resistance mutations in terms of in vitro virus replicability and mouse model survival (transmissibility was not studied). Viruses were prepared by reverse genetics and it was found that N1 subtype resistant mutations were not significantly compromised for replication (N2 and N9 subtype mutations were largely compromised). Possible explanations for the lack of compromised fitness include the high replication efficiency of H5N1 viruses, the high neuraminidase activity of the Vietnam strain or a less than optimal design of oseltamivir for the N1 subtype. If the animal data can be extrapolated to humans then, contrary to previous optimism, if resistance to oseltamivir develops, the resistant variant is viable and pathogenic.

The implications of the animal and clinical data were further explored in discussion. It was generally accepted that, historically, data from the ferret model have been extrapolated to humans but researchers must be cautious when assuming that different H5N1 strains will respond equivalently to antiviral drugs. The good animal efficacy of amantadine and its clinical side effects can be attributed to its high CNS penetration. The animal efficacy of ribavarin in combination may be accounted for, at least in part, to immunomodulation, which raises the possibility of other therapeutic approaches based on interfering with the host cytokine response.

To capitalise on individual clinical research studies, it was suggested that there would be considerable value in creating an integrated clinical and treatment outcomes database to analyse determinants of the response, and to encourage sequential sampling from trials for assessing the development of antiviral resistance.

4 Human vaccines

4.1 Dr George Kemble, MedImmune Vaccines, USA

Dr Kemble reviewed the experience with FluMist in seasonal influenza; in vaccine-naïve individuals (children 24-59 months) a highly favourable risk-benefit profile was observed. In total, approximately seven million doses have been distributed with no new safety signals identified since licensature for this new technology platform of a live attenuated vaccine produced by genetic reassortment.

When considering the demanding issues for increasing production capacity in development of pandemic vaccines, only limited scale-up of production would be possible using the current manufacturing procedures with specific pathogen-free eggs. An alternative MedImmune approach, MDCK cell line cultures, has significant advantages in yield and scale-up for a microcarrier-based

process and a planned clinical programme 2008-2010 under a Department of Health and Social Security contract has a target to produce 150 million doses within a six month period.

MedImmune is also now generating prototype pandemic live attenuated vaccines in collaborative R&D with the NIH. A genetic library of vaccines has been constructed and pre-clinical efficacy assessment in the ferret model shows protection against both homologous and heterologous challenges. Open label, in-patient (isolation unit) studies at John Hopkins University with the vaccine administered by nose drops (H9N2 variant) or nasal spray (H5N1 variant) show that both vaccines are well tolerated and that virus replication is highly restricted. Clinical samples are being banked for future cross-reactivity assessments; studies are now also underway with an H7N7 vaccine.

4.2 Dr Gerald Aichinger, Baxter Bioscience, Austria

Dr Aichinger presented guinea pig and CD1 mice data for a cell culture (Vero cell)-derived H5N1 Vietnam strain whole-virus vaccine, used without adjuvant, achieving high immunogenicity and effective cross-protection against heterologous strains. Clinical Phase I/II dose escalation (n=270) has also now been completed for the vaccine based on the Vietnam strain, evaluating immunogenicity and safety profile when dosed at days 0 and 21 with the primary efficacy endpoint of antibody response 21 days after first and second vaccination. A benign safety profile was observed in terms of systemic and local reaction end points. Evaluation of immunogenicity by seroprotection (micro-neutralisation test) identified a non-adjuvanted dose as the optimum for future trials. Preliminary clinical results on the non-adjuvanted H5N1 Indonesia strain disclosed a similar safety profile for both systemic and local reactions to that shown by the Vietnam strain vaccine and initial immunogenicity data identified a low dose as optimum. Dr Aichinger concluded that Vero cell-derived whole virus H5N1 Vietnam and Indonesia strain vaccines appear similar in safety to seasonal influenza vaccines and show strong immunogenicity. Non-adjuvanted formulations are more immunogenic than adjuvanted ones and the vaccines demonstrate cross-neutralisation against widely divergent H5N1 strains.

Some of the implications of the clinical results were explored in discussion. For example, how well is seroconversion correlated with protection, and is partial protection valuable? What might be the explanation for the complex relationship between dose and induced antibody level and for the apparently paradoxical effect of adjuvant? These questions may be answered in future studies with larger groups and a broader range of doses.

The policy context was also introduced in discussion with the recent recommendation from the Nuffield Council on Bioethics relating to the responsibility of vaccine manufacturers in benefit sharing. The companies responded by saying that they are committed to working with WHO and industry-sponsored bodies to provide cohesion in tackling the global challenges. Discussants suggested that there might be opportunities in study design for the independent conduct of novel vaccine comparison studies. While direct comparisons may be difficult for the industry sector to undertake, companies are doing a significant amount to standardise assays in reference laboratories (an important advance given the historic variability, for example, of the micro-neutralisation assay) and to benchmark reagents and vaccine batches.

5 Epidemiology and social science

5.1 Dr John Edmunds, Health Protection Agency

Dr Edmunds provided a perspective from the Health Protection Agency on work done since the Academies' 2006 report with regard to those recommendations that required the application of epidemiology and modelling expertise.

Social distancing measures
Modelling, using Christmas holidays as a proxy for enforced school closure with data taken from previous influenza outbreaks, showed that closure has an impact on the epidemic pattern, largely confined to school age children.

However, this positive effect of school closure might be offset by the concomitant negative economic impact occasioned by parents staying at home to care for children. Analysis using data from the Labour Force Survey suggested that sectors of the economy would be affected differently by school closure and employees in the Health and Social Care sector would be among those most affected (30% of these employees would have children at home after school closure), potentially exacerbating a shortage of frontline workers. Therefore, in a mild epidemic it may not be cost effective to close schools.

Current stockpile of oseltamivir
The Academies' report queried whether the then-designated stockpile (to treat 25% of the population) would be sufficient in a pandemic. While there will always be uncertainties in the science used to inform preparedness (for example, likely clinical attack rate, possible influence of antiviral use on the course of the pandemic) and while there are also confounding factors in making the economic analysis (for example, whether or not to employ a strategy of triaging to conserve stocks), modelling can help to identify likely benefits and costs in increasing the size of the stockpile.

Calculating the incremental cost per Quality Adjusted Life Year (QALY) gained on the basis of data from previous epidemics, it can be concluded that increasing the stockpile is likely to be cost-effective even if the pandemic is not "severe" and even if there is significant delay in the start of antiviral use, providing that antivirals significantly protect against mortality, a reasonable extrapolation from the Toronto study on seasonal influenza, cited earlier.

Pandemic influenza vaccines in children
Related modelling work has now been done to determine which groups should be targeted by pre-pandemic vaccination if supplies are insufficient for the whole population. Key target groups are those at high risk (the elderly) and virus spreaders (children). Assuming that the primary objective is to prevent early deaths, the conclusion varies according to which scenario is employed (that is, which previous pandemic is used to furnish data) and there is no clear indication as to which group – children or the elderly – should be targeted.

Non-pharmaceutical interventions
Data for modelling were taken from the US experience in the 1918 pandemic but it is difficult to distinguish the effectiveness of individual interventions because they tended to be used in concert. A strategy for social distancing (school closure, reduction in public gatherings) is generally associated with a diminished impact of the epidemic, but more research is needed.

Data on behavioural and attitudinal patterns
There is a lack of baseline data on behaviour in the absence of a pandemic but the European POLYMOD study is now collecting diary-based information on the nature of individual contact patterns in order to improve parameter setting for the models. For the assessment of how individuals might modify their behaviour, a preliminary survey using computer-aided telephone interviews in Europe and Asia is currently evaluating risk perceptions and precautionary behavioural changes associated with social distancing.

5.2 Dr Maureen Baker CBE, Royal College of General Practitioners

Dr Baker contributed a GP's view on pandemic planning in the UK, observing that frontline primary care accounts for 90% of the contacts with the NHS. The GP's role in a pandemic will be to assess those patients at particular risk or those that are developing complications and to provide urgent care for non-pandemic problems which may be exacerbated by a pandemic, in particular by the increased difficulty in admitting non-pandemic patients to hospital.

The GP's best expected outcome from pandemic planning is for a stable society with regard to supply of food, utilities, transport; a reliable supply chain of essential medicines, including antibiotics for secondary bacterial complications; support for the healthcare workforce; and access to specialist advice, with hospital admission for cases that would derive the greatest benefit. GPs assume that pandemic-specific vaccines are unlikely to be available during the first and second waves of a pandemic (in discussion it was noted that GPs also have few expectations of pre-pandemic vaccines but could deliver such vaccines, if available, quickly and efficiently).

The Academies' 2006 report advised that "*…planning and preparedness for a pandemic need to be informed by the best available scientific advice at every level.*" From the GP perspective, some of the expert disciplines that need to be incorporated into the planning include:

- operations research, using modelling and algorithms to determine the most efficient ways to act;
- queuing theory, for example to evaluate probable waiting times and numbers waiting; and
- logistics, for managing the supply chain.

Capitalising on these and other areas of expertise (to support objectives for panic minimisation, assessment of economic impact, scenario-based decision-making, optimisation of telecommunications resilience) can only be successful if planning draws on skills from multiple sectors – including the military and media as well as business and academia. Who should take a lead on this collective engagement? The Department of Health has a major responsibility but, reinforcing the introductory point made by Lord Rees, Dr Baker proposed that the Academies should also continue to grow their active role.

The value of modelling was further exemplified in discussion - in comparing the relative cost-effectiveness of antiviral agents and vaccines (when available). The need to take account of other variables when setting parameters, if models are to be robust, was highlighted – for example, the greater frequency of co-morbidities in the elderly when comparing with children to select target populations for intervention and the impact of population density on behavioural change (taken into account in the POLYMOD study). It was considered important, both for improved modelling and for evaluating interventions, to develop the capacity for real-time tracking during a pandemic.

6 Science, communication and policy

6.1 Dr Mark Walport FMedSci, Wellcome Trust

Dr Walport provided the Wellcome Trust perspective on areas of current scientific uncertainty and policy imperatives within the global context where there is continuing difficulty in identifying and managing human influenza cases. The role of research funders is not only to support good research but also to catalyse collaboration between funding agencies and between researchers, and to facilitate research uptake, translating research into policy and clinical practice. The Wellcome Trust is responding to the global challenges by fast tracking key grant decisions and by funding a broad range of relevant research. Among current projects are those focusing on the epidemiology and transmission dynamics of avian influenza; on the generation and characterisation of human monoclonal antibodies to highly pathogenic H5N1 viruses (although the practicality of these as a treatment remains to be established); on pipeline development for the sequencing of human and animal viruses; and on the pathogenesis of H5N1 in humans in terms of macrophage and other cell-virus interactions (ascertaining the host response to understand why the infection is so deadly).

A consortium of research funders, including the Wellcome Trust, is establishing an initiative to coordinate the development of the research agenda around human influenza: preparing global roadmaps that describe both current studies and future needs for vaccine development, novel drug therapies and epidemiology and surveillance. The Wellcome Trust is also providing support, through its South East Asia programme, to a network for clinical research using protocol-based studies to tackle the impediments to research arising from the low rate of accumulation of cases and their relatively late presentation.

Two major policy concerns were highlighted. First, the unsolved problem for effective sharing of human virus sequences. Current sharing is inadequate and improved sharing would, in turn, encourage further research and collaboration. But in order to improve sharing, it is also necessary to address the needs for those countries where the sequences originate – building their research capacity and access to derived diagnostics and vaccines and this is contingent on building trust between national laboratories and international agencies. Subsequent discussion emphasised that while the research funders must require deposition of sequence data in the public domain as a condition of the research grant, it is also necessary to ensure that the academic contribution is appropriately recognised and that the rapid translation of sequence information into novel diagnostic or vaccine is rewarded.

The second policy priority is pandemic preparedness, to include clarifying the options for supply of pre-pandemic vaccines, identifying specific pandemic vaccines and supporting vaccine manufacturers, developing the UK national plan and understanding the issues for developing countries,as explored throughout the symposium.

The stakeholders for communicating on science and policy in this area are diverse – research funders, researchers, international agencies, national politicians and policy makers, the media and the public-at-large.

6.2 Professor Lindsey Davies CBE, Department of Health

Professor Davies reviewed progress achieved by the new National Framework for responding to an influenza pandemic published the previous week and benefiting from the advice contained in the Academies' 2006 report. The National Framework assumes a worst case scenario as 25-50% of the population with clinical symptoms, 50,000-750,000 deaths, 80,000-1,115,000 requiring hospital care and 15-20% absent from work at the peak. Coherent planning is challenging while the science is uncertain.

The aims of the Pandemic Influenza Preparedness Programme are:

- to minimise illness and death;
- to reduce the burden on the NHS during a pandemic;
- to secure the confidence of the UK population;
- to reduce the economic impact on the UK; and
- to reduce societal disruption as much as possible.

Recent progress in preparedness has included developing the evidence base, reconstituting the scientific advisory group as an independent advisory group, providing the Cross Government Framework, developing the NHS and local plans, conducting a pandemic exercise (Winter Willow 2007) based on existing resources, promoting international cooperation and selecting the countermeasures. Progress is also continuing in other areas, for example in development of the national and local guidelines in infection control and funding Strategic Health Authorities (SHAs) to support their preparedness.

A major programme of public engagement about respiratory hygiene is about to be launched.

In the 2007 Framework, coordinating the response of all government departments, and public and private bodies, the key defence measures are prioritised as promoting hygiene, increasing the antiviral stockpile for treatment (and, perhaps, prophylaxis) as described by Dr Edmunds, and stockpiling antibiotics, expecting that it will take at least two years to accumulate the desired stockpiles. Options for use of pre-pandemic vaccines are being considered. A contract for the supply of pandemic-specific vaccines will be activated when supplies become available. The key message for the public is "stay at home" and use the national FluLine (telephone service to provide information and advice before and during a pandemic) for advice and supply of antivirals.

6.3 Fred Landeg, Defra

Mr Landeg discussed Defra policy on the control of avian influenza: rapid intervention in the UK is important not only because of the potential public health risk but also because of the economic impact of animal infection on international trade and food production.

Illustrated by the recent H5N1 outbreak on the Norfolk/Suffolk border, Defra communication activities on prevention, surveillance and education have concentrated on poultry keepers. The poultry register provides the population denominator data for modelling work; overlaying the wild bird surveillance data onto the poultry register data identifies the priority areas for live sample collection. Surveillance has not detected any highly pathogenic avian influenza in wild birds in the UK so far in 2007. Laboratory rapid diagnosis facilities include validated real-time PCR for H5 and H7, backed up by genetic sequencing that can determine homology between viruses in different outbreaks.

Defra control policy is based on the principles of identifying dangerous contacts, culling quickly and evaluating post-mortem. Defra control activities are set out in the framework contingency plan, revised annually, informed by science and based on risk assessment with key elements including surveillance, movement and gathering controls, housing requirements, vaccination (in zoos) and biosecurity.

General discussion of the planning for human and avian influenza revisited a wide range of issues: how the UK compares with other countries (the UK is in the vanguard for preparedness according to WHO); the need for more behavioural research; whether the Critical National Infrastructure, in particular the supply chain, is sufficiently robust; the selection of farm workers as a key target group for seasonal influenza vaccine, to prevent risk of reassortment of viruses. The UK experience in use of antivirals was also discussed. Some perceive that current NICE guidance is a disincentive to pandemic preparedness; GPs have relatively little experience in use of antivirals but might gain that experience if encouraged to prescribe more for seasonal influenza. FluLine will become the vehicle for distributing antivirals during a pandemic; this requires a change to the prescribing regulations, currently open for consultation and, more broadly, it is important to test the effectiveness of FluLine in seasonal influenza to ensure that implementation plans are robust.

7 Summary of discussion

- The challenge of managing H5N1 avian influenza is significant, given its atypical characteristics in infecting water fowl, wild birds and mammals, and the unprecedented scale of infection. Thus, there is a need to improve control of avian influenza in bird rearing and husbandry systems, to better understand how the virus moves between different populations, and to advance knowledge of virology and pathobiology, for instance, identifying markers of resistance and collecting data on the prevalence of infection in Africa.
- A particular risk has been identified for live poultry markets in disseminating H5N1.
- The breadth of genetic and antigenic diversity of influenza in avian populations must be taken into account when developing pre-pandemic vaccines. A number of poultry viruses, such as

H9N2, fulfill criteria for pandemic potential but H5N1 remains a top priority owing to its severity.

- Avian vaccines are an important control measure but compliance is poor and different products - of variable quality - are used in many developing countries. There is a need for investment in infrastructure and resources, and development of an internationally recognised standard of antigen content for avian vaccines.
- The neuraminidase inhibitor oseltamivir has been shown to be effective in reducing mortality in prospective cohort studies and it is recommended for use as the primary antiviral agent by the World Health Organization (WHO). However, where resistance to oseltamivir has emerged in H5N1 patients, it has been associated with fatal outcomes. Emerging surveillance data shows low-level transmission of resistant variants in seasonal influenza; corresponding development and transmission of resistance for the H5N1 virus could compromise oseltamivir use.
- Data from animal models indicate that higher doses, or extended treatment periods at equivalent doses, are necessary for efficacy, which may have implications for antiviral stockpiling. Data from animal studies also suggest that oseltamivir treatment against certain strains may be more effective in combination with other antiviral drugs.
- Promising data are emerging on the use of live attenuated (MedImmune) and whole-virus (Baxter Bioscience) vaccines against influenza.
- Modelling data has demonstrated the impact of school closure and increases in stockpiling of antiviral drugs on managing a pandemic but more research on the impact of behavioural patterns and social distancing measures is needed.
- There is a need for pandemic plans to incorporate primary care needs such as measures to ensure a reliable supply chain of essential medicines (including antibiotics), support for the healthcare workforce, access to specialist advice and hospital admission for cases that would derive the greatest benefit.
- Whilst it is important to improve sharing of human virus sequences to encourage further research and collaboration, it is also necessary to build capacity and access to derived diagnostics and vaccines in countries where the sequences originate, which is contingent on building trust between national laboratories and international agencies.

We are grateful to the following for their input into the report and symposium:
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Professor Wendy Barclay	Imperial College London
Professor John Beddington CMG FRS	Imperial College
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Mr Nick Blayney	British Veterinary Association
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Dr Pat Goodwin	Wellcome Trust
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Dr Fiona Harrison	Department for Innovation, Universities and Skills
Dr Alan Hay	World Influenza Centre
Dr Fred Hayden	World Health Organisation
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Dr Helen Lee	University of Cambridge
Dr Georgie MacArthur	Academy of Medical Sciences

Dr Nadya Mason	Roche Products Ltd
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Professor Malik Peiris FRS	University of Hong Kong
Dr Hilary Pickles	Hillingdon Primary Care Trust
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Dr Nathan Richardson	Medical Research Council
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