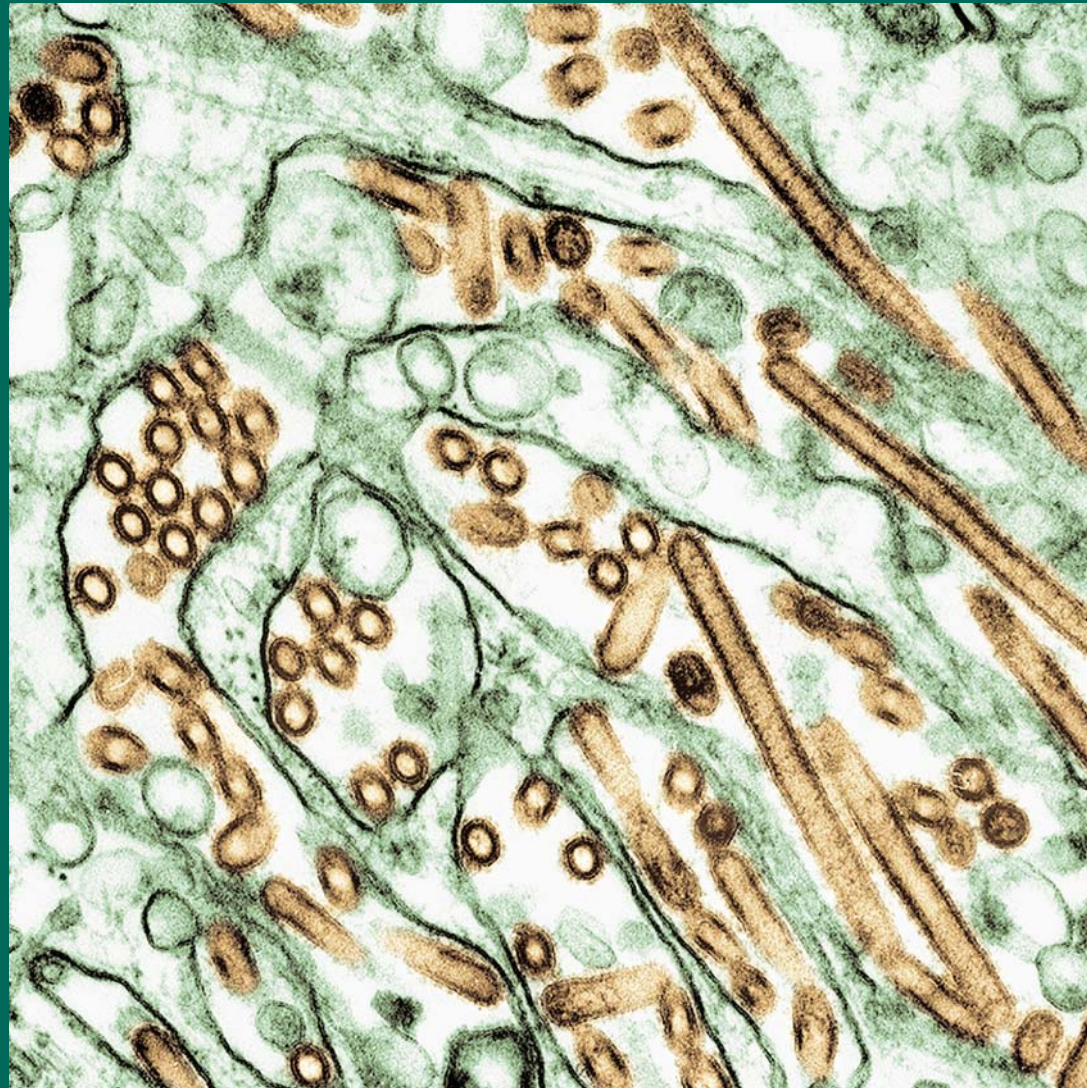


Pandemic influenza: science to policy



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Cover image: Colorized transmission electron micrograph of Avian influenza A H5N1 viruses (seen in gold) grown in MDCK cells (seen in green). CDC/ Courtesy of Cynthia Goldsmith, Jacqueline Katz and Sherif R Zaki

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Summary

Science advice and policy

Influenza pandemics are caused by new influenza viruses that have adapted to replicate and spread efficiently in humans. During the twentieth century there were three influenza pandemics that began in 1918, 1957 and 1968. Each was caused by a virus related to a different avian influenza virus. The threat of a new pandemic resulting from infection with the widely distributed avian H5N1 viruses, although far from certain, has stimulated considerable work at both national and international levels in preparation for this possibility. We consider that planning and preparedness for a pandemic need to be informed by the best available scientific evidence at every level. Whilst the UK is better prepared than most countries in planning for pandemic influenza, there is scope to improve the extent to which scientific evidence is used in policymaking. We accept the concerns expressed to us in the evidence we received that there is insufficient dialogue between government departments and scientists on the use to which scientific advice is put. The UK government should therefore be receptive to, and recognise the value of, close interactions with the scientific community in developing policies for preparedness for any pandemic influenza virus that may emerge.

The focus of pandemic planning in the UK is the Ministerial Committee of the Cabinet on Influenza Pandemic Planning (MISC32), which ultimately guides all activity in the UK for pandemic preparedness. The Government's Chief Scientific Adviser (CSA) and Chief Medical Officer (CMO) have a central function in advising this Committee directly. However, following evidence submitted to this study, we believe this Committee needs a specialist scientific adviser. We therefore recommend the appointment of a leading non-governmental scientist in the area of influenza as adviser to MISC32 to complement the roles of the CSA and the CMO. This scientist should be appointed jointly by the CSA and CMO in discussion with relevant learned societies. This model should be adopted in all future ministerial committees for other animal and human health emergencies.

The role and remit of government science advisory committees in relation to pandemic influenza should be made explicit and the organisational decision making routes should be clarified to show how scientific advice is utilised. In order to incorporate scientists from a broad range of disciplines, and the scientific advice being generated by the range of science advisory committees across government, into a focal point we recommend that the Department of Health's Pandemic Influenza Scientific Advisory Group becomes a cross-government Scientific Advisory Committee on pandemic influenza jointly chaired by the CMO and the CSA. In addition to

relevant cross-governmental representation and the specialist scientific adviser (recommended above), the Committee's membership should be drawn directly from the scientific, veterinary, social science and medical communities as well as from the commercial sector.

We also recommend that the Department of Health, the Department for Environment, Food and Rural Affairs (Defra) and the Civil Contingencies Secretariat continue to ensure the collection and use of evidence from a wide range of sources, both from within and external to government. We urge all departments involved in pandemic preparedness to be open and transparent in their decision making and to make available as soon as possible minutes of meetings and the evidence on which their decisions are based, in keeping with the CSA's *Guidelines on scientific analysis in policy making*.

Avian influenza

The circulation and spread of highly pathogenic avian influenza in wild and domestic bird populations remain of great concern, not least in some developing countries where surveillance systems are either absent or inadequately resourced. We recognise the importance of the objectives of Defra, together with the World Organisation for Animal Health (OIE) and the Food and Agriculture Organization of the United Nations (FAO), to identify, control and eradicate avian influenza as quickly as possible. We urge the UK government to provide additional financial support for their work and to encourage potential donors to do the same.

Epidemiology

A wide range of epidemiological data will have an important role in informing policy decisions and research, both before and during a pandemic. Diagnostic data, such as the genotype and phenotype of the viruses isolated from the first outbreaks, will be important in providing early warning of the transmission of avian influenza to humans and its spread within the population. It is essential that national governments work closely with the World Health Organization (WHO) to increase the effectiveness of current data collection systems and to share the data that are produced.

To ensure the availability of data in a pandemic, we recommend that the UK government leads efforts to coordinate plans for real-time data collection and data sharing, at both the European and WHO/UN level. We hope that recent announcements of agreements to share sequence data within the research community will gain momentum globally. As an essential part of the surveillance data collection, we recommend that the worldwide collection of information on neuraminidase inhibitor resistance should be increased and made available to those organising treatment regimes.

Antivirals

Antivirals are likely to be the first line of defence in the event of an influenza pandemic and as such form the backbone to pandemic preparedness both in the UK and globally. They will be essential in trying to contain an initial outbreak wherever it occurs and in reducing transmission and illness. Owing to the uncertainty about the effective dose of oseltamivir (Tamiflu) for different viruses, we recommend that the Department of Health continues to review the size of the current stockpile of oseltamivir and considers whether the stockpile should be used for large-scale prophylaxis as well as for treatment. We also recommend that as a matter of urgency the Department of Health revisits the decision not to stockpile zanamivir (Relenza) at the same level as oseltamivir, especially for use where resistance to oseltamivir is suspected. Moreover, we recommend that the Department of Health and the Medical Research Council (MRC) support research during the early stages of a pandemic to determine ways to use the current antivirals most effectively and to ensure the continued development of new anti-influenza drugs.

Vaccination

Vaccination will play a key role in a pandemic but its initial use may be limited by the time taken to identify the virus involved and to manufacture, test and distribute the resulting vaccine. There is unanimous agreement that the worldwide capacity to manufacture influenza vaccines will be insufficient in a pandemic. However, there are a number of possibilities for vaccine use that require further research and evaluation as a matter of urgency. These include: the use of adjuvants in dose sparing and to broaden the immune response; the use of whole virus vaccines for the same purposes; and the possibility of population-priming at the beginning of a pandemic with a previously prepared vaccine containing a virus related to the pandemic virus.

We find limited evidence that the UK government is engaging with industry or other experts to develop increased and sustained capacity, or new technologies for vaccine production. We therefore recommend that, as a matter of urgency, the Department of Health takes the lead in organising a work programme with industry and academia for the development of new adjuvants and vaccines. This should be conducted in parallel with

clinical trials to compare directly the effectiveness of current adjuvants with existing H5N1 pandemic vaccines and whole virus vaccines. We also recommend that these studies should be supported by government funding, for example through the Department of Health and the MRC, in partnership with the vaccine industry. More generally, we are concerned that, outside the procurement process, dialogue between the Department of Health, industry and academic immunologists and vaccine researchers is inadequate and should be improved.

Further research

A number of initiatives were announced in 2006 by the Biotechnology and Biological Sciences Research Council, MRC and Wellcome Trust to begin to address some of the research questions relating to avian and pandemic influenza. We encourage research funders to continue to solicit high-quality proposals in areas such as basic influenza research (including studies of pathogenesis), avian immunology, novel antivirals, innovative technologies for vaccine production, novel adjuvants, paediatric vaccination, the use of public health interventions, diagnostics and critical care capacity in a pandemic. If necessary research funders should commission specific research in these areas. We also recommend that research to examine behavioural modelling assumptions in relation to pandemic influenza is commissioned by the Economic and Social Research Council in partnership with other research funders.

Forward planning

Regardless of whether a pandemic occurs in the near future, surveillance, diagnostic systems and research projects put in place now will provide an important basis for the future monitoring of a range of infectious diseases, in addition to avian influenza. It is essential that the increased capacity resulting from influenza pandemic preparedness within the UK should be multifunctional and be applied to other infectious and zoonotic diseases wherever possible. We recommend that the UK government, in collaboration with WHO, OIE and the scientific and medical communities, should review the potential applications of the data collected, with the aim of improving overall global disease surveillance and control.

1 Introduction

1.1 Overview

The scientific understanding of avian and human influenza must play an important role in both short and long term planning to deal with the threat of a pandemic. The Royal Society and Academy of Medical Sciences established a joint working group (see Annex 1 for the membership) to examine the extent to which scientific evidence is being incorporated into preparedness for a pandemic, and to identify areas where policymakers might make better use of the scientific evidence in policy development and contingency planning. The study, chaired by Sir John Skehel FMedSci FRS, was launched in March 2006 with an open call for evidence to consider the following questions:

- What does the scientific understanding (basic research to clinical application) of avian and pandemic influenza, in the short and long term, imply for:
 - treatment: the use of existing, and the development of, new drugs and vaccines?
 - clinical care: diagnosis, basic understanding of the diseases; infection control; transmission?
 - strategies and preparedness for an outbreak: modelling and surveillance?
- What lessons can be learnt from other disease outbreaks and more general public emergencies and the associated emergency planning responses?
- How do wider ethical, social and regulatory issues, including those associated with the development of new technologies or treatments, influence current policymaking and future preparedness?
- How is the scientific evidence (academic, public or commercial) being incorporated into policymaking?

This report comes at a time of considerable investment by countries around the world in preparation for a potential pandemic. In the UK, in response to the increasing spread of avian influenza and in follow-up to its previous report *Fighting Infection* (House of Lords Science and Technology Committee 2003), the House of Lords Science and Technology Committee published the report of its inquiry into the government's preparations to meet the threat of pandemic influenza in December 2005 (House of Lords Science and Technology Committee 2006). The report called for the government to increase its support for international efforts to prevent an influenza pandemic, and to improve its coordination of domestic

contingency planning. The government's response to the report was published in February 2006 (Department of Health 2006). This study by the Royal Society and the Academy of Medical Sciences was initiated primarily to assess the use of scientific evidence in policymaking, relevant to preparing for a possible influenza pandemic.

The call for evidence was met with 29 responses. Six oral evidence sessions took place between April and July 2006 where views were taken from an additional 29 individuals and organisations. A full list of contributors can be found in Annex 2. In many cases their comments have been reflected in the report and both academies are grateful to the individuals and organisations that provided valuable input to this study.

We hope this report will be of interest to policymakers and research funders, as well as to researchers and other stakeholders. It has eight sections:

- Section 1 provides a background to previous influenza pandemics, an introduction to avian and pandemic influenza, the current concerns about transfer of H5N1 avian influenza into humans and preparedness for a pandemic.
- Section 2 discusses avian influenza, covering viral reservoirs, the transmission and surveillance of disease, vaccines for avian influenza and facilities for research.
- Section 3 gives an overview of the epidemiology and surveillance of influenza, both before and during a pandemic.
- Section 4 discusses antivirals – their use in the UK, stockpiling, delivery, resistance, and the need for new antiviral agents.
- Section 5 examines human vaccination including the use of seasonal influenza vaccines, current H5N1 vaccines and the production of pandemic vaccines, and it identifies further research that is needed.
- Section 6 examines the public health measures that are required during a pandemic. It covers the planning and preparation needed, delivery in a pandemic and post-pandemic evaluation.
- Section 7 describes the use of science in policymaking, including the processes for obtaining scientific advice. It also discusses cross-governmental and international coordination and communication.
- Section 8 lists the report's recommendations.

1.2 Background

Three pandemics occurred in the twentieth century, beginning in 1918, 1957 and 1968. In the 1918 'Spanish influenza' pandemic an estimated 40 million people died worldwide. The subsequent pandemics of 1957 and 1968 were similar in causing extensive morbidity but resulted in fewer deaths with estimates of two million in the 1957 'Asian influenza' and one million in the 1968 'Hong Kong influenza'.

All three pandemics were caused by viruses that were related to avian influenza viruses. Avian populations, especially waterfowl, are hosts to large numbers of influenza viruses which are distinguished primarily by differences in the haemagglutinin (H) and neuraminidase (N) glycoproteins that project from the virus surfaces. There are 16 subtypes of haemagglutinin (H1-H16) and nine of neuraminidase (N1-N9). Viruses with numerous combinations of haemagglutinin and neuraminidase subtypes are found in birds, and in humans. The 1918 pandemic virus was classified as H1N1, the 1957 pandemic virus as H2N2 and the 1968 Hong Kong virus, which had the same neuraminidase as the 1957 virus, as H3N2. Currently H3N2, H1N1 and H1N2 are in circulation in humans.

Since the mid-1990s viruses of the H5N1 subtype have become widespread in avian populations in South-East Asia and have caused outbreaks of disease in domesticated poultry and in wild birds. In 1997 these viruses were isolated from 18 cases of human influenza in Hong Kong, six of which resulted in death. The source of the infection was traced to H5N1 influenza-infected birds in the Hong Kong live poultry markets and extensive culling in the markets prevented further human cases. However, two more fatalities were recorded in 2003 in Hong Kong of visitors to South China. Since December 2004 over 250 human cases of H5N1 avian influenza have been treated globally with over 150 fatalities.

The World Health Organization (WHO) now considers that the world is closer to another influenza pandemic than at any time since 1968. There is general agreement in the scientific community that the risk of a human pandemic is elevated because of the wide distribution of H5N1 viruses, but there is a range of opinions about the likelihood of a pandemic, primarily because the H5N1 viruses have now been widely distributed for over a decade without the occurrence of a pandemic. There is also the possibility of a pandemic resulting from infection with other avian influenza viruses, such as H9N2 avian viruses which have caused mild infections in humans in recent years in several countries in Asia.

1.3 Avian influenza

Most influenza virus infections of wild birds are asymptomatic. However, during infections of

domesticated poultry, some viruses that contain haemagglutinins of the H5 or H7 subtypes mutate to become highly infectious and highly pathogenic. The infections by these viruses are systemic rather than restricted to replication in the respiratory and enteric tracts and complete flocks often die within a day of infection.

Although rare in the past, in recent years highly pathogenic H5N1 viruses appear to have spread from domesticated birds to waterfowl. Depending on the avian species, these infections can either cause severe disease or be asymptomatic. In either case, but especially in the latter, the infected birds serve as a reservoir for viruses that are potentially highly pathogenic, which may be the source of their widespread distribution. Transmission by migratory birds may be involved in this distribution, for example by contamination of water by respiratory and faecal excretions, but the importance of migrating birds in the spread of influenza viruses remains to be ascertained.

1.3.1 Methods of control in poultry

The implementation of strict sanitary and biosecurity measures and the restriction of movement of live poultry, both within and between countries where there are avian influenza outbreaks, are important control measures. The logistics of these controls are most easily met in commercial farms where birds are housed in large numbers, usually under strictly controlled conditions. Control is more difficult when poultry are kept in smaller flocks scattered throughout rural areas or on the periphery of urban areas. Vaccination of poultry is also used in some countries, particularly in South-East Asia and China (see section 2.3).

1.4 Pandemic influenza

Influenza pandemics are caused by new influenza viruses that have adapted to replicate and spread efficiently in humans. Genetic analysis of the H2N2 and H3N2 viruses of the 1957 and 1968 pandemics has shown that they arose by genetic reassortment between avian viruses and seasonal human viruses, in which genes for haemagglutinin and neuraminidase glycoproteins were transferred from the avian viruses in the change from H1N1 to H2N2 influenza in 1957, and for the haemagglutinin gene in the change from H2N2 to H3N2 in 1968. In this way the viruses acquired genetic material from the circulating human virus that was adapted for growth in humans but the genes for the glycoproteins that induce antibody-mediated immunity, the haemagglutinins, were from an avian virus. For H1N1 viruses of the 1918 pandemic a similar process may have occurred or an H1N1 avian virus may have infected humans directly without reassortment. In addition to genetic reassortment, mutation of the H2 and H3 avian haemagglutinins was required to allow the viruses to

bind to human cell receptors rather than to the chemically distinct avian cell receptors that the viruses use to infect birds. For H1 viruses the same haemagglutinin mutations were not required for human-to-human spread.

The continued spread of H5N1 viruses in birds increases the opportunities for direct infection of people in contact with them and as a consequence for the selection of mutant viruses that are able to recognise human cell receptors efficiently. Similarly, the more frequently humans are infected with H5N1 viruses the greater the possibility of mixed infections with the current seasonal influenza viruses where genetic reassortment could occur to generate H5N1 viruses that contain genes adapted for growth in humans.

1.4.1 Clinical features

As an emerging disease, H5N1 influenza in humans is poorly understood, and a lack of autopsy data to date has been a limiting factor in understanding more about the disease progression. However, in most patients, the disease caused by the avian H5N1 virus follows an unusually aggressive clinical course, with rapid

deterioration and high fatality. Current data for H5N1 infection indicate an incubation period ranging from two to eight days and possibly as long as 17 days. A recent study of patients infected with H5N1 indicates that the presence of high levels of the virus and the resulting intense inflammatory responses are central to the development of the disease (de Jong et al 2006). Initial symptoms include a high fever and diarrhoea. Vomiting, abdominal pain, chest pain, and bleeding from the nose and gums have also been reported as early symptoms. Almost all patients developed pneumonia that did not respond to treatment with antibiotics. In patients infected with the H5N1 virus, clinical deterioration is rapid. In severe cases, respiratory failure occurs three to five days after symptom onset. Since 2003, over 50% of those people who have been treated for infection with the avian H5N1 strain have died. It is not known if there have been other unreported cases of less severe disease.

In sections 4 and 5 we discuss the use of antiviral drugs that block the replication of the virus in a number of different ways, to treat H5N1 and the potential development of vaccines.

Box 1 UK influenza pandemic contingency plan

The most recent UK Health Departments' influenza pandemic contingency plan was published in October 2005 (UK Health Departments 2005). It is currently under revision and is expected to be republished in spring 2007. This document provides the overall framework for the UK's response in the event of a pandemic, which will be led by the Department of Health. It sets out the work that is required before a potential pandemic emerges followed by a step-wise escalating response as a pandemic evolves. A summary of the plan is given below:

- The contingency plan is based on assumptions derived from current evidence, previous pandemics, expert opinion and mathematical modelling. The assumptions concentrate on the 'most likely' scenario in terms of the origins of a pandemic, its timing, geographical spread and infectivity, the extent and severity of illness and the number of deaths. For example, the plans consider the base scenario to be a cumulative clinical attack rate of between 10% and 50% of the population over 15 weeks, with a likely fatality rate of between 0.37% and 2.50% of those infected. The value used for planning purposes is that one in four people will be infected (a clinical attack rate of 25%) with a 0.37% fatality rate.
- It estimates the impact this fatality rate would have on health and social services, GP consultations and hospital admissions.
- It sets out the extent to which interventions such as antiviral drugs and vaccination might ameliorate the impact of a pandemic and puts forward potential strategies for how they could be deployed in the event of a pandemic.
- It sets out in detail the roles and responsibilities of the main organisations at each phase or wave of an influenza pandemic situation. These are identified as the Department of Health, which will direct and coordinate the UK health response, the UK National Influenza Pandemic Committee (UKNIPC), the Civil Contingencies Committee, other government departments, the Devolved Administrations, the Health Protection Agency (HPA), the National Health Service and various other organisations at a local level. Organisations such as the WHO Collaborating Centre for Reference and Research on Influenza at the Medical Research Council National Institute for Medical Research (NIMR), the National Institute for Biological Standards and Control (NIBSC) and the National Influenza Reference Centres also have a role in the response.

1.4.2 Pandemic preparedness

Most estimates of the impact of a future pandemic are based on extrapolations from previous pandemics. However, the modern world is very different, particularly from 1918. Since then there have been considerable improvements in nutrition, health care, international travel (particularly air travel) and opportunities for interventions. WHO has set out guidelines and recommendations to help individual countries develop their own pandemic preparedness plans (World Health Organization 2005). In accordance with WHO guidelines, the UK government has developed its own plan (see box 1) to support its response to a pandemic, setting out specific measures

and actions required from health and other government departments and organisations at national and local levels.

1.5 Joint Royal Society and Academy of Medical Sciences study

This study was initiated to review current scientific knowledge of influenza viruses and has examined the extent to which scientific evidence has been used as a basis for preparedness for a pandemic. It has identified areas where additional evidence could be used in policy development and contingency planning and makes recommendations to policymakers.

2 Avian influenza

A number of strains of avian influenza are always in circulation around the world of which H5, H7 and H9 currently are known to infect humans. To reduce the threat of pandemic influenza in humans the current H5N1 outbreaks in bird species need to be controlled.

The current H5N1 virus is of special significance as:

- it is unusual for highly pathogenic avian influenza viruses to be so widespread and to be found in wild bird populations and the spread from poultry to wild birds is unprecedented;
- the mortality rate in humans of 50% of those treated is a major concern for public health; if the virus attains human-to-human transmissibility and retains this level of virulence in humans then the impact of an H5N1 pandemic would be catastrophic.

Wild waterfowl and gulls are a natural reservoir for influenza viruses but their current role in the spread of H5N1 is not fully understood. Within domestic poultry populations low pathogenicity avian influenza can often circulate undetected. Highly pathogenic avian influenza infections are much more dramatic and are usually detected quickly within a flock. It has, however, been observed that previous infections with H9N2 may mask the disease signs of H5N1 infection as a result of cross-reactive immunity or through the production of the anti-viral protein interferon (Seo et al 2002).

The focus for the control of avian influenza virus infection is likely to be in domesticated species since they are in closer contact with humans while being farmed and when processed in the food chain. Moreover, it is more feasible that enhanced management practices with increased awareness of disease security can be implemented to control infection and ultimately eliminate it. The tools to control avian influenza in poultry will include vaccination and surveillance. Both will be demanding. Where an outbreak occurs in domestic poultry culling is the most effective disease control method.

2.1 Avian reservoirs and transmission

The major reservoir of avian influenza viruses is the Anseriformes (ducks, geese and swans). Typically, these host species harbour low pathogenicity avian influenza viruses but two subtypes of low pathogenicity avian influenza, H5 and H7, can rapidly evolve into highly pathogenic avian influenza upon transfer to chickens and other Galliformes such as turkeys and quails.

The highly pathogenic H5N1 virus emerged as a disease problem in domestic fowl in southern China in 1997 and again in 2003. The 2003 H5N1 outbreak rapidly spread to domestic fowl in countries in South-East Asia including Indonesia, Thailand and Vietnam probably as a result of commercial trading. H5N1 has also spread to wildfowl, which has led to wide geographical dispersal as a result of bird migration.

There is only limited understanding of the factors influencing transmission of influenza viruses within species and between species. This knowledge is needed to assess the risk of spread of viruses in the field from domesticated or wild birds. Investigations are required into the parameters of virus host range within bird species. These studies are likely to include investigations of cross-species transmission between infected ducks, geese and poultry and of the characteristics of viruses as they are transmitted between species. In this connection, current H5N1 viruses have caused fatal systemic infections of tigers, leopards and domestic cats. Infections of cats will need to be considered in the epidemiology of H5N1.

2.2 Avian influenza surveillance

The World Organisation for Animal Health (OIE) has responsibility for coordinating and setting guidelines for global surveillance of avian influenza, principally in domestic poultry, for collating and publishing global surveillance data and for defining procedures for the control of avian influenza outbreaks. In general, standards for animal health are more tightly regulated globally than are those for human health, with OIE having a statutory responsibility for animal health under World Trade Organization (WTO) rules. This means, for WTO members at least, OIE regulations have something close to the force of law (albeit mediated by national or supranational bodies, such as the European Commission). Surveillance of wild bird populations is mandated by a recently adopted European Directive (2005/94/EC).

Under OIE rules, it is compulsory for member states to report all outbreaks of highly pathogenic avian influenza in domesticated or wild birds. To confirm an outbreak, virus detection and genotyping must be undertaken by an OIE reference laboratory (eg the Veterinary Laboratories Agency (VLA), Weybridge). However, not all countries have provided viral samples in practice, and certainly not for every outbreak. From the evidence we received, concerns exist about the availability and sharing of avian influenza virus isolates and related data – particularly in relation to H5N1. These are discussed in greater detail in section 3.2.1.

Outbreaks, particularly in wildfowl, may not always be obvious in countries with poor surveillance and few keen volunteer ornithologists. The infrastructure for animal disease surveillance is completely lacking in many countries, to the extent that the first signal that H5N1 has reached several areas of the world has been the detection of human cases. Surveillance data are often limited, with only the number of 'outbreaks' per region reported. Definitions of an outbreak may also differ between countries and may be reported as a single infected farm, an affected village, or even an affected province. **Innovative methods for improving surveillance of avian influenza and other zoonotic diseases in areas lacking animal disease surveillance infrastructure should be developed. We recommend that OIE and FAO consider developing sentinel networks of farmers or villages in these regions for outbreak reporting (Recommendation 1 (R1)).**

Wild migratory birds have a potential role in the international spread of H5N1 and measures need to be in place to minimise the transfer from wildfowl to domestic birds and humans. To date, H5N1 has not spread among wildfowl in the UK, the dead swan found in Celladyke in April 2006 being an exception of uncertain provenance. However, given that the virus has spread out of East Asia to Western Asia, Eastern Europe, the Baltic coast and West Africa, it is probably only a question of time before it reaches the UK.

Studies to increase knowledge of the role of wild birds in the spread of infection should be expanded both nationally and internationally and involve collection of data and collaboration of major international agencies specifically for this purpose. In the UK these bodies would include the Department for Environment, Food and Rural Affairs (Defra), VLA, ornithological charities and the HPA (R2). A European Research Network for Early Warning of Influenza Viruses in Migratory Birds in Europe (NEW_FLUBIRD) has been established in which the VLA and the Wildfowl and Wetland Trust UK are participants. **The surveillance and collection of samples from wildfowl are labour intensive and we recommend that participants in the surveillance networks should receive adequate funding from Defra and the European Commission to continue to operate efficiently in the UK, Europe and globally (R3).**

In most circumstances highly pathogenic avian influenza infections are plainly evident due to the sudden mortality observed in domestic poultry. This has not always been the case for H5N1 infection and it may be linked to the presence of other avian influenza virus infections (such as H9N2) in poultry populations, particularly in the non-intensively reared sector. Surveillance needs to be carried out for infection of domesticated species with avian influenza viruses of all subtypes. Research should be done to ensure that

surveillance is effective, virus detection is sensitive, and a wide range of avian species is examined and accurately identified. It is important to ensure that modern molecular methods for virus detection are not allowed to displace traditional virus isolation since complete analysis of the viruses depends on their isolation. The new methods should complement traditional virology.

We recommend that research should be done by Defra and the Biotechnology and Biological Sciences Research Council (BBSRC) to ensure that procedures for avian influenza virus collection are robust, that the subsequent transport of samples is secure, and that methods used for virus isolation and characterisation are the most appropriate and up-to-date (R4).

The transmission of an avian virus to humans is more likely to occur from domestic fowl than from wildfowl because of increased frequency of contact, although transmission from wildfowl is not implausible. It is unlikely that a pandemic caused by the H5N1 virus will first arise in the UK because there is limited contact between humans and domestic poultry. All countries harbouring H5N1 in birds need to have active surveillance of bird-to-human transfer and of human-to-human adaptation of the virus. Surveillance systems to detect the emergence of a pandemic are discussed in section 3.2.

2.3 Avian influenza vaccines

Domestic and commercial birds are not routinely vaccinated against avian influenza in most countries. During the current H5N1 avian influenza outbreak, some affected countries are attempting to eradicate the virus from their domestic and commercial flocks by vaccination as well as by culling (eg China and Vietnam). Other countries, for example Hong Kong and Thailand have employed culling exclusively.

Although it is clearly not possible to remove the H5N1 virus from the many species of wild birds that now carry it, often without signs of infection (see section 2.1), an extensive domestic bird vaccination policy in countries such as China and Vietnam may reduce the risk of transmission of the virus between birds, and possibly as a consequence to humans. Although difficult to assess, the absence of cases of H5N1 human infections in Vietnam since August 2005 may be a result of its vaccination policy and public education about high risk practices, such as handling sick chickens. Within Europe, the Netherlands and Italy are the only countries to have initiated an avian influenza vaccination programme.

The UK's policy is that poultry will not be vaccinated in advance of an outbreak of avian influenza. The Deputy Chief Veterinary Officer explained in his evidence to this study that this is because of the well-documented limitations of the vaccines currently available (Department for Environment, Food and Rural Affairs

2005). Defra believe that the most effective means of protection are the maintenance of a high standard of biosecurity; separating poultry from wild birds; and careful surveillance for signs of disease. It was suggested to us that vaccination might be employed if avian influenza became endemic in the wild bird population at a level so high that there was frequent 'spillover' into the domestic poultry population. In September 2006 Defra placed an order for ten million doses of avian influenza vaccine for potential use in poultry and other captive birds in the UK. This vaccine could be used against both H5 and H7 viruses. This is in addition to the 2.3 million doses of vaccine Defra bought earlier in 2006 for a possible preventive vaccination of zoo birds.

Defra does not have a specific committee to advise on developments in vaccines and new technologies for the control of avian influenza and other animal diseases, though some advice on vaccines comes through the VLA. The processes for evaluating the evidence used to procure avian influenza vaccines are unclear, as is the way in which scientific advice is incorporated into decision making. The establishment of an animal vaccination advisory committee by Defra to include independent experts would ensure an evidence-based approach. **We recommend that Defra should set up a vaccination committee, similar to the Department of Health's Joint Committee on Vaccination and Immunisation. This committee should advise the department on the development of its vaccination strategies across all animal diseases, including avian influenza (R5).**

Research into the efficacy of vaccination of domesticated species against avian influenza is a high priority. Laboratory studies need to be undertaken to quantify the levels at which vaccinated birds shed viruses, following not only from optimal vaccination practices but also following suboptimal vaccination. The possibility of selecting virus variants by vaccine selection, either immune escape mutants or viruses with increased virulence, needs to be assessed. These studies will require detailed analysis of viruses that may be shed from vaccinated and challenged birds. Priorities for research on existing vaccines include:

- detailed analysis of the virus-shedding trajectory;
- the duration and level of virus-shedding following challenge of vaccinated birds;
- the effect of suboptimal vaccination on protection and virus-shedding;

- detailed characterisation of virus shed from vaccinated birds following challenge, to check for the appearance of antigenic variants and;
- the effects of age, breed and other factors that may influence vaccine efficacy.

New approaches to developing avian influenza vaccines are needed. These could include the use of new adjuvants (compounds which increase the efficacy of vaccines when given at the same time) and the development of new vaccine vectors such as the recently developed Newcastle Disease Virus, which expresses the influenza virus haemagglutinin. Other possibilities include the use of genetically engineered Marek's Disease virus vaccine, or infectious bronchitis virus vaccine that can be used at an early age or for *in ovo* vaccination. Each new approach will need detailed study for efficacy and any vaccine-induced selection of virus variants. **We recommend that as part of their current calls for proposals, research funders, in collaboration with Defra and the vaccine industry, should solicit proposals from the research community to address these research priorities for avian influenza vaccines (R6).**

2.4 Avian immunology

Although studies undertaken in domesticated birds have contributed considerably to our knowledge of avian immunology generally, advances in our understanding of the host response to influenza virus infection are limited. There is very little understanding of the cellular immunology of poultry. Research needs to address:

- how host genetics influence the production of neutralising antibody and protection in response to infection or vaccination;
- the location and nature of virus-specific immune responses to both low pathogenicity and high pathogenicity avian influenza viruses;
- whether protection of poultry from lethal H5N1 infections occurs as a result of previous infection by another avian influenza virus, for example H9N2, and how disease signs might be suppressed;
- the application to avian influenza infections of the techniques for studying the immune system of chickens as they develop.

2.5 Facilities and research

High-quality scientific research and surveillance are being funded by Defra within the remit of the VLA, but we remain concerned that wider research to understand more about avian influenza is not being supported. **We recommend that Defra, in collaboration with the BBSRC and the Medical Research Council (MRC), examines areas where further research could be funded such as basic avian influenza research and avian immunology (R7).**

Work in the UK with highly pathogenic avian influenza viruses is required to be done in high-containment laboratories and animal houses to ensure that viruses

are not released from the laboratories. There are six laboratories in the UK equipped to work with highly pathogenic avian influenza which in some cases are ageing and require significant improvement work. Those organisations with suitable animal facilities for handling highly pathogenic avian influenza-infected poultry and birds are the Institute of Animal Health (IAH) Compton and VLA Weybridge. It is anticipated that the merger of the VLA Weybridge and IAH facilities for avian influenza research will result in an overall loss of facilities for work with highly pathogenic avian influenza. It is essential that the option to expand these facilities should be investigated further. **We recommend that the government should provide increased funding to expand high containment facilities to enable vital research in this field (R8).**

3 Epidemiology and surveillance

3.1 Introduction

This section focuses on the epidemiology and surveillance of human disease before and during an influenza pandemic. It considers some of the issues concerning sharing of data and aspects of epidemiology and mathematical modelling. Surveillance for avian influenza is discussed in section 2.

3.2 Human pre-pandemic surveillance

WHO has responsibility for coordinating global influenza surveillance, determining pandemic alert levels (and hence 'declaring' a pandemic), setting international recommendations for surveillance and pandemic preparedness, and investigating and responding to clusters of disease.

The scientists that we took evidence from believe that the existing WHO-coordinated system of surveillance works well. The WHO Global Influenza Surveillance Network was established in 1952 and its activities have progressively expanded in relation to international coverage and the antigenic and genetic characterisation of viruses. The quality and breadth of the surveillance are essential aspects of the annual recommendations provided by WHO on the composition of influenza vaccines for use in the northern and southern hemispheres (see section 5.2).

Globally, WHO coordinates influenza surveillance through the four WHO Collaborating Centres (in Atlanta, London, Tokyo and Melbourne), which provide state-of-the-art strain-typing and genotyping facilities and expertise to WHO centrally and to National Influenza Centres. The first WHO Centre (the World Influenza Centre) was established under the auspices of the MRC at the NIMR in London, and the UK has played a major role in the scientific and technical development of the international surveillance system.

At a country level, there are 112 WHO-recognised National Influenza Centres in 83 countries that coordinate national surveillance. These centres vary dramatically in capabilities. In addition, in 2000 WHO established a more general emerging infection surveillance network: the Global Outbreak Alert and Response Network (GOARN) (World Health Organization 2000). The input of information to GOARN mainly comes from the Global Public Health Intelligence Network (GPHIN), which is a largely automated information-gathering tool that searches the World Wide Web for reports of unexplained disease clusters. GPHIN is thought to have provided the first international early warning of the 2003 outbreak of

Severe Acute Respiratory Syndrome (SARS), by highlighting reports of a cluster of severe respiratory infection in southern China (World Health Organization 2003).

In contrast to the situation in birds (see section 2.2), there is no legal requirement on member states of WHO to report avian influenza infections in humans, though this is expected to change under the International Health Regulations adopted in May 2005 and scheduled to enter into force in June 2007 (World Health Organization 2005b). However, international pressure means that most member states report cases they detect, though not always as promptly as would be desirable.

The quality of surveillance for human infections with H5N1 is highly variable and, although many countries in South-East Asia have made efforts to improve surveillance, other regions have almost non-existent surveillance infrastructures (eg most of sub-Saharan Africa). When a suspected human H5N1 case is detected, local teams, often with invited WHO support, investigate the case and look for contacts and evidence of a larger-case cluster. Where possible, viral samples are taken and sequenced, though not all countries permit export of samples. In newly affected areas, viral samples are not always immediately available and often those infected have died and funerals have been conducted without samples being taken.

Where a cluster of cases is detected in a single location at a single time, investigations have greater urgency as evidence for human-to-human transmission is sought. In such circumstances, the WHO Pandemic Influenza draft protocol for Rapid Response and Containment (World Health Organization 2006) can be invoked, with use of targeted antiviral prophylaxis, contact tracing, quarantine and other social distance measures such as school closures, household quarantine and travel restrictions intended to reduce contacts in the community.

Modern genetic sequencing methods allow rapid diagnosis in index cases of influenza virus strains and variants. Thus in January 2006, within 48 hours of receiving samples from suspected human cases in Turkey, the WHO Collaborating Influenza Reference Centre in London was able to issue the full genome sequence of the virus and to identify a mutation potentially affecting binding to human sialic acid receptors in one of the patients.

There should, however, be no complacency about the WHO influenza surveillance system. Despite the advances outlined above, there remain many

underdeveloped areas of the world where it is perhaps unlikely that human-to-human transmission of H5 infection would be identified early enough to contain the outbreak. It is important that national authorities work closely with WHO to increase the effectiveness of the system, including its global coverage and its scientific and technical capacity.

We recommend that European Union (EU) member states, including the UK, should work closely with WHO to support scientific research relevant to the quality and value of influenza surveillance and research to improve the understanding of the epidemiology of influenza (R9).

Whether or not the current avian H5N1 virus causes a pandemic in the near future, surveillance and diagnostic systems put in place now should provide an important basis for the future monitoring of a range of infectious diseases, in addition to avian influenza. It is essential that the increased capacity within the UK should be able to be applied to other infectious and zoonotic diseases wherever possible. **The Department of Health and Defra, in collaboration with WHO and the scientific and medical communities, should review the potential applications of the data collected in infectious disease surveillance generally (R10).**

3.2.1 Data sharing

As highlighted in section 2.2, the working group heard concerns that there are problems with the availability and sharing of both human and avian influenza virus isolates and other scientific data, particularly in relation to H5N1. Greater sharing of data would accelerate research on the virus. **We recommend that genetic, antigenic and pathogenic data relating to new avian viruses, especially H5, H7 and H9 subtypes, should be made widely and rapidly available. In particular, samples of virus isolates should be made available as a matter of urgency to bona fide laboratories for research and development purposes (R11).**

In a letter to Nature, 70 scientists proposed the creation of a Global Initiative on Sharing Avian Influenza Data that would promote the sharing of data via public databases within six months of it being analysed and validated (Bognor et al 2006). Such sharing of virus strains is an essential aspect of international collaboration and pandemic preparedness. **We recommend that the UK government supports the Global Initiative on Sharing Avian Influenza Data and ensures that government and publicly funded laboratories put in place plans to publish all surveillance data (R12).**

3.3 Surveillance during a pandemic

In the UK, the Department of Health and the HPA are currently planning real-time surveillance systems for use during a pandemic. There will inevitably be constraints on what data it is possible to capture during a pandemic, owing to the extreme demand for healthcare services. The priority is therefore to collect data that will inform decision makers on the progress of the epidemic (eg its rate of growth and whether it has peaked), the burden on the healthcare system (including the availability and usage of antiviral drugs and vaccines), mortality, and the effectiveness of the interventions in place. Real-time surveillance will integrate data from: sentinel surveillance of disease reported to General Practitioners (GPs); the disease-reporting and drug distribution system put in place to deliver antivirals to the population in a pandemic (see section 4.6); hospital patient records and death registrations.

In the earliest stages of a pandemic there will be an urgent need to collect very detailed information on the first few hundred cases arising in the UK, in order to enable age-specific mortality rates to be estimated and the risk factors for severe morbidity to be characterised. Such data may also allow key epidemiological parameters to be determined – in particular the reproduction number and the doubling time of the epidemic. These estimates will be important for updating epidemic models and thereby predictions of the speed of spread and impact of the pandemic in the UK. Clinical data on the first few hundred cases are also likely to be critically important for informing best clinical practice in treating cases; for example in determining whether antiviral drug dosing levels or schedules need adjustment for the particular strain of virus encountered.

It would also be beneficial if detailed case data were available on the first cases in the source country or in other countries affected before the UK. Rather than waiting for data to be collected in the UK, this would allow earlier refinement of the UK pandemic plan and clinical treatment protocols. However, the availability of such data cannot be currently relied upon.

In the UK, the HPA will have the primary role in analysing real-time surveillance data and providing reports to the Department of Health and the government's emergency response committee COBR. The membership of COBR depends on the nature of the issue and it, and the HPA, will be supplemented by external epidemiological experts as needed.

Internationally, it is much less clear-cut what data will be available once the pandemic has really become

established. Many western countries (eg the US, France and Germany) have plans to collect similar data to the UK, but in many cases these are not currently as developed as the UK's. In the less developed world, systematic surveillance is likely to be patchy or non-existent. In many countries, the only data that are likely to be available are the absence or presence of infection in a region. **We recommend that the UK government should lead efforts to coordinate plans for real-time data collection and data sharing during a pandemic, at the EU, EU and G8, and WHO/UN level. Achieving consistency of the detailed data collected on the first few hundred cases in each country and the summary data collected thereafter could offer significant benefits to collaborating countries prepared to share data in real time, since the data collected in a country affected early could aid final preparedness planning in countries not yet affected (R13).**

3.4 Epidemiological analysis and modelling

Epidemiological analysis consists of much more than just epidemic modelling. The statistical analysis of case data from unexplained clusters of H5N1-like or influenza-like respiratory disease will, in combination with detailed epidemiological investigation on the ground, play a key role in determining whether a new virus has emerged that is capable of being transmitted from person-to-person at a rate capable of causing a self-sustaining epidemic.

Mathematical modelling has a key role in pandemic planning by giving quantitative estimates of the likely pattern and speed of spread of a pandemic and the possible impact of different interventions, such as antiviral treatment and prophylaxis (see section 4), vaccination (see section 5), school closure, other 'social distancing' and travel restrictions.

Models are only as reliable as the estimates of the biological and epidemiological parameters they require. In the case of pandemic influenza, although it is possible to use data from past pandemics to constrain some important parameters (such as the transmissibility of a new pandemic influenza virus), many uncertainties remain. This is in part owing to the many societal changes that have occurred since the last pandemic in 1968 (eg much greater international travel, reductions in household sizes), and in part because H5N1 infections in humans have very different clinical characteristics from past pandemic viruses or seasonal influenza.

In particular it is not possible to give meaningful predictions of the likely mortality that will result from future pandemics, given that H5N1 has a much higher human lethality than any previous influenza virus seen (currently greater than 50% of those treated).

Furthermore there is a complete lack of scientific knowledge about whether the current avian virus would be likely to become less lethal if it became transmissible from person-to-person. It is not even possible to estimate a meaningful upper bound on lethality. The Department of Health's use of 0.37% and 2.50% case mortality scenarios for planning is solely based on mortality seen in the 1957 and 1918 pandemics.

A further uncertainty concerns the likely impact on transmission of non-pharmaceutical interventions (see section 6.2.2) such as mass use of personal protective equipment (ie masks) or social distancing measures. In theory such measures might be highly effective at reducing transmission if rigorously and correctly applied, but the reality, given imperfect adherence to policy recommendations by affected individuals and communities, is likely to be much different. Unfortunately, almost no population data currently exist to quantify the effectiveness of non-pharmaceutical interventions, as highlighted by a recent WHO working group paper (World Health Organization Writing Group 2006).

In addition, modelling to date has not incorporated the possible impact of spontaneous reductions in population contact rates in the face of a lethal pandemic. It is not known how the public would react; for example, changes in the population's behaviour were observed in Singapore and Hong Kong during the 2003 SARS outbreak. Again, no quantitative data on the likely impact of such measures on transmission currently exist. This is discussed in greater detail in section 6.3.3. **Additional epidemiological studies are needed to analyse existing disease and social data to estimate the likely impact of social distancing measures (especially school closure) on a future pandemic and to examine the evidence for population behavioural changes in a pandemic that might affect disease transmission (R14).**

Current modelling should therefore be best viewed as exploring the range of feasible future pandemic scenarios, rather than providing detailed predictions. The UK has been traditionally strong in developing the field of epidemic modelling generally, though not until recently in modelling influenza epidemics and pandemics. Expertise in modelling human influenza is largely restricted to two centres in the UK: the HPA and Imperial College London. Both these groups have been advising the Department of Health since 2005 on pandemic planning. The modelling results from the two groups, although not identical, have had sufficient consistency to enable broad conclusions to be drawn about the relative effectiveness of different control measures to be drawn.

During a pandemic, epidemiological analysis and modelling will play a key role in interpreting real-time

data. Outputs derived from detailed data collected on the first few hundred cases will include estimation of the case mortality ratio, transmissibility, the age distribution of morbidity and mortality and the impact of interventions (treatment, prophylaxis, vaccination, isolation, social distancing measures). Later in the epidemic, modelling will provide predictions of epidemic trends; eg time to the peak of the epidemic, peak clinical attack rate, likely cumulative attack rate, healthcare burden through time, and likely absenteeism. These estimates will be crucial for strategic and operational decision making in the management of a pandemic. The HPA has the primary role in providing the UK government with the results of epidemiological modelling and analysis during a

pandemic, working closely with key academic research groups with expertise in this area.

Internationally, many more groups in the US and other EU states have expertise in influenza modelling, with several being actively involved in advising their national governments and more widely. There are informal networks between subsets of these researchers, but no overall structure within which to collate results, compare approaches or present analyses to policymakers in a consistent manner. It would be advantageous if long-term mechanisms were put in place for enhancing international coordination of epidemiological modelling and analysis, especially where modelling is directly influencing policymaking.

4 Antivirals

4.1 Introduction

Antiviral drugs have been developed for the treatment of a number of viral infections. In the case of influenza, antiviral drugs are available that differ in their mode of action, side effects, routes of administration, dosages and costs. Treatment with antiviral drugs is expected to shorten the duration of the disease, alleviate symptoms and reduce complications and serious illness.

4.2 Existing antivirals

One of the major developments that has influenced preparations for future influenza pandemics is the availability of two groups of licensed anti-influenza drugs. One of the groups, the amantadine-related compounds (M2 inhibitors), was discovered in the 1960s to block virus production in cell cultures and in animals. These drugs, such as Symetrel, target the virus membrane proton channel, M2, and by blocking the channel inhibit replication of the virus. Drugs of the second group, neuraminidase inhibitors, include oseltamivir (Tamiflu) and zanamivir (Relenza). These compounds target the virus membrane neuraminidases, which remove sialic acid from virus and cellular glycoproteins during infection. This activity is essential because influenza viruses use cell surface sialic acids as receptors and if neuraminidase activity is blocked, newly produced viruses bind to the infected cell surfaces and are not released to spread the infection. These observations prompted the search, beginning in the 1960s, for small molecule inhibitors, which was further stimulated by determination of the three-dimensional structure of the neuraminidase molecule by X-ray crystallography in 1983 (Varghese et al 1983).

4.3 Antiviral use and resistance

Experience of the use of amantadine-related M2 drugs has shown that they can cause neurological side effects and that they readily select transmissible-resistant viruses; for example, many of the H3N2 influenza viruses isolated in the US since 2004 are resistant. The neuraminidase inhibitor drugs oseltamivir and zanamivir are well tolerated, although oseltamivir occasionally causes nausea. In clinical trials of either drug few resistant viruses were recovered. In cell culture, resistance has been observed to result from mutations not only in the neuraminidase but also in the haemagglutinin receptor-binding glycoprotein. Studies have indicated that, unlike amantadine-resistant viruses, the neuraminidase inhibitor-resistant viruses are

frequently unstable and their enzyme activity and infectivity are compromised (McKimm-Breschkin 2000).

There have been limited observations to date on the use of oseltamivir in humans infected with H5N1. However, the use of oseltamivir in one study to treat H5N1 infections in Vietnam resulted in the isolation of resistant viruses from two out of eight patients, both of whom died (de Jong et al 2005). Additional studies of the production of resistant mutants during seasonal H3N2 influenza in Japan concluded that 18% of the viruses isolated from a group of children treated with oseltamivir contained mutant neuraminidases (Kiso et al 2004). These observations highlight the possibility that extensive use of neuraminidase inhibitors could generate large numbers of resistant viruses and therefore severely caution against dependence on one anti-influenza drug for use in a pandemic. They will also re-stimulate the search for compounds that block influenza virus replication by targeting, in addition to the neuraminidase and the M2 proton channel, other essential virus processes such as RNA polymerase activity and haemagglutinin sialic acid receptor binding. The use of additional drugs in combination with both anti-neuraminidase and anti-M2 compounds could be invaluable.

4.4 The use of antivirals in the UK

In the UK, three antiviral agents – oseltamivir, zanamivir and amantadine – are currently licensed for the treatment of all strains of influenza: two of these, oseltamivir and amantadine, are also licensed for prophylaxis. Although antivirals are licensed for the treatment of seasonal influenza in the UK, the current guidelines from the National Institute of Health and Clinical Excellence recommend vaccination as the first line of protection (see section 5).

In the UK, antivirals are recommended for treating influenza-like illness only in those considered to be at risk of developing complications from infection and providing treatment can commence within 48 hours of symptoms starting. Use of antivirals in the UK has therefore been limited since their launch in 1999. Most experience of the use of antivirals for treatment of seasonal influenza comes from Japan, where oseltamivir is used regularly.

In an influenza pandemic in the UK, the current intention is to use oseltamivir for treatment of cases with clinical symptoms of influenza infection (see box 1). Prophylactic use on a large scale is not currently envisaged by the Department of Health.

4.5 Antiviral stockpiling

As a result of the problems with amantadine resistance and the fact that the current H5N1 viruses are susceptible to neuraminidase inhibitors, WHO and national governments have focused on stockpiling neuraminidase inhibitors, in particular oseltamivir, which is manufactured by Roche. The demand for antivirals for stockpiling has been substantial since the recent outbreaks of H5N1. However, both oseltamivir and zanamivir have a sufficiently complicated and long production process to limit their availability. To date, over 70 governments have sought contracts for contingency stocks, with 400 million courses of oseltamivir being supplied around the world by the end of 2006.

The UK government placed an order for 14.6 million courses of oseltamivir in March 2005, to cover approximately 25% of the population. This order was completed in September 2006. The selection of this particular drug was largely on the basis of its tablet formulation and its commercial availability. The stockpile is being held at several locations around the country, though not in hospitals. No advice appears to have been sought from the HPA, the manufacturers or other external experts regarding the size of stockpile that was ordered.

Key questions exist about whether a 25% stockpile will be sufficient to treat all clinical cases in a pandemic and, indeed, whether the actual pandemic virus will be susceptible to the drugs. In its evidence, the Department of Health told us that the strategy around the stockpiling and use of antivirals remains constantly under review and it is looking at the practicalities, risk, benefits and costs of extending the stockpile of antivirals beyond 25% of the population.

In addition to oseltamivir many countries have placed smaller orders for zanamivir. However, the Department of Health has not to date placed an order for zanamivir, although it has held discussions with its manufacturer, GlaxoSmithKline (GSK). Observations that oseltamivir resistance occurs in H5N1 viruses that retain sensitivity to zanamivir suggest that both drugs should be in the UK's stockpile. There are indications that higher doses of oseltamivir will be necessary for successful treatment of H5N1, and therefore a larger stockpile may be required of both oseltamivir and zanamivir (see section 4.7). The stockpile needs to be large enough to cope with multiple waves of a pandemic because the interval between waves may not be long enough to manufacture and purchase more antivirals.

We recommend that the Department of Health continues to review the size of the current stockpile of oseltamivir and as a matter of urgency revisits the decision not to stockpile zanamivir at

the same level for use especially where resistance to oseltamivir is suspected (R15).

An additional factor influencing the size of the stockpile that will be required is the preferential prescription of the drugs for healthcare or other essential workers as a prophylactic, as well as the choice generally between prophylaxis following exposure and therapy following infection. Such decisions will depend on observations on the effectiveness of treatments during initial outbreaks. The Department of Health stated in its evidence that the possibility of adding household prophylaxis to the current treatment strategy is under review.

4.6 Methods of delivery

The majority of the UK's stockpile of oseltamivir is supplied as packs of ten 75mg capsules. It is also available as the active pharmaceutical ingredient, supplied in bulk, which can be reconstituted as an oral suspension with benzoic acid and water. This oral suspension will be used at a dose based on weight for children under five years of age, who are too young to take the drug in capsule form. Roche is conducting research to examine alternative formulations of oseltamivir such as intravenous administration for individuals who are unable to take oseltamivir in capsule form.

Zanamivir is inhaled by mouth using a delivery device called a Diskhaler® which has limited its use in seasonal influenza. GSK is currently examining the feasibility of developing an intravenous formulation of zanamivir, and is in discussion with the regulators. The availability of an intravenous formulation of antiviral medication for unconscious patients in an intensive care setting would be an important development.

It is important that an effective disease reporting and drug delivery system is put in place to ensure that sick individuals get antivirals within 24 hours of the onset of symptoms, and thus gain the best possible clinical benefit from the drug. The current proposed method of delivery of antivirals involves telephone reporting of symptoms and sick individuals 'phoning a friend' to ask them to collect a course of antivirals from a drug distribution centre (the aim being that sick people stay at home). We were concerned about the possibility of fraud in this system and about its feasibility for many people in single person households. The Department of Health stated in its evidence that the delivery system is currently being reviewed. We agree that no system can prevent fraud completely, but current plans seem especially inadequate in this regard. We support the Department of Health's plans to investigate innovative means of delivery, preferably with drugs being delivered to the household, thus minimising the degree to which potentially infected individuals mix in the community.

4.7 Research during a pandemic

Following clinical experience in Vietnam (de Jong et al 2005) it is apparent that details of the use of antiviral drugs such as dosage and resistance need to be established for H5N1 infections and research in this area is essential, particularly in initial outbreaks, to optimize subsequent use of the stockpile. The collection and interpretation of clinical data during the initial stages of a pandemic will be needed to establish differences between the novel pandemic strain and seasonal influenza (see sections 3.3 and 6.3.2). Differences such as severity, extended length of illness and non-respiratory shedding of viruses will also need to be established. This may lead to the need for an increase in the recommended doses of oseltamivir used in treatment and possibly, prophylaxis. **WHO will have a central role in ensuring that the data are available from the first reported outbreaks and the resulting information is effectively disseminated to decision makers to guide interventions. The Department of Health should use its influence internationally to ensure this research is supported and can be done wherever the initial outbreaks occur (R16).**

In the evidence that we received, resistance to antivirals was raised as an issue that requires careful monitoring at the international level. The Neuraminidase Inhibitor Susceptibility Network (NISN) is an international group drawn from WHO laboratories, public health experts and academics, and the network is funded by Roche and GSK. NISN facilitates the exchange of information on drug resistance internationally, but it requires the relevant support, data and endorsement for it to succeed. There is a need to improve the technology for detecting the emergence of resistance, including improvements in genotyping and phenotyping and high-throughput screening. **We recommend that intensification of the surveillance of the sensitivity of current human and avian influenza viruses (H5N1 in particular) to antiviral drugs (the M2 and neuraminidase inhibitors) should be coordinated by WHO and undertaken on a global basis. In particular, the system should ensure that surveillance has the sensitivity to measure the degree to which a resistant virus is being transmitted in the community (R17).**

Illness severity associated with the emergence of antiviral resistance will need to be monitored both in patients in whom resistance develops and, if it occurs,

in people infected with resistant strains. In conjunction, the effectiveness of antivirals and the benefits of combination antiviral therapy (ie two neuraminidase inhibitors or a neuraminidase inhibitor and an M2 inhibitor) compared with a single drug needs to be investigated. With combination and effectiveness trials there are ethical issues associated with providing different treatments to a group of individuals that need to be addressed in advance (see section 6.3.2). The use of seasonal influenza as a model to conduct these clinical trials should be considered. Early data should also indicate what is the most cost-effective use of antivirals in the pandemic situation by identifying groups such as children, high-risk patients or working adults for whom treatments are most effective. **The evidence base for antiviral treatment of individuals in risk groups (eg those with an immune deficiency condition) needs to be reviewed by the Department of Health and if necessary expanded, with particular emphasis being placed on protocols to minimise the emergence of resistance in such populations (R18).**

Suitable diagnostic tests are not currently available but research on various procedures to capture the virus from clinical samples and on different detection processes are in progress. The availability of diagnostics will be discussed further in section 6.3.1.

4.8 New antiviral agents

The development of new antiviral agents would allow further flexibility in developing treatment and prophylaxis options during a pandemic. In the evidence we received from Roche and GSK neither company said it had plans to develop novel antiviral drugs. We understand that few, if any, novel compounds for treating influenza are in the development pipeline of the other large pharmaceutical companies involved in research and development in the field of infectious disease, but there are some in development by smaller companies. **We recommend that research in both industry and academia aimed at the development and evaluation of novel antivirals for influenza should be encouraged and supported. Extensive links already exist between academic research and the pharmaceutical industries and public-private partnerships could be developed in this area (R19).**

5 Human vaccination

5.1 Introduction

Influenza vaccines are used to stimulate antibody production against the virus, in order to prevent or reduce the effects of infection. This section will discuss the use of seasonal influenza vaccines in humans, the current H5N1 avian influenza vaccines and the use of vaccines in a pandemic.

5.2 Seasonal influenza vaccines

It is well established that vaccines, either inactivated whole virus or subunits of haemagglutinin and neuraminidase, are very effective against seasonal influenza. The effectiveness correlates with the capacity of the vaccine to stimulate neutralising antibodies (antibodies that inhibit the infectivity of the influenza virus) and the vaccines are effective if there is a good match between the antigen in the vaccines and the antigens of the seasonal virus.

The system for selecting the expected virus strains is coordinated by WHO. Twice a year WHO recommends the strains to be included in the vaccine ahead of the influenza season in either the northern or the southern hemisphere. Standard methods for vaccine production were developed more than 50 years ago and involve growing the identified virus strains in embryonated chicken eggs before harvesting, chemically inactivating, and purifying the virus, followed by detergent disruption where appropriate. Newer methods of vaccine production are mentioned in section 5.6.

In general the system works well and provides sufficient vaccine for those countries with influenza vaccination programmes. Current global capacity for the manufacture of trivalent seasonal influenza vaccine is estimated to be 350 million doses per year. In the UK these vaccines are targeted at those most at risk: those aged 65 and over and those with chronic illness. Vaccination is required each year to achieve a high level of protection and production capacity would be severely stretched if public or government demand was to increase suddenly (see section 5.4). The threat of a new pandemic influenza virus, H5N1 or otherwise, is real and the present capacity in vaccine manufacture is not able to meet the challenges that would be posed by a pandemic. These challenges are discussed further in section 5.4.

Experience in the UK in relation to the efficacy of paediatric vaccination in children under the age of five is limited. **Many very young children are immunologically naive to influenza and further research is needed on the characteristics of primary immune responses and the safety and**

efficacy of the use of seasonal and pandemic influenza vaccines in children. We recommend that this research is supported by the Department of Health as a matter of urgency (R20).

5.3 Human H5N1 vaccines

Since the emergence of H5N1, the pharmaceutical industry has shown a real interest in preparing vaccines against pandemic influenza and will undoubtedly be in the forefront of any vaccine strategy if a pandemic appears.

Several H5N1 influenza virus vaccines, based on avian viruses that have infected humans in Asia, are currently undergoing phase 1 or 2 clinical trials in human volunteers. To date, the most promising results have come from a Chinese study by Sinovac Biotech Ltd using a modified whole virus vaccine at two doses of 10 μ g with an alum adjuvant (Lin et al 2006). Studies by Sanofi-Pasteur in France and CSL in Australia using a subunit vaccine with alum were not as successful. In the Sanofi Pasteur study two vaccine doses of 30 μ g were required to achieve a good immune response and CSL reported a response with two doses of 15 μ g, but only in half of the people tested (Bresson et al 2006; Treanor et al 2006; CSL 2006). In July 2006, GSK announced promising results of a whole virus vaccine with a proprietary adjuvant at a dose of only 3.8 μ g, but the full results of this study are not published and the adjuvant used is not approved for general use.

Current H5N1 vaccines therefore require two or more immunizations three to four weeks apart to stimulate levels of antibody that are considered to be neutralizing, and in the majority of cases, the dose of vaccine needed is significantly higher than standard seasonal influenza vaccines. Urgent research is needed in this area to find low-dose vaccines that generate a good immune response, ideally after one dose. It is also unclear how well the antibodies stimulated by these vaccines cross-react with the range of avian H5N1 viruses isolated from both birds and humans in different countries to date. This information is critical if an informed judgement is to be made on the chances of such a vaccine stimulating an antibody response against a mutated avian H5N1 virus that might become a human pandemic strain.

Live attenuated influenza virus vaccines are also licensed for use in some countries and could be valuable in a pandemic. Their production involves the use of reverse genetics (see section 5.6) and reassortment procedures to prepare attenuated vaccine viruses. Similar issues to those discussed for inactivated virus vaccines in relation to the preparation of appropriate vaccine viruses, cross-

reactivity, and establishing their effectiveness in the face of an H5N1 pandemic, need to be addressed. Vaccines of this sort may have an additional, but as yet unproven, advantage of stimulating cellular (T cell) immune responses.

5.3.1 Population priming

Another strategy to be considered is to stockpile vaccine for population priming. Even without an exact match in virus strain, it may be possible to provide broad immunity in the population by vaccinating with a pre-pandemic vaccine. Once a pandemic virus is identified and a vaccine produced, it could also mean that only one dose of the up-to-date vaccine will be required following such priming (rather than the predicted two doses) and at much lower doses. This has obvious implications for the number of people that could be immunised with vaccines prepared from the pandemic virus once they became available. One of the current H5N1 vaccines being developed might be considered for use as a priming dose, for delivery once a pandemic has begun.

5.3.2 Cross-reactive immunity

Pre-pandemic vaccination with the current avian influenza virus vaccines might lead to the emergence of 'original antigenic sin'. This term is used to describe the surprising finding that people who had not been exposed to an influenza virus subtype for decades still had antibodies to that virus. This finding can now be interpreted as resulting from persistence in the immune system of B cell memory cells (which make antibodies), maintained in the blood, with possible help from cross-reacting T cells. It has been suggested that immunological priming by natural infection might be so strong that vaccination would not be effective, only restimulating the original and less useful antibody response. However there is no convincing evidence that repeated vaccination, such as seasonal influenza vaccination, with updated viruses becomes less effective with time. Thus it seems very unlikely that immunisation of humans with a pre-pandemic H5N1 vaccine would increase any health risk during a subsequent pandemic by adversely affecting the antibody response made to the infecting virus. The question remains whether pre-pandemic vaccination would be useful for protection. Vaccines that stimulate cellular (T cell) immune responses which cross-react with different influenza virus subtypes, may affect the severity of infection, irrespective of the infecting virus. The development of such preparations and research on their effectiveness are priorities.

5.3.3 Purchase of pandemic vaccines

Some countries are making advance purchase agreements with vaccine manufacturers for pandemic vaccines, with the aim of vaccinating their entire

populations. In the UK, the Department of Health has purchased a total of 3.3 million doses of vaccine against an H5N1 virus to be used for the vaccination of key healthcare workers in the event of a pandemic. The two contracts for the supply of these vaccines were awarded in March 2006 to Novartis Vaccines (formally Chiron Vaccines) and Baxter Healthcare Corporation. The Novartis product is an egg-grown subunit vaccine adjuvanted with a proprietary agent, MF59, and the Baxter product is a cell-grown whole virus vaccine with alum as the adjuvant. Vaccine production using cell culture involves growing animal or human cells and then infecting them. The virus produced by the infected cell is harvested, inactivated and purified, as for the egg-grown vaccine. Recently the Department of Health has announced the purchase of further H5N1 virus vaccines that would be sufficient for priming and boosting injections for the whole population of the UK.

In its evidence to this study, the Department of Health said that the two vaccines were purchased on the basis of preliminary immunogenicity data but that no data from animal or human studies were available for these particular pandemic vaccines at the time of the contract being awarded. It also reported that the different production methods and adjuvants spread the risk of buying an ineffective product. It is crucial that those who decide what vaccines are commissioned and stockpiled make transparent and accountable decisions. However, owing to commercial sensitivities, very little information is publicly available on these vaccines and the type of immune response stimulated. In particular, the extent to which the immunity that they produce is cross-reactive with the different H5N1 viruses currently in circulation has not been reported. It is therefore difficult to assess whether the best decisions have been made. Under the MRC's influenza initiative, funding of up to £7million over the next 18 months has been made available for research on H5N1 vaccines.

We recommend that the Department of Health makes samples of the recently purchased H5N1 vaccines available to the research community, as soon as is practicably possible, and that the MRC solicits high-quality research applications specifically to analyse these vaccines (R21).

Independent high-level scientific advice should be sought in an open way before any decision is made to take a particular approach to vaccination that could affect the lives of millions. The working group found difficulty in penetrating the barrier of confidentiality that surrounds the industry and its relationship with the Department of Health. **We urge the Department of Health to make arrangements with industry that allow it to be open and transparent in its decision making and procurement processes, to use independent experts to advise as appropriate, and to make the evidence on which decisions are made available to the scientific community (R22).**

5.4 Problems with producing a pandemic vaccine

Vaccination will be a key element in dealing with a pandemic and there are advantages in developing a vaccine prior to the pandemic, focusing on potential pandemic strains such as H5N1 either for use either in pre-pandemic vaccination or to stockpile in the event of a pandemic. However, this is not a perfect solution because of the possibility that the emerging pandemic strain may differ significantly from a pre-prepared vaccine.

The most efficacious vaccine will be the one based on the pandemic virus itself, but production can begin only once the virus is isolated and rendered safe. It is estimated that, using current production methods, it is likely to take seven to nine months before initial doses of a pandemic vaccine are available. By this time the first wave of the pandemic is likely to have passed, and possibly a second wave.

The regulatory agencies also have a part to play in ensuring that in an emergency vaccines could be produced and licensed safely but without delay. In March 2004 the European Medicines Agency issued guidelines on 'core dossiers' for the submission of marketing authorization applications for pandemic influenza vaccines. These guidelines provide a route for accelerated regulatory approval through the submission of the prototype pandemic vaccine files before the pandemic arrives.

Despite the probability that a vaccine against a pandemic virus would contain only one virus rather than three in the trivalent seasonal vaccine, global capacity for the production of influenza vaccines is not sufficient to meet the demands of pandemic vaccine production. In a pandemic, the demand for vaccination may be ten times or more the current 350 million doses of seasonal influenza vaccine. Seasonal influenza vaccines will also probably be required in a pandemic. It is unrealistic to believe that demand would be met by investments in additional manufacturing plants. We were told in evidence to this study that it is not commercially viable for the vaccine industry to commit the necessary resources to scale up production in advance of a pandemic when there is no existing market, the threat of a pandemic may be years away and the risk in any single year may be considered to be low. Increasing the uptake of seasonal influenza vaccines by recommending vaccination for those over 50 years of age and, in the UK, by allowing individuals to purchase seasonal vaccines from their own GP may increase capacity slightly but, in order to meet demand, more efficient 'antigen sparing' strategies are required (see section 5.4.1). **We recommend that the Department of Health continues to expand its seasonal influenza vaccine programme and relaxes rules about**

individuals outside the 'at risk' groups purchasing seasonal influenza vaccines directly from NHS GPs, to encourage industry to increase production capacity (R23).

5.4.1 Antigen sparing

In the long-term, there is a need to develop innovative technologies for vaccine production (see section 5.6). However, immediate attention for vaccines must be directed to a coordinated international approach to vaccine evaluation, paying attention to ways in which the least amount of virus can immunise the largest number of people which is known as antigen sparing.

At low doses, a whole virus vaccine induces a greater antibody response than a subunit vaccine and therefore more people could be vaccinated using the same quantity of vaccine. However, whole virus vaccines can cause more side effects, particularly in the young, and these must be balanced against the chances of severe illness or death from a pandemic virus. Vaccine manufacturers are currently producing mainly subunit seasonal influenza vaccines. In order to change to a whole virus vaccine for use in a pandemic, the process for seasonal influenza vaccine production would need to be changed. This is a significant undertaking, but **we recommend that the Department of Health and the vaccine industry continue to evaluate the use of whole virus vaccines and to monitor the results of ongoing trials of whole virus vaccines against H5N1 (R24).**

An alternative method of antigen sparing is the use of adjuvants which reduce the antigen dose required in a vaccine. The use of adjuvants can also broaden the immune response to a vaccine and there is evidence of cross-protection against antigenic variants. There is considerable scope for developing novel adjuvants.

We recommend that as a matter of urgency the Department of Health takes the lead in assembling a work programme with industry and academia for the development of new adjuvants for vaccines. This should be done in parallel with clinical trials to compare directly the effectiveness of current adjuvants with existing H5N1 pandemic vaccines, with whole virus vaccines and with information sharing from ongoing trials (R25).

5.5 Passive antibodies

In addition to vaccination, intravenous or intramuscular injection of antibodies with a high neutralising titre against avian influenza could be useful in treating infected people or offering prophylaxis. Several examples exist of the use of antibodies in other infectious diseases, such as palivizumab, a monoclonal antibody that is used to prevent and treat severe

infections with respiratory syncytial virus in young children. Furthermore, passive administration of immunoglobulin from hepatitis A virus immune donors was used as an effective prophylaxis against that virus, although it has now been superseded by a successful vaccine.

Monoclonal antibodies against H5N1 avian influenza virus are being prepared for human use by a number of biotechnology companies, and serum donations could be requested from those who have recovered. However, such treatments will depend on the pre-prepared antibodies cross-reacting efficiently with the pandemic strain and are likely to be very expensive and limited in availability.

5.6 Further research

This study has found that there is no coordinated approach to vaccine research, development and evaluation, so there may be duplication of some approaches and omission of others. A greater understanding is clearly required of cellular, innate, and adaptive immune responses in protection from disease and in determining disease severity. Standardised clinical

assay methods for the evaluation of pre-pandemic and pandemic vaccines are also urgently needed.

We recommend that WHO coordinates a global project for sharing information and data on ongoing influenza vaccine research and development, in both the commercial and academic sectors (R26).

Several newer and faster methods exist for producing influenza vaccines, including reverse genetics and DNA vaccines. The technology of reverse genetics allows rapid production of vaccine candidate viruses containing the required haemagglutinin and neuraminidase proteins and is often faster than traditional methods for generating a vaccine virus.

DNA vaccines are prepared by inserting virus DNA into plasmids that are purified and delivered by injection. The viral DNA in the plasmids is transcribed in the transfected cell and the expressed viral protein induces an immune response. Recently announced results of a preliminary trial of a seasonal influenza DNA vaccine delivered into the skin using a 'gene gun' appear promising. Further research and development and data sharing are needed in these areas.

6 Public health

6.1 Introduction

As discussed in sections 4 and 5, the most effective public health interventions to mitigate the impact of a pandemic are through the use of antiviral drugs and immunisation with an effective vaccine against the virus. This section will discuss the additional public health response to a pandemic; three areas were considered:

- pre-pandemic planning and preparation (section 6.2);
- delivery during a pandemic (section 6.3);
- post-pandemic evaluation (section 6.4).

These areas are obviously broad and cannot be covered in detail by this report. Several reports and reviews have considered the public health questions that are raised in detail, for example those by Fleming (2005) and Pickles (2006).

6.2 Pre-pandemic planning and preparation

Public health pre-pandemic planning requires integrated activity across all government departments and between central and local government in the UK. This is being achieved through central government planning together with local and regional systems. Feedback from local health, emergency, educational and social services providers is being used to assess the viability of proposed methods of intervention in medical and social care following the outbreak of a pandemic virus.

However, devolution of planning to local organisational levels (for example in the education sector), which is necessary to customise plans according to circumstances and resource availability, inevitably means that central control is eroded. In conditions where there is considerable uncertainty (for example about the timing of the outbreak, its scale, its source and, its treatment), scenario planning, such as that occurring now, can cause confusion and doubt among practitioners and their managers. Any ambiguity in the requirements of central government imposed on local systems will be magnified and is likely to undermine efficiency. Central government may need to use a core briefing team in the period when plans are being confirmed. This could comprise one or more mobile multidisciplinary groups that could respond to individual local planning problems with a clear and centrally determined approach. Such teams could profitably include public health experts and behavioural and operational researchers.

Emergency plans should always be tested to the point of collapse – not only to identify ways in which they can be improved but also to provide indications of how much confidence should be placed in them. Particularly important for testing pandemic plans will be an examination of what happens if there is escalation beyond the ‘worst case’ scenarios upon which the plans are predicated (see box 1).

Testing the critical assumptions within the plans should be done independently of those who formulate the plans, though being informed by them. Recognising that such testing is iterative, the process could be done by a team of behavioural scientists on standby to provide state-of-the-art advice on attitudinal, motivational and behavioural factors that might be relevant for policy development or implementation. We hope that the updated UK Health Departments’ influenza pandemic contingency plan, due to be published in spring 2007, takes account of the results of recent simulation exercises and includes a strategy to test further the plan’s critical assumptions.

We recommend that the Department of Health should commission external experts to scrutinise the revised pandemic influenza plan and where appropriate should form expert groups to review critical aspects of the plan (R27).

6.2.1 Clinical management guidelines

The current pandemic influenza clinical guidelines were compiled by a multi-professional committee comprising representatives from the British Thoracic Society, the British Infection Society and the HPA, acting on behalf of the Department of Health. These guidelines were revised and published online in March 2006 (British Thoracic Society, British Infection Society, Health Protection Agency and the Department of Health 2006). They were based on current knowledge and data extrapolated from previous influenza pandemics, seasonal influenza and the limited data available from human cases of H5N1.

However, the true nature of the disease caused by a new pandemic influenza virus will become apparent only as a pandemic develops and it will be vital to study the first few cases in a pandemic extensively (see section 6.3.2). The determinants of the clinical course of influenza are currently poorly understood, as are the most effective clinical care programmes. It is therefore essential that any guidelines can be rapidly updated and revised as experience emerges during a pandemic and communicated rapidly throughout the NHS. Investigations in South-East Asia suggest that an enhanced immune response

in the nature of a 'cytokine storm' may have been involved in the extreme pathogenesis observed (de Jong et al 2006) and research should be undertaken on processes to control such responses.

Clinical management guidelines must also take into account the practicalities of reduced facilities and services that many clinicians may face in practice in a pandemic, eg the acute shortage of intensive care and ventilatory facilities. A recent study used community modelling to examine the demand for intensive care beds in England in a pandemic and predicted that capacity will be needed at more than 200% of that presently available (Menon et al 2005).

6.2.2 Infection control and non-pharmaceutical interventions

Infection control and 'non-pharmaceutical interventions' such as personal protective equipment and social distancing measures are likely to play a role in modifying the impact of a pandemic. Preparations should be made in advance, and the necessary research conducted, to identify those interventions likely to have the greatest impact.

Information on the practicality and efficacy of infection control is currently incomplete and the preventative measures to be employed are not clear. Since vaccines may not be available at the onset of a pandemic and the supply of antivirals may be limited, advice is needed on practical infection control steps. These measures may help prevent the spread of disease in hospitals and community settings. This advice needs to be communicated effectively to healthcare workers and the public and should include:

- the value, if any, of personal protective equipment such as face masks;
- protocols for hand washing;
- disinfection routines for hospitals;
- information on the isolation of 'known infected' and 'not known to be infected' individuals, hospital wards or residential homes.

Such non-pharmaceutical interventions may be the only measures available for many countries in a pandemic. As discussed in section 3.4, these measures may be highly effective in theory, but may require correct and rigorous adherence to protocols to be effective, which may be difficult in practice. Little is known about the measures that are likely to work and there are several reasons for this. In the situation of seasonal influenza, the availability of vaccines and antivirals means that there has not been any incentive to study these interventions. It is also difficult to draw conclusions about activities that are not easily subject

to randomised trials. Therefore observational studies may be the only way to provide the necessary information. Although it may be possible to obtain data using modelling to inform decision making on the use of non-pharmaceutical interventions, as used to inform appropriate use of vaccines and antivirals.

We are concerned that the commissioning of studies on the effectiveness of non-pharmaceutical interventions may fall between the remits of different agencies, departments and of the MRC. **Therefore we recommend that the HPA, and the Department of Health identify research that should be conducted to identify those non-pharmaceutical interventions likely to have the greatest impact and, where appropriate, commission trials to assess the effectiveness of these interventions (R28).**

Observational studies and modelling could also be used to provide the necessary information. The appropriate process for the ethical approval of research during a pandemic must also be completed in advance so as not to hinder essential work.

6.3 Delivery in a pandemic

This section describes areas that are important for an effective public health response in a pandemic.

6.3.1 Diagnostics

Current clinical guidelines give GPs and other healthcare professionals reasonable means to diagnose influenza. However, during an outbreak the symptoms of pandemic influenza may not always be specific enough to discriminate between those who have influenza and those who are worried they may be infected and are requesting antivirals.

Ideally a fast-acting near-patient test (such as a dip-stick test), with a sufficiently high positive predictive value coupled with a simple delivery system, which could be used in both developed and developing countries, would be available. However, such a test does not currently exist and, from the evidence we received, there is little interest from commercial companies to develop one. Further research in this area is needed to enhance work that is already underway to develop such a test and make testing a routine laboratory procedure rather than a specialised skill. **We recommend that bodies such as the European Commission should consider ways to stimulate an environment which would encourage investment in new diagnostic products for influenza (R29).**

Current virological and molecular tests to track and characterise the viruses involved for antigenic variation and drug sensitivity will be of great epidemiological importance in a pandemic (section 3). Both expertise and equipment are in place for these in laboratories of

the HPA. However, currently available diagnostics are likely to have little impact in primary care because they are time consuming and expensive (costing more than a dose of oseltamivir) and have low sensitivity. Diagnostics may have some benefit in selected settings such as hospitals, especially in the early phases of an epidemic, for recognition of infection in frontline healthcare staff. It will also be important to diagnose the first cases to provide as much information about the type of virus. However, near-patient diagnostics may not be relevant once the pandemic has become a population problem.

6.3.2 Clinical research during a pandemic

Clinical and translational research will be needed to increase understanding about an emerging pandemic strain and the respective host and virus mediated contributions to clinical disease and outcome. Although some studies can use seasonal influenza as a model, much of this research can be undertaken only where and when human cases arise (hence, to date, most data have come from Vietnam and China). It will be important to compile and compare clinical data on human cases in order to understand more about the routes of transmission, to identify the groups most at risk, to guide preventive measures and early interventions, and to find improved treatments. At the start of a pandemic, epidemiological data on the modes of transmission and virus pathogenicity will inform decisions about the target groups for vaccination and antiviral drugs. Furthermore, a greater understanding of the efficacy of antiviral drugs, their optimum dose, prescribing regimens and the monitoring of antiviral resistance will lead to improved treatment during a pandemic, as outlined in section 4.

However, the practicalities of conducting research in a pandemic must be addressed in advance. Research programmes are often conducted in several centres, require consent from patients (who may well be unconscious), must have defined protocols and require ethical and regulatory approval in advance, as well as needing to be funded and staffed by appropriate healthcare professionals. In the UK, the Department of Health is working with the MRC to design research studies in advance and to deal with ethical clearance as far as possible ahead of time.

During a pandemic ethics cannot be disregarded, so approval for protocols must be granted in advance. The Department of Health indicated in its evidence to this study that the problems of ethical approval are currently being considered. The Director of Pandemic Influenza Preparedness within the Department of Health has formed a Committee on Ethical Aspects of Pandemic Influenza to advise on the ethical issues in health and social care and in public health arising from an influenza pandemic. This committee will not take the place of the ethical review process but will decide what changes should be made to current processes in a pandemic.

Regarding funding in advance of a pandemic, the MRC issued a call for proposals on influenza research in December 2005 and an additional £15 million for influenza research has been made available until March 2008. The call for evidence included proposals for 'readiness' grants to support research that could be put into effect only in the early stages of a pandemic. The MRC plans to put these peer-reviewed grants in place in order to address important, urgent questions if a pandemic occurs, for example clinical work on a newly circulating strain. In addition, the MRC also considered requests temporarily to suspend existing MRC grants in other areas of research so that urgent influenza research might be undertaken. We welcome the MRC's initiative to promote and solicit the best possible research proposals on influenza from researchers and to recognise that response-mode research proposals may not sufficiently address the areas of work required.

6.3.3 Behavioural modelling

The success of public health operational delivery plans will to a large extent depend upon having made the correct predictions about the behaviour of the public and of emergency service workers. Making such predictions is hampered by the absence of relevant information. There are historical studies of the behaviour of individuals in earlier pandemics but the quality of the data collected is unknown, particularly when it comes to changes in individual or group behaviour in what might be characterised as the three phases of the pandemic (the threat stage; the outbreak; the aftermath). In any case, it is inappropriate to use such data as do exist from these past pandemics to predict what would happen today. The bases of so much of social life have changed – not just the age profile but family structures, the authority-responsibility hierarchies, the accepted technologies of communication and expectations of mobility.

Baseline data on relevant current behavioural and attitudinal patterns (beyond those needed for modelling the spread of the disease) could be brought together to inform planning. This would also provide the baseline for subsequent evaluation of the impact of the pandemic. The social science community would be able to advise on the availability of extant data and the methods for collecting new data. Special attention would need to be paid to subcultural and international variations in behaviour that may be important during and after the pandemic. There would be merit in a cross-department governmental approach in this (ie minimally incorporating key health-related, mobility-related and economic-related behaviour patterns).

We recommend that the government, together with the Economics and Social Research Council (ESRC), should consider procedures to collect data on behavioural and attitudinal patterns, both currently and throughout a pandemic. These data would also allow subsequent analyses of the

impact of the pandemic and, more importantly, provide the basis for predictive models of behaviour that could be used in refining and improving planning for future pandemics of influenza and other infectious diseases (R30).

6.3.4 Communications strategy

The government has invested in research on risk communication and we heard evidence that the strategies of the Department of Health and Defra are informed by this work. In September 2005 the Royal Society held a joint workshop with the Food Standards Agency to explore potential social science insights for risk assessment. The report of the meeting identified five key principles to enable more effective risk assessment and related management and communications processes that are directly relevant to preparedness for an influenza pandemic (Royal Society and Food Standards Agency 2006):

- stakeholders and the public (where appropriate) should be consulted on the framing of questions to be put to expert scientific advisory committees;
- a cyclical and iterative process to inform risk assessment, management and communication should be developed;
- assumptions and uncertainty in risk assessment should be acknowledged;
- public and stakeholder engagement should be broadened at the different stages of the process, particularly on issues of controversy or high uncertainty; and
- it is important to be clear about your audiences and communicate the things that matter to them.

Effective communication in a pandemic will be vital in optimising the behaviour of the public and emergency service workers. Yet the communications strategy will need to be different from probably any other constructed in response to an emergency, disaster or crisis because:

- the messages will issue from many sources simultaneously, they will be frequent, they will be multilayered (with information, instruction, reassurances, threats), they will be aimed at multiple audiences (the public will not be susceptible to being treated as a homogeneous mass), and they will be channelled through a greater variety of media (including possibly text messages and web-based sources);
- the messages will be part of the management of what might be called a 'chronic emergency' – not something that is finished in a finite, relatively

short, period – and is also a 'diffuse emergency' – not located in one place or attacking selected groups of people;

- the messages will need to explain decisions that will themselves be based upon many uncertainties, and justification for decisions based on uncertainty (and thus the gaining of support or compliance) is notoriously difficult. Tactics for dealing with a situation in which the general public (or even some subset of the public) rejects government advice or loses faith in government credibility concerning the pandemic should be developed, especially since there is some evidence that the public does not trust government to deal honestly and effectively with health crises.

The need to establish that the proposed communications strategy is capable of dealing with these issues is evident. It is necessary to have a strategy that is fit for purpose throughout the three phases of the pandemic (before the outbreak, during it and in the aftermath) and the same tactics of communication may not be appropriate in all of them. It will also be important to know whether the communication with the public that has already happened has been effective and sufficient. Informing and alerting the public to what will be expected of them prior to the outbreak is necessary. This anticipatory communication will be vital because it must be expected that the 'normal' channels of communication (eg the websites) will fail, even those dedicated to specific audience groups. Mechanisms for reaching difficult to access subsets of the public who are difficult to access such as those who will not be ready recipients of media-based messages, need to be considered. Given the growing number of single-person households, the assumption that person-to-person routes of communication will operate may be erroneous. **To ensure the communications strategy is fit for purpose we recommend that the government's planned communications strategy should be subject to independent review and testing within six months of the publication of the revised Pandemic Plan (R31).**

6.4 Post-pandemic evaluation

The viability of effective evaluation of the impact of the pandemic or of the way in which it was managed will depend upon the collection of the right data before, during and after the outbreak. What constitutes the 'right' data will be a matter of debate. **Accordingly, consultations should be undertaken now with stakeholders about the most appropriate data to be collected and the most effective methods to collect these data in order to evaluate the impact of a pandemic. Having a database that will serve the purposes of modelling and prediction as well as evaluation should be attempted (R32).**

7 Science and policymaking

7.1 Introduction

The incorporation of science into both national and international policymaking on pandemic preparedness is crucial, and policies must be updated regularly as the evidence base relating to influenza grows. In this section we consider the structures for scientific advice in policymaking in the UK in relation to pandemic influenza.

The UK is responsible for preparing its own contingency plans but international bodies such as WHO, OIE and the United Nations (UN) have central strategic and coordination roles. WHO has responsibility for coordinating global influenza surveillance, for determining pandemic alert levels (and hence 'declaring' a pandemic), for setting international recommendations for surveillance and pandemic preparedness, and for cluster investigation and response. OIE has responsibility for coordinating and setting guidelines for global surveillance of avian influenza, principally in domestic poultry, for defining guidelines for control of avian influenza outbreaks, and for collating and publishing global surveillance data. Dr David Nabarro was appointed as UN System Coordinator for Avian and Human Influenza in September 2005. Dr Nabarro is responsible for ensuring that the UN system makes an effective and coordinated contribution to the global effort to control the epidemic of avian influenza and supports effective local, national, regional and global preparations for a potential influenza pandemic. In turn, the UN is guided by its specialised agencies responsible for animal and human health (FAO and WHO).

7.2 Policymaking in the United Kingdom

The Cabinet Office has the overall cross-government coordinating role, though the Civil Contingencies Secretariat (CCS), in planning for civil contingencies including pandemic influenza. Response planning and implementation are the responsibilities of the relevant department: the Department of Health in the case of pandemic influenza and the Defra in the case of avian influenza in animals. A number of other departments such as the Department of Education and Skills, the Department of Transport and the Home Office have roles in the wider delivery of pandemic preparedness.

All government departments have access to scientific advice through various mechanisms. These include the Government's Chief Scientific Adviser (CSA), the Chief Medical Officer (CMO), the Chief Veterinary Officer, and the departmental Chief Scientific Advisers. There are numerous advisory committees that provide scientific advice to inform government policy in this area. The following section describes these committees and

discusses the extent to which scientific evidence is incorporated into policymaking.

7.2.1 Advisory committee structure

The UK government is well equipped with science advisory committees with some responsibility for avian and pandemic influenza and both Defra and the Department of Health have expended considerable resources in developing contingency plans.

The Ministerial Committee of the Cabinet on Influenza Pandemic Planning (MISC32) has terms of reference 'to guide the preparations for a potential influenza pandemic and related international activity'. This Committee is chaired by the Secretary of State for Health and receives its scientific advice from the CSA. The CMO also attends as required. This Committee has held a number of pandemic influenza exercises within government, which have proved useful in identifying shortcomings in existing planning. In the evidence we received we were told that the CSA provides a 'challenge function' regarding the science base of decision making within this Committee and to each government department.

Whilst the CSA and CMO play a vital role in providing advice to MISC32, we believe that the scientific advice given to the Committee could be strengthened by the input of an independent scientist with expertise specifically in pandemic influenza. **We therefore recommend the appointment of a leading non-governmental scientist in the area of influenza as lead questioner and adviser to MISC32 for specific issues, complementing the roles of the CSA and the CMO. This scientist should be appointed jointly by the CSA and CMO in discussion with relevant learned societies. This model should be adopted in all future Ministerial committees for other animal and human health emergencies (R33).**

The UK National Influenza Pandemic Committee (UKNIPC) is the main forum for the provision of specialist advice to the UK Health Departments on the health response before and during an influenza pandemic and it is chaired by the CMO. The Department of Health for England's National Director of Pandemic Influenza Preparedness jointly chairs the cross-government group with the head of the CCS which includes membership from the key departments involved in planning for an influenza pandemic.

Ministers and UKNIPC are advised about the scientific evidence base for health-related pandemic influenza policies by the Department of Health's Pandemic Influenza Scientific Advisory Group (SAG). Membership of SAG includes independent scientists as well as

medical and scientific representatives from across government, HPA, NIBSC, MRC, the WHO Collaborating Centre for Reference and Research on Influenza, NIMR, the Joint Committee on Vaccination and Immunisation, the Advisory Committee on Dangerous Pathogens, the National Expert Panel on New and Emerging Infections and the European Centre for Disease Prevention and Control. Two sub-groups advise on, and review, work on mathematical modelling and surveillance.

The European avian influenza legislation is the main driver that shapes Defra's policy in the form of the UK's contingency plans and its stakeholder engagement. Defra and UKNIPC are advised on the scientific evidence base for avian influenza by Defra's Scientific Advisory Council (SAC) which is made up of expert, independent scientists and veterinarians across a range of disciplines. The Epidemic Diseases subgroup of SAC recently reviewed Defra's contingency plan for avian influenza outbreaks in UK poultry and reported to the SAC in June 2006 with a number of recommendations (Defra Science Advisory Council 2006). Defra and UKNIP are also advised by an ad hoc ornithological advisory group convened the Veterinary Exotic Diseases Division of Defra. Defra has not established any further committees to advise on avian influenza.

7.2.2 Advisory committee remit

Although each cross-governmental and departmental committee operates under a specific remit, it is difficult to understand the complex relationship between advisory committees and different government departments in determining how policy is developed in the areas of avian and pandemic influenza and how science is incorporated into the process.

The role of science in policymaking at the ministerial level in the lead departments is unclear from the evidence we received. In particular, the decisions relating to seeking advice, the source of advice, and whether the advice and available evidence are used, must all be more transparent. From the evidence we received, the basis for choosing a source of scientific advice also seems a closed matter. Although the quality of in-house government scientists is undoubtedly good, it is clearly difficult for these scientists to be expert across all of the issues of concern to their departments. **The role and remit of science advisory committees in relation to pandemic influenza should be made explicit and the organisational decision making routes should be clarified to show how scientific advice is utilised (R34).** An organisational flow chart to clarify the decision making routes should be available on each department's website to explain to the public and other stakeholders how decisions are reached.

All committees should aim to operate in a transparent manner wherever possible by making minutes publicly available shortly after the meeting. The CSA's *Guidelines*

on scientific analysis in policymaking

(HM Government 2005) state that there should be a presumption at every stage towards openness and transparency in the publication of expert advice. Furthermore, the guidelines state that it is good practice to publish the underpinning evidence for any new policy decision, and that any important omissions in the data should be clearly documented and identified as such in a way that is meaningful to the non-expert. In relation to pandemic influenza, we believe that the scientific basis for key decisions, such as the purchase of oseltamivir and H5N1 vaccines, has not been made publicly available in full, nor have the reasons for the restriction of complete transparency and openness by commercial confidentiality. This was confirmed in the evidence we received and we were told that there is insufficient dialogue between departments and scientists on the use to which scientific advice is put.

There should be increased use of scientific information and advice from independent specialist scientists in the formulation of government and public policy relevant to preparedness for combating pandemic influenza. Examples of areas where further scientific input is required include the selection and stockpiling of pandemic vaccines and antiviral drugs and the provision of appropriate healthcare resources. The committees should explicitly seek input and advice from experts outside the committee membership and co-opt members on an ad hoc basis where relevant.

7.2.3 Further sources of advice

As discussed above, the ministerial and departmental committees with a remit for avian and pandemic influenza receive scientific advice from a number of independent and governmental sources. However as we outline below, the expert scientific advice available to government could be further improved by incorporating scientists from broader disciplines, such as the commercial sector and the social science community.

Neither the Department of Health nor Defra has formal mechanisms for incorporating advice from the commercial sector, for example manufacturers of (human and avian) vaccines and antivirals. From the evidence we received we understand that, although informal meetings occur on an ad hoc basis, the greatest source of commercial information appears to be made available to the departments through discussion of tenders to supply vaccines or antivirals. Despite possible issues of confidentiality, embedding experts from the commercial sector into the departments' science advisory committees would provide valuable information that is not currently readily available to them.

Social science is also underrepresented in the advisory structures to the lead departments. It can inform policy not only on issues such as contingency planning should

pandemics occur but also when considering the root causes of pandemics. There are roles for social science professionals such as medical anthropologists and behavioural scientists in, for example, understanding the role that human behaviour plays in disease spread or in communicating with and mediating between biomedical professionals and local communities (see section 6.3.3). In ensuring that policymakers receive the best support and advice on this issue, it is important to recognise and value contributions from the full range of social science disciplines in order to achieve a well-rounded view of the array of socioeconomic factors involved. This can be achieved by embedding appropriate social science professionals within interdisciplinary teams from the outset so that, through cross-fertilisation of ideas with natural scientists, questions are framed and response strategies developed based on as full an understanding of the problems as possible.

There are many scientific advisory committees throughout government that provide a range of useful scientific advice to their departments. However, the current system lacks a mechanism to bring together advice from across government departments to provide a clear channel of scientific advice to MISC32. **In order to incorporate scientists from a broad range of disciplines, and the scientific advice being generated by the range of science advisory committees across government, into a focal point we recommend that the Department of Health's Pandemic Influenza SAG becomes a single cross-government Scientific Advisory Committee on pandemic influenza jointly chaired by the CMO and the CSA. In addition to relevant cross-governmental representation, the committee's membership should be drawn directly from the scientific, veterinary, social science and medical communities as well as from the commercial sector (R35).**

We also recommend that the Department of Health, Defra and the CCS continue to ensure that they are collecting and using evidence from a wide range of independent sources, both from within and external to government. We urge all departments involved in pandemic preparedness to be open and transparent in their decision making by publishing minutes of meetings and the evidence on which decisions are made as soon as possible, in keeping with the CSA's *Guidelines on scientific analysis in policymaking* (R36).

7.3 Cross-government coordination and communication

Together with the Research Councils, government agencies and arms-length bodies are a key source of a wide range of independent expertise outside government departments. These include the HPA, VLA,

NIBSC and the Medicines and Healthcare products Regulatory Agency. Communication within departments and their agencies appears to be generally good eg between the Department of Health and the HPA, or Defra and the VLA. Communication occurs regularly through a variety of formal and informal means and representatives of many of these agencies sit on governmental advisory committees. However, boundaries of responsibility are not always clearly defined and we have observed some tension between the scientific advisory role of HPA and VLA and their operational roles. Furthermore, we heard evidence that two-way communications between the departments and their agencies could be improved if the government department informed the agencies how their advice was utilised.

Communication between veterinary and medical scientists within the Department of Health and Defra is improving and we heard evidence of a number of joint projects being initiated between the two departments. Cross-representation between the departments also exists on several advisory committees such as the Advisory Committee on Dangerous Pathogens, Defra's Animal Health Group and the UK Zoonoses Group.

It is evident that certain areas of scientific knowledge, essential for the development of effective policy in relation to pandemic influenza, are underdeveloped. The role of the Research Councils in providing communication frameworks and resources that allow the research community to produce this knowledge in a timely fashion needs to be strengthened. This is as true for the ESRC as for the BBSRC or the MRC. The recent commitment by the Department of Health to establish a 'cross funders forum' to coordinate research and development funded by a variety of government and other bodies is a step in the right direction.

7.4 International policy development and communication

The scientific response to pandemic influenza needs to be coordinated internationally and many countries have plans in varying states of detail and completeness. Both WHO and OIE have held a large number of consultations with panels of invited experts, as well as having a number of standing committees. In addition, the reference laboratories and WHO Collaborating Centres provide substantial expertise to both organisations. However, formal and transparent processes for determining who is asked for advice internationally are lacking. This means that there is a degree of arbitrariness as to who gets consulted on what issue. The role of the international scientific community in offering advice also seems unclear.

We recommend that WHO and OIE review their processes for obtaining scientific advice on pandemic influenza and introduce a clearly

defined, open and transparent mechanism. Nations around the world need to continue to support WHO, and to allow data and results to be made immediately available internationally (R37).

In terms of contingency planning, the UK can do a certain amount of planning nationally but this is not going to be effective without international cooperation. Areas such as scientific and clinical research, surveillance and the production capacity of vaccines and antivirals

would benefit from international cooperation. International coordination of any restrictions on the movement of poultry, of social distancing measures in a pandemic (such as school closures), and to keep the global economy going will also be important. More needs to be done in these areas and must be tackled at a European and global level. The evidence to this study heard that there is no cross-sector mechanism within the EU to bring the planning of different countries together.

8 Table of recommendations

Section 2 Avian influenza	
R1	Innovative methods for improving surveillance of avian influenza and other zoonotic diseases in areas lacking animal disease surveillance infrastructure should be developed. We recommend that the World Organisation for Animal Health (OIE) and the Food and Agricultural Organisation of the United Nations (FAO) consider developing sentinel networks of farmers or villages in these regions for outbreak reporting.
R2	Studies to increase knowledge of the role of wild birds in the spread of infection should be expanded both nationally and internationally and involve collection of data and collaboration of major international agencies specifically for this purpose. In the UK these bodies would include the Department for Environment, Food and Rural Affairs (Defra), the Veterinary Laboratories Agency (VLA), ornithological charities and the Health Protection Agency (HPA).
R3	Surveillance and collection of samples from wildfowl is labour intensive and we recommend that participants in the surveillance networks should receive adequate funding from Defra and the European Commission to continue to operate efficiently in the UK, Europe and globally.
R4	Research should be done by Defra and the Biotechnology and Biological Sciences Research Council (BBSRC) to ensure that procedures for avian influenza virus collection are robust, that the subsequent transport of samples is secure, and that methods used for virus isolation and characterisation are the most appropriate and up to date.
R5	Defra should set up a vaccination committee, similar to Department of Health's Joint Committee on Vaccination and Immunisation. This committee should advise the department on the development of its vaccination strategies across all animal diseases, including avian influenza.
R6	As part of their current calls for proposals, research funders, in collaboration with Defra and the vaccine industry, should solicit proposals from the research community to address new approaches to avian influenza vaccines.
R7	Defra, in collaboration with the BBSRC and the Medical Research Council (MRC), should examine areas where further research could be funded such as basic avian influenza research and avian immunology.
R8	Government should provide increased funding to expand high containment research facilities to enable vital research in the field of highly pathogenic avian influenza.
Section 3 Epidemiology and surveillance	
R9	European Union (EU) member states, including the UK, should work closely with WHO to support scientific research relevant to the quality and value of influenza surveillance and research to improve the understanding of the epidemiology of influenza.
R10	The Department of Health and Defra, in collaboration with WHO and the scientific and medical communities, should review the potential applications of the data collected in infectious disease surveillance generally.
R11	Genetic, antigenic and pathogenic data relating to new avian viruses, especially H5, H7 and H9 subtypes, should be made widely and rapidly available. In particular, samples of virus isolates should be made available as a matter of urgency to bona fide laboratories for research and development purposes.

R12	The UK government should support the Global Initiative on Sharing Avian Influenza Data and ensures that government and publicly funded laboratories put in place plans to publish all surveillance data.
R13	The UK government should lead efforts to coordinate plans for real-time data collection and data sharing during a pandemic, at the EU, EU and G8, and WHO/UN level. Achieving consistency of the detailed data collected on the first few hundred cases in each country and the summary data collected thereafter could offer significant benefits to collaborating countries prepared to share data in real time, since the data collected in a country affected early could aid final preparedness planning in countries not yet affected.
R14	Additional epidemiological studies are needed to analyse existing disease and social data to estimate the likely impact of social distancing measures (especially school closure) on a future pandemic and to examine the evidence for population behavioural changes in a pandemic that might affect disease transmission.
Section 4 Antivirals	
R15	The Department of Health should continue to review the size of the current stockpile of oseltamivir (Tamiflu) and as a matter of urgency revisits the decision not to stockpile zanamivir (Relenza) at the same level for use especially where resistance to oseltamivir is suspected.
R16	WHO will have a central role to ensure that the data are available from the first reported outbreaks and resulting information is effectively disseminated to decision makers to guide interventions. The Department of Health should use its influence internationally to ensure this research is supported and can be done wherever the initial outbreaks occur.
R17	Intensification of the surveillance of the sensitivity of current human and avian influenza viruses (H5N1 in particular) to antiviral drugs (the M2 and neuraminidase inhibitors) should be coordinated by WHO and undertaken on a global basis. In particular, the system should ensure that surveillance has the sensitivity to measure the degree to which resistant virus is being transmitted in the community.
R18	The evidence base for antiviral treatment of individuals in risk groups (eg those with an immune deficiency condition) needs to be reviewed by the Department of Health and if necessary expanded, with particular emphasis being placed on protocols to minimise emergence of resistance in such populations.
R19	Research in both industry and academia aimed at the development and evaluation of novel antivirals for influenza should be encouraged and supported. Extensive links already exist between academic research and the pharmaceutical industries and public-private partnerships could be developed in this area.
Section 5 Human vaccination	
R20	Many very young children are immunologically naive to influenza and further research is needed on the characteristics of primary immune responses and the safety and efficacy of the use of seasonal and pandemic influenza vaccines in children. We recommend that this research is supported by the Department of Health as a matter of urgency.
R21	The Department of Health should make samples of the recently purchased H5N1 vaccines available to the research community, as soon as is practicably possible, and the MRC should solicit high-quality research application specifically to analyse these pandemic influenza vaccines.
R22	The Department of Health should make arrangements with industry that allow it to be open and transparent in its decision making and procurement processes, to use independent experts to advise as appropriate, and make the evidence on which decisions are made available to the scientific community.

R23	The Department of Health should continue to expand its seasonal influenza vaccine programme and relax rules about individuals outside the 'at risk' groups purchasing seasonal influenza vaccines directly from NHS General Practitioners, to encourage industry to increase production capacity.
R24	The Department of Health and the vaccine industry should continue to evaluate the use of whole virus vaccines and monitor the results of ongoing trials of whole virus vaccines against H5N1.
R25	As a matter of urgency the Department of Health should take the lead in assembling a work programme with industry and academia for the development of new adjuvants for vaccines. This should be done in parallel with clinical trials to compare directly the effectiveness of current adjuvants with existing H5N1 pandemic vaccines, with whole virus vaccines and with information sharing from ongoing trials.
R26	WHO should coordinate a global project for sharing information and data on ongoing influenza vaccine research and development, in both the commercial and academic sectors.
Section 6 Public health	
R27	The Department of Health should commission external experts to scrutinise the revised pandemic influenza plan and where appropriate should form expert groups to review critical aspects of the plan.
R28	The HPA, and Department of Health should identify research that should be conducted to identify those non-pharmaceutical interventions likely to have the greatest impact and, where appropriate, commission trials to assess the effectiveness of these interventions.
R29	Bodies such as the European Commission should consider ways to stimulate an environment which would encourage investment in new diagnostic products for influenza.
R30	The government, together with the Economics and Social Research Council, should consider procedures to collect data on behavioural and attitudinal patterns, both currently and throughout a pandemic. These data would also allow subsequent analyses of impact of the outbreak and, more importantly, provide the basis for predictive models of behaviour that could be used in refining and improving planning for future pandemics of influenza and other infectious diseases.
R31	To ensure the communications strategy for pandemic influenza is fit for purpose we recommend that the government's planned communications strategy should be subject to independent review and testing within six months of the publication of the revised Pandemic Plan.
R32	Consultations should be undertaken now with stakeholders about the most appropriate data to be collected and the most effective methods to collect these data in order to evaluate the impact of a pandemic. Having a database that will serve the purposes of modelling and prediction as well as evaluation should be attempted.
Section 7 Science policy	
R33	A leading non-governmental scientist in the area of influenza should be appointed as lead questioner and adviser to MISC32 for specific issues, complementing the roles of the Government's Chief Scientific Adviser (CSA) and the Chief Medical Officer (CMO). This scientist should be appointed jointly by the CSA and CMO in discussion with relevant learned societies. This model should be adopted in all future Ministerial committees for other animal and human health emergencies.
R34	The role and remit of science advisory committees in relation to pandemic influenza should be made explicit and the organisational decision making routes should be clarified to show how scientific advice is utilised.

R35	In order to incorporate scientists from a broad range of disciplines, and the scientific advice being generated by the range of science advisory committees across government, into a focal point we recommend that the Department of Health's Pandemic Influenza Scientific Advisory Group becomes a single cross-government Scientific Advisory Committee on pandemic influenza jointly chaired by the CMO and the CSA. In addition to relevant cross-governmental representation, the committee's membership should be drawn directly from the scientific, veterinary, social science and medical communities as well as from the commercial sector.
R36	The Department of Health, Defra and the Civil Contingencies Secretariat should continue to ensure that they are collecting and using evidence from a wide range of independent sources, both from within and external to government. We urge all departments involved in pandemic preparedness to be open and transparent in their decision making by publishing minutes of meetings and the evidence on which the decisions are made as soon as possible, in keeping with the CSA's <i>Guidelines on scientific analysis in policy making</i> .
R37	WHO and OIE should review their processes for obtaining scientific advice on pandemic influenza and introduce a clearly defined, open and transparent mechanism. Nations around the world need to continue to support WHO, and to allow data and results to be made immediately available internationally.

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Annex 1 Preparation of this report

This report has been prepared by the joint Royal Society and Academy of Medical Sciences working group on pandemic influenza. The following members of the working group were invited in their personal capacity rather than as a representative of their organisation:

Chair

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Director of the Medical Research Council National Institute for Medical Research (until October 2006)

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Review panel

This report was reviewed on behalf of the Councils of the Royal Society and the Academy of Medical Sciences by a review panel comprising the following people. The reviewers were not asked to endorse the findings or recommendations of the report.

Professor David Read FRS (Chair)
Biological Secretary and Vice-President, the Royal Society

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Annex 2 Individuals and organisations giving evidence

On 1 March 2006, the Royal Society and the Academy of Medical Sciences issued a call for written evidence for the pandemic influenza study. This was followed by a number of oral evidence sessions.

The following is a list of the individuals and organisations who gave evidence to the study in writing and/or orally. The views of individuals do not necessarily represent those of their organisations. Reports of the oral evidence sessions and the written evidence submitted are available on both academies websites (www.royalsoc.ac.uk/influenza and www.acmedsci.ac.uk).

The Royal Society and the Academy of Medical Sciences are most grateful to all who assisted this study by providing evidence.

Evidence submitted at meetings of the working group

Sir Roy Anderson FMedSci FRS
Chief Scientific Adviser, Ministry of Defence

Professor Robert Belshe
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Dr Ian Brown
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Sir Liam Donaldson FMedSci and Dr David Harper
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Dr John Edmunds
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Dr Douglas Fleming FMedSci
Royal College of General Practitioners Birmingham Research Unit

Stephen Gardner
Novartis Vaccines

John Harrison
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WHO Influenza Centre, National Institute for Medical Research

Howard Hellig
Consultant poultry veterinarian

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Head of the Civil Contingencies Secretariat, Cabinet Office

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Dr Ann Norwood
Department of Health and Human Services, Washington DC, USA

Dr David Salisbury
Director of Immunisation, Department of Health

Jeffrey Vergerson
Free range egg producer and trustee of the British Egg Marketing Board

Dr Alison Webster, Dr Margaret Tisdale, Dr Hillar Kangro and Dr Chris Worth
GlaxoSmithKline

Professor John Wilesmith
National Emergency Epidemiology Group, Department for Environment, Food and Rural Affairs

Dr John Wood and Dr James Robertson
Division of Virology, National Institute for Biological Standards and Control

Professor Maria Zambon and Dr John Watson
Health Protection Agency

Written responses to the call for evidence

(i) Organisations

Association of the British Pharmaceutical Industry
Biotechnology and Biological Sciences Research Council
British Medical Association
Department for Environment, Food and Rural Affairs
Department of Health
Economic and Social Research Council (submitted in confidence)
European Medicines Agency
Food and Agriculture Organisation of the United Nations
Health Protection Agency
Medical Research Council
National Institute for Biological Standards and Control
Novartis Vaccines (formerly Chiron Vaccines)
Royal College of General Practitioners
The Royal College of Physicians and the British Thoracic Society
Royal Society for the Protection of Birds
Society for General Microbiology
Veterinary Laboratories Agency
Wellcome Trust

(ii) Individuals

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MRC Biostatistics Unit Cambridge

Dr Royston Flude and Dr Pete Moore

Dr John Godfrey
London

Dr Kathleen Harriman
Infection Control and Antimicrobial Resistance Unit, Minnesota Department of Health, USA

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Professor Graeme Laver FRS
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Professor Arnold Monto
School of Public Health, University of Michigan, USA

Dr Hilary Pickles
Director of Public Health, Hillingdon Primary Care Trust

Acronyms and abbreviations

BBSRC	Biotechnology and Biological Sciences Research Council
CCS	Civil Contingencies Secretariat
CMO	Chief Medical Officer
CSA	Government's Chief Scientific Adviser
Defra	Department for Environment, Food and Rural Affairs
ESRC	Economics and Social Research Council
EU	European Union
FAO	Food and Agriculture Organisation of the United Nations
G8	Group of Eight industrialised nations
GOARN	Global Outbreak Alert and Response Network
GP	General Practitioner
GPHIN	Global Public Health Intelligence Network
GSK	GlaxoSmithKline
H	haemagglutinin
HPA	Health Protection Agency
MISC32	Ministerial Committee of the Cabinet on Influenza Pandemic Planning
MRC	Medical Research Council
N	neuraminidase
NIBSC	National Institute for Biological Standards and Controls
NIMR	Medical Research Council National Institute for Medical Research
NISN	Neuraminidase Inhibitor Susceptibility Network
OIE	World Organisation for Animal Health
R	Recommendation
SAC	Science Advisory Council of Defra
SAG	Pandemic Influenza Scientific Advisory Group of the Department of Health
SARS	Severe Acute Respiratory Syndrome
UKNIPC	UK National Influenza Pandemic Committee
UN	United Nations
VLA	Veterinary Laboratories Agency
WHO	World Health Organization
WTO	World Trade Organization

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