



This submission was prepared in consultation with Academy Fellows drawn from across the Fellowship, from laboratory to clinic. We have also drawn upon the report of the Academy's meeting with the Chief Medical Officer, Sir Liam Donaldson FMedSci, which took place on 20 September 2005. We are much indebted to Sir Liam for sharing his thoughts and concerns with us and much of the discussion is reproduced here. A list of the Academy Fellows who were present at the meeting is annexed.

The evidence presented here is endorsed by the Academy's Officers.

### **The risk**

*How is the risk of pandemic influenza emerging in South-East Asia, and reaching the UK, being assessed; and how can this assessment be improved?*

*How great are the risks, and what confidence can be placed in these figures?*

*How is the UK working with international bodies to: monitor the development of the virus; and reduce the risk of pandemic influenza emerging and spreading?*

1. Evidence shows that H5 bird flu is spreading ever wider and it is now acknowledged that it is not a matter of whether a pandemic will occur, but more a matter of when. It seems most likely that a pandemic will originate in South East Asia. There are significant concerns about the lack of surveillance in likely pandemic influenza source countries. Following the SARS episode, China took advice from the UK Health Protection Agency (HPA), World Health Organisation (WHO) and others on improving surveillance mechanisms, but progress appears to have been slow. The Government, in conjunction with WHO, must work for greater openness and improved surveillance in the relevant countries. Ultimately, it is unrealistic to suppose that an emerging infection will be contained in South East Asia.
2. It should be noted that an outbreak may not necessarily occur in the Far East. Influenza can spread via wild migrating birds, as well as poultry and people. The American experience with West Nile Virus demonstrated that migratory birds can rapidly spread infectious disease from East to West, as well as North to South. It is therefore crucial that disease in bird populations is monitored across Europe and the UK, in addition to South East Asia. Similarly, in the event of an outbreak, measures must be taken to protect British bird flocks. Current surveillance work by the Department for Environment, Food and Rural Affairs (DEFRA) in this area should be strengthened and communication between the human and animal health sectors encouraged.

### **Contingency planning in the UK**

*What is the current assessment of the likely impact of pandemic influenza on the UK (both in terms of health and on wider society, including the economy)?*

3. The current H5N1 strain of avian influenza circulating in South East Asia is extremely virulent, killing approximately half of those people infected. Although this information is based on only small number of human

infections (~120) it is reinforced by the viruses' very aggressive behaviour *in vitro*. If virulence does not diminish when the virus achieves human-to-human transmission, mortality will be significantly greater than the 1968 pandemic. The Academy therefore considers that the Government should plan for more than the currently estimated 50,000 pandemic flu cases.

4. Pandemic flu, unlike seasonal strains, does not disproportionately affect older people, but will impact on all age groups. However, morbidity and mortality are likely to be particularly high in already vulnerable populations such as those with diabetes, cardiovascular disease and those taking immunosuppressants. Babies under 1 year old are also especially vulnerable.

*How well co-ordinated are health, emergency and other essential services for responding to a pandemic?*

5. As mentioned previously, the Academy is concerned that an underestimate of the likely number of UK pandemic flu cases will prevent effective co-ordination of health and other services. A significant concern is the assumption that local healthcare managers have robust local plans for coping with a flu pandemic. The Government should consider potential difficulties in switching largely devolved health administrations to a centralised system of 'command and control' for the duration of the outbreak.
6. The Academy is particularly concerned about the lack of planning for management of critical care services in the event of a flu pandemic. Modelling work carried out by the Professor David Menon *et al* has shown that an 8-week pandemic with 25% attack rate could create a demand for critical care beds at 208% of current capacity. An optimistic estimation of impact factors (50% reduction in critical care demand with neuraminidase inhibitors and upgrading of some beds to critical care levels), results in critical care bed occupancy at 75%<sup>1</sup>. It should be noted that staff illness rates of 25% will severely undermine normal, let alone enhanced, critical care services.
7. However, critical care capacity can be expanded, for instance by co-opting surgical recovery areas and/or operating theatres. There is a further problem that current critical care bed density does not reflect population density and may not reflect the geography of an outbreak. The need to transfer both patients and staff must therefore be examined.
8. Planning for the management of critical care services during a pandemic should include:
  - Creation of libraries of equipment to be mobilised if an expansion of critical care services is needed;
  - Details of how critical care departments could expand into theatre recovery areas and some operating theatres;
  - Provisions to transfer patients and staff between critical care facilities;
  - Careful logging of non-NHS critical care resources;
  - Clear recognition of triggers to signal the cancellation of elective surgery (and planning for the period of catch up in the months following a pandemic);

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<sup>1</sup> Menon DK *et al* Modelling the impact of an influenza pandemic on critical care services in England *Anaesthesia* 2005; 60: 952-4

- The impact of how the critical care focus on influenza will negatively affect facilities available for other services.
- Expansion of mortuary facilities.

*What is being done to ensure that the general public are aware of the risks and likely effects of a pandemic, and of how they should react?*

9. The Academy considers public understanding of the risks and effects of a pandemic to be crucial. There appears to be a general lack of understanding about the nature of pandemic flu and its relationship/differences with bird flu and 'normal' seasonal flu. There also appears to be a lack of appreciation amongst the public that some harm will result from a pandemic, whatever measures are put in place. The Government must be explicit in communicating that a pandemic cannot be entirely prevented, but work can be done to limit the damage. Public health measures such as school closures and patient isolations will operate more effectively if there is full public understanding of the issues involved. Effective communication will be crucial in potential instances where measures appear counter-intuitive to journalists and the wider public. For instance, preventing incoming flights from affected countries might provide public reassurance, but there is little evidence that such social controls of movement are effective in preventing the spread of infection.
10. Care should be taken to ensure that public messages regarding a pandemic are accurate. For instance, the public should be aware of the true number of antiviral doses available and who will receive them. Issues relating to 'essential workers' are relevant to this and are discussed below.

*Is the UK's stockpile of antiviral treatments adequate, and how will it be distributed? What steps are being taken to ensure that the UK has access to sufficient antiviral treatment and vaccine in the event of a flu pandemic?*

11. Current Government information indicates that the target stockpile of 14 million antiviral doses will be reached in approximately one year (covering 25% of total UK population). The Academy is concerned by the lack of detailed plans on who should receive antiviral treatments and when. A key element is defining an 'essential worker', upon which Government policy is unclear. Essential workers are not necessarily restricted to the public sector, for instance supermarket lorry drivers would provide a key service in delivering food during a pandemic. The size of the 'essential worker' population must be known in order to assess the impact on the antiviral stockpile. The identification of key workers within health care institutions and those who should hold a limited antiviral supply is particularly important.
12. It is also unclear how the Government intends to use antivirals in a pandemic situation. Relatively little is known about the impact of antivirals on disease outbreaks, with the only available data originating from Japan. Therapeutic and prophylactic treatment would require a supply of 1 week and up to 6 weeks per individual respectively. Current Government policy does not appear to favour prophylactic antiviral use, which would deplete the stockpile very rapidly. Rather, antivirals would be given to people displaying early flu symptoms, in order to reduce severity, infectivity and mortality. However, it might be considered unreasonable to ask essential workers to expose themselves to infection without prophylaxis. If essential workers are to be given prophylactic antivirals, the longer duration of treatment will significantly impact on the number of doses available.

13. A programme of research on the effects of antivirals is therefore very important. While the mechanism of antiviral action allows viral replication, it is unknown whether this elicits immunity to re-infection. It is also unknown how long any such immunity would last. Viruses that become resistant to antiviral treatment show a considerable drop in neuraminidase activity. However, more research is needed into the transmissibility of resistant strains. It would also be useful to know if antiviral treatment reduces transmissibility within households.
14. Effective distribution of, and access to, antivirals must be ensured. Similarly, essential workers who may be required to 'self-diagnose' and commence antiviral treatment will require clear and robust guidance. Pressure on those holding small antiviral supplies may become intense in a pandemic situation. It is essential that such people receive effective guidance and support.
15. The Government should review the licensing arrangements for antivirals. For instance, neuraminidase inhibitors are not licensed in babies, who would be particularly vulnerable in a pandemic situation.

*What will be the role of vaccine development, manufacture and distribution in responding to a pandemic?*

16. Government policy on vaccination accepts the inherent difficulty that the particular strain of a pandemic can never be known in advance. Policy is therefore focused on early identification of the strain and shortening the time for vaccine production. However, it appears that this position has evolved and the Government has now tendered for 1-2 million doses of vaccine active against the current H5N1 bird flu strain.
17. There is a question of whether, in mutating to a human transmissible form, vaccines against current bird flu virus would be rendered ineffective. Alternatively, the mutation may be small enough to allow some vaccine protection. The Academy therefore welcomes the Government's initiative and recommends that expansion of vaccination with current bird flu vaccines should be considered. We understand that the Government has considered adding the bird flu vaccine to the seasonal flu jab, but manufacturing difficulties have prevented taking this further.
18. However, further R&D must be undertaken to establish an optimal vaccination strategy. The Academy is concerned that the Department of Health (DH) is not sufficiently active in the field of vaccine R&D to confront an emerging threat. The UK has previously been at the forefront of work on the development and assessment of candidate pandemic flu vaccines. Research on an avian H5 Duck Singapore virus vaccine, as well as on an H9 vaccine highlighted several challenges. Current H5 flu vaccines are poorly immunogenic when given in conventional subunit form (i.e. as currently manufactured), with 80-90µg protein required to elicit an immune response. This significantly reduces the number of available doses.
19. It cannot be assumed that a new vaccine is safe, especially if it is very different from existing vaccines. It is likely that immunising a large proportion of the population would give rise to side effects. It is therefore essential that safety and efficacy trials on potential H5 vaccines be performed in advance of an epidemic.

20. The Academy urges the DH to initiate studies to:
- Investigate different vaccine formulations (adjuvanted and non-adjuvanted, subunit and whole virion);
  - Investigate different vaccine doses;
  - Evaluate priming to a future antigenic variant
  - Evaluate safety and antigenicity in different populations (children, adults, older people)
21. When planning R&D strategies it is important to consider that pharmaceutical companies are committed to making conventional vaccines for both northern and southern hemisphere countries and only have a short period available each year to research 'experimental' avian flu vaccines. Researchers also stress that generic difficulties with the regulatory framework for clinical research may prevent studies being approved and undertaken quickly.

*What is the long-term strategy for reducing the threat of pandemic influenza?*

22. Long term strategies for reducing the threat of pandemic influenza must be multi-faceted. Research needs and opportunities are the focus of this response. It is crucial that research agencies and funders consider in advance what research questions should be carried out during a pandemic, as it will be extremely difficult to conduct research in an emergency situation. Current work in this area by the DH and Medical Research Council should be strengthened. It may be the case that researchers working in other areas would be keen to switch to flu-related research in a pandemic situation. The DH should compile a list of such researchers.
23. In the event of a pandemic, the Government should consider the collection and fractionation of serum from convalescent patients (as soon as they exist), perhaps to provide a bank of immune immunoglobulin for future prophylaxis. Similarly, it will be important to know whether there are any genetic associations with mortality, morbidity or survival with pandemic influenza. Preparations should be made to collect and store DNA samples for future association studies.

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Annex: List of Academy Fellows who attended a meeting with CMO on 20 September 2005

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Sir Keith Peters FRS PMedSci (Chair)  
Professor Frances Ashcroft FRS FMedSci  
Professor Jangu Banatvala CBE FMedSci  
Professor Charles Bangham FMedSci  
Professor Tony Butterworth CBE FMedSci  
Dame Barbara Clayton CBE DBE FMedSci  
Professor John Collinge CBE FRS FMedSci  
Professor Mary Collins FMedSci  
Professor Marcela Contreras FMedSci  
Professor Dorothy Crawford OBE FRSE FMedSci  
Professor Sally Davies FMedSci  
Professor James Edwards CBE FMedSci  
Professor Alfred Emmerson OBE FMedSci  
Dr Douglas Flemming OBE FMedSci  
Sir Charles George FMedSci  
Sir Andrew Haines KBE FMedSci  
Professor Frank Harris CBE FMedSci  
Professor Christopher Higgins FRSE FMedSci  
Professor Anne Johnson FMedSci  
Professor Sanjeev Krishna FMedSci  
Professor Simon Kroll FMedSci  
Professor Michael Langman FMedSci  
Professor Ian Lauder FMedSci  
Professor Andrew Lever FMedSci  
Mrs Mary Manning (Executive Director)  
Professor William McDonald FMedSci  
Professor Andrew McMichael FRS FMedSci  
Professor Klim McPherson FMedSci  
Professor Thomas Meade FMedSci  
Professor David Menon FMedSci  
Baroness Onora O'Neill CBE PBA FMedSci  
Lord Naren Patel FRSE FMedSci  
Professor Mark Pepys FRS FMedSci  
Dr Sohaila Rastan FMedSci  
Professor Elizabeth Simpson OBE FMedSci  
Sir John Skehel FRS FMedSci  
Professor Stephen Smith FMedSci  
Lord Turnberg of Cheadle FMedSci  
Professor Peter Tyrer FMedSci  
Professor Herman Waldmann FRS FMedSci  
Professor Robin Weiss FRS FMedSci

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The Academy of Medical Sciences  
10 Carlton House Terrace  
London, SW1Y 5AH  
Tel: +44 (0) 20 7969 5288  
Fax: +44 (0) 20 7969 5298  
e-mail: [apollo@acmedsci.ac.uk](mailto:apollo@acmedsci.ac.uk)  
Web: [www.acmedsci.ac.uk](http://www.acmedsci.ac.uk)

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