HEALTH PROTECTION AGENCY

Submission of Evidence

to

Royal Society/Academy of Medical Sciences
Study on Pandemic Influenza

4 April 2006

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INTRODUCTION

This study is welcomed by the HPA, much has been achieved in developing the UK's preparedness for a pandemic due to a novel influenza virus, but there is still more to be done. The World Health Organisation and the European Communicable Disease Centre recently inspected the UK's plans and commented that the UK was amongst the best prepared in the world. The HPA considers this challenge as its most important priority and there is an enormous amount of ongoing work with the Department of Health, other government departments, its partner agencies and the National Health Service. The HPA believes that this study will help to focus future activities to achieve improved preparedness. The HPA's responsibilities and activities are set out in the first section of this submission, in the second section the questions set out in the call for evidence are addressed. The study has already requested oral evidence from two of its experts, Dr. Maria Zambon, Head of the Influenza Laboratory and Dr. John Watson, Head of Respiratory Infections at the Centre for Infections. They will be able to amplify this submission. We note the composition of the working group and recognise their expertise and eminence but wonder if a wider public health input would help their deliberations. The HPA's activities in preparing for pandemic influenza and for avian influenza are coordinated through the Influenza and Respiratory Viruses Programme and the Pandemic Influenza Coordination Office. The Programme Lead and other members will be available to give evidence to the study, as required. Finally, an appendix is attached giving details of plans and guidance documents published on the HPA website.

THE HPA'S RESPONSIBILITIES AND ACTIVITIES

Pandemic Influenza

- **Surveillance and Diagnostics**
  - ***Clinical surveillance***
    - obtain and analyse information on international and national influenza activity (including laboratory, clinical and mortality data)
    - distribute data on a regular basis
    - coordinate surveillance from the devolved administrations to produce data for the UK
    - ensure that appropriate data collections are in place to provide information of sufficient details to inform UK decisions
    - have mechanisms in place to collect information on the outcomes of the various treatment regimens being used nationally and internationally
    - monitor vaccine uptake to include pandemic influenza vaccine when it becomes available, seasonal influenza vaccine and pneumococcal vaccine
  - ***Virology and Microbiology***
    - characterise strains of human influenza viruses isolated in the UK, both through routine and structured sampling
    - work with partner agencies to understand the impact of animal influenza viruses
    - assess antibody status of samples of the population
    - collect data on bacteria complicating influenza and their antimicrobial sensitivities and make recommendations to incorporate into clinical guidance
  - ***Outbreaks***

- identify clusters of unusual respiratory illness that may be caused by a new virus
- investigate suspected human cases of avian influenza, particularly if there is a history of travel to affected areas or contact with sick birds
- assess the threat to the UK posed by outbreaks of avian influenza in other countries

o ***International***

- contribute to WHO and European influenza surveillance schemes and maintain close links with WHO
- maintain capacity to contribute effectively to WHO's Global Influenza Surveillance Network

o ***Laboratory Services***

- lead the laboratory investigation of samples, the arrangements for laboratory testing in the UK and develop a strategy for escalation
- optimise and maintain laboratory capability and capacity to monitor prevalent viruses, identify new viruses and monitor antiviral susceptibility
- improve and standardise NHS laboratory investigation and protocols for the referral of isolates/specimens to the National Influenza Reference Laboratory
- ensure that the HPA has an adequate regional diagnostic capability

- **Advice, Guidance and Operational Support**
  - provide specialist public health advice together with operational and investigative support to DH and the NHS
  - provide specialist emergency planning advice to DH and the NHS
  - advise the DH on control policies for seasonal and pandemic influenza
  - produce infection control guidance for all health care settings
  - assist other departments and agencies in the development of control of infection guidelines for specific settings
  - coordinate the development of UK national guidelines for health professionals to include outline treatment and case management protocols
  - maintain public health advice on the HPA website

- **Operational**
  - in England, through local Health Protection Units, coordinate the local public health response, support NHS Trusts and Local Authorities in their responses and ensure cross linkages between HPUs and NHS Trusts are specified in local plans
  - participate in HPA-led UK arrangements to ensure as far as possible a consistent UK-wide public health response

- **Research & Development**
  - research the virology and epidemiology of influenza viruses
  - support the development of improved influenza vaccines
  - research into mathematical, epidemiological and operational modelling to inform planning
  - discuss research needs with relevant stakeholders in the event of a pandemic and develop and maintain research protocols to implement during the pandemic

The HPA responsibilities do not include:

- procurement, storage, distribution and prescribing of antivirals to the population. This is a DH responsibility

- procurement, storage, distribution and prescribing of pandemic influenza vaccines. This is a DH responsibility.

Avian Influenza

- the development of plans and protocols to assist the State Veterinary Service of DEFRA in their responses to suspected and confirmed avian influenza outbreaks
- to carry out the public health risk assessment for those exposed to sick or dead birds
- the delivery of appropriate public health measures and medical countermeasures including antivirals and seasonal influenza vaccine
- to provide information to the public in the locality
- to keep records of those exposed and potentially exposed and carry out serological surveillance as required

THE FOCUS OF THE STUDY

- *What does the scientific understanding (basic research to clinical application of avian and pandemic influenza, in the short term and long term imply for*
  a) Treatment: the use of existing and the development of new drugs and vaccines

The HPA has not been involved in the development of antiviral drugs, this is a matter for the pharmaceutical industry, but will monitor for resistance to antiviral drugs during a pandemic. The modelling carried out by the HPA in conjunction with modellers from DH and Academia has informed the requirement for antiviral drugs.

Vaccine programmes for avian influenza have been slow to develop internationally. This is a reflection of the formidable technical and regulatory hurdles involved in making vaccines which are lethal to embryonated eggs, and which pose a biohazard to humans and the environment. Nevertheless, with cooperative working of government agencies (the Health Protection Agency and the National Institute for Biological Standards and Control (NIBSC), with industry (Chiron/Aventis/Berna), and academia (the Universities of Leicester and Reading), most of the information that is available globally about the human immune response to avian influenza vaccines has been garnered through Phase I clinical trials held in the UK.

This work, and other international initiatives, is summarised in a Lancet review article published in 2003. Further H5 H7 and H9 vaccine trials are planned in the UK and Europe over the next 12-18 months. The pace of vaccine trials in increasing as international efforts in the US, Japan and Australia add to the pool of knowledge that will allow us to design better pandemic vaccines in a short time frame.

At present, the time it will take to respond with vaccine production means that very little vaccine would be available until 6 months after the emergence of a new pandemic. It is also essential that we learn how to make less vaccine go further, and develop processes which allow rapid scale up for mass vaccination campaigns. Future UK clinical trials are directed at developing a strategy for delivery of pandemic vaccines to all age groups and understanding how to develop the best immune responses.

HPA has been requested by DH to put together proposals based on the HPA's contribution to pandemic influenza vaccine development and production. The HPA can undertake a number of activities in support of industry for the production of pandemic influenza vaccines. These are:

- Support NIBSC in its production of a library of PR8 reference strains reflecting virus strains that are thought to have the potential to become pandemic strains, such as avian influenza strains that have caused disease in humans (H5N1, H7N7, H9N3).

- Cross-protection studies of the library reference strains in a suitable animal model (e.g., ferrets) to ensure the strains can protect against wild type and related strains.

- Clinical trials of mock-up vaccine strains produced by industry in different populations (healthy adults, children, senior adults, people with underlying diseases).

- Setting up a network and protocols in advance for post-marketing surveillance of the pandemic vaccine once deployed in a pandemic situation.

b) Clinical care: diagnosis, basic understanding of the diseases, infection control, transmission

The HPA is responsible for diagnostic test development and the roll-out of the capability to ensure the UK is prepared.

Development of laboratory molecular diagnostic capability, including rapid molecular diagnostic tests with high specificity and sensitivity, are already required in the interpandemic period to rule out H5 infection in travellers returning from SE Asia with influenza like illness (ILI) and a history of contact with birds. At present there are approximately two requests a week for such tests from somewhere in the UK. Clinical diagnostic algorithms used to apply such tests are explained on the Agency's website (www.hpa.org.uk/infections/topics_as/avianinfluenza/pdfs/Algorithm.pdf). There are currently no commercial kits for H5 molecular diagnosis.

Most influenza molecular diagnostic approaches depend on detection of conserved internal genes. This allows typing (influenza A or B), but not sub-typing. Specific detection of H5 requires identification of the haemagglutinin (HA) gene, which is highly variable, and, it would be difficult for medical companies to achieve the validations necessary to ensure recognition of all circulating H5 strains. This would have to include recent strains where sequence information is not in the public domain and rapid changes in sequence are to be expected. The fact that circulating H5 viruses are also highly virulent adds a further layer of complexity to the validation of any laboratory assays.
National diagnostic preparedness there relies upon assays developed in the Agency's national influenza reference laboratory which, I collaboration with the WHO global influenza network, has the facility to work on the highly pathogenic influenza viruses. Information and virus strains are shared between laboratories in this network.

Regional Laboratory Capability: A network of 19 laboratories across the UK has been established to provide a capability for rapid molecular testing for H5 and with confirmatory molecular strategies. This has involved a training programme and the setting up of a proficiency testing scheme. Whilst provision of molecular diagnostic capability for diagnosis of H5 is important during interpandemic periods, and would be important in the early stages of an actual H5 pandemic to confirm the presence of the virus in the UK, it is unlikely that at the height of a pandemic there could be application of molecular diagnosis to even a fraction of clinical cases.

Near Patient Test: It is much more likely that at the height of a pandemic, clinical judgement coupled with a rapid triage of cases that included selective testing would be the way that diagnostic tests would be used. Some of the most recent "near patient" test kits for influenza, such as QuickVue™ or QuickS-influA.B "Seiken" might be used for triage of cases to detect all influenza subtypes, including H5, but don't distinguish between them. They require little specialist skill and no special equipment to complete. They provide information that a person has influenza but do not define the subtype. Such information would be a useful adjunct to clinical judgement and might provide a rational way to use antivirals for treatment in the acute

hospital setting. It would also be feasible for such tests to be available in all hospital settings, even those that currently do not provide virological diagnosis, without referring samples to specialist centres. Familiarity with such kits can be gained in managing ordinary seasonal influenza.

The Agency's national reference laboratory maintains a watching brief on tests that are intended for the UK market, summarising data on sensitivity and specificity, and assessing the tests for user friendliness.

The basic understanding of the disease requires an understanding of the science of pathogenicity and transmissibility of the potential pandemic viruses.

Transmissibility and Pathogenicity may be on either side of a scale of balances, and are not identical biological properties. Tipping the balance in favour of one may diminish the other. Attempts to understand these properties of influenza viruses have gathered momentum internationally with the availability and use of reverse genetics techniques. These allow dissection of individual molecular motifs and determination of their contribution to transmission and virulence. Such work requires high containment laboratories and extensive negotiation with safety regulators as designer viruses created in this way to address precise questions, may be viewed as laboratory monsters unless appropriate safeguards are in place.

Nevertheless, important information will emerge about the necessary gene constellations for Pathogenicity and transmissibility which in turn will inform risk assessment about the probability of current circulating H5 strains acquiring the capacity to transmit between humans. Most of this work is carried out in the US, where the funding for such work is more easily obtained. The Agency's influenza laboratory's work, in collaboration with the University of reading, has already identified that a minimum of two amino acid changes at the viral receptor binding site are required to shift binding to the receptor on the host cell from an avian to a mammalian host preference. This may be important in understanding the nature of changes required for adaptation from an avian host to a human host.

The HPA has developed and published Control of Infection Guidelines for health care settings. These have been available on its website since October 2005 (www.hpa.org.uk). They were prepared by examining the evidence base available from previous outbreak studies and are centred around the basic facts about the disease; infectivity, shedding and survival of the virus outside the respiratory tract and transmissibility. These guidelines have been examined and approved by the Advisory Committee on Dangerous Pathogens and the Health and Safety Executive. They are currently being reviewed and updated.

The wearing of masks by the public to prevent infection in the wearer during a pandemic has not been systematically investigated to provide a clear cut answer. The public may wish to wear masks of their own volition but are not aware of the limitations of mask wearing. The HPA has looked at the evidence base that is available, three studies have been reported in recent years, and is currently working with DH on this potentially contentious subject

c) strategies and preparedness for an outbreak: modelling and surveillance

The HPA modelling teams at the Centre for Infections, Colindale, and the Centre for Emergency Preparedness and Response, Porton Down, have worked together with the Department of Health's operational modelling team and the academic department of Imperial College (Professor Neil Ferguson) to provide information on likely effects of a new pandemic influenza virus. This work has looked at the evidence base available from the previous pandemics and the expected characteristics of a new virus giving a range of outcomes expressed as expected numbers. They are modelling the potential interventions effects on the course of the pandemic in the UK.

This is a substantial piece of work and is continuing, the group is recognised as probably the most advanced in the world demonstrating the UK's joined up approach. A summary of this work can be made available.

The HPA's surveillance programme is essential for monitoring the current UK situation, recognising any new viruses and then moving rapidly into action to provide daily reporting and the information and data for real time modelling. The data collected from the first cases of a new pandemic will be vital to re-parameterise the existing models and consolidate the predicted course of the new pandemic.
The Health Protection Agency carries out surveillance of influenza in England, in collaboration with NHS and academic bodies, and collates influenza surveillance data from across the UK. The surveillance assesses influenza virus activity in the population and its impact on health, but not the impact of influenza on health services or its wider societal impact. Rapid assessment of influenza vaccine uptake is also carried out. Current surveillance has been developed for monitoring annual seasonal activity but is being revised and strengthened to enable it to continue to provide timely and detailed information during a pandemic. Surveillance information is used to inform local, national and international (European Commission and World Health Organisation) bodies of current UK activity.

Clinical and virological indices form the main elements of current surveillance. Consultation rates with general practitioners for influenza-like illness are obtained through sentinel practice schemes and complemented with aggregated data from computerised general practice consultation records. Rates of telephone requests from the public for advice from NHS Direct relating to relevant illnesses, mortality data from the Office for National Statistics, and reports of outbreaks of influenza are also collated.

Reports of influenza diagnoses made by hospital laboratories as part of routine clinical practice are collated locally and nationally, and supplemented by the examination of specimens from selected patients in the community by a network of regional laboratories and the national reference laboratory. The latter carries out detailed characterisation of virus isolates circulating in the UK.

The potential for an influenza pandemic to overwhelm the health service and routine surveillance mechanisms within the health service, and the possibility that methods of health care delivery may change during a pandemic, mean that current surveillance systems may not adequately capture pandemic influenza activity. Consideration should be given to health service independent methods of capturing activity and impact information through methods such as telephone polling.

- *What lessons can be learnt from other disease outbreaks and more general public emergencies and the associated emergency planning responses*

The lessons identified that are being learned relate to integration of emergency plans, exercising of emergency plans and communication with the public.

The requirement for integration of plans has become law in the Civil Contingencies Act and requires that responders work with each other to share plans. Cross-government working has been effectively achieved through the joint Cabinet Office/Department of Health Pandemic Influenza Working Group reporting to the Ministerial Select Committee on Pandemic Influenza (MISC 32).

As well as integration of plans, exercises of these plans on a multi agency basis provide a system for checking and improving plans. The HPA first developed exercises to test plans for SARS and terrorist threats in 2003. The exercise programme is funded by DH and delivers 10 exercises per year including pandemic influenza scenarios, these have been run in several regions. The European Commission contracted the HPA to deliver a pan EU exercise in 2005. The HPA is a world leader in delivering pandemic influenza exercises and has recently

been requested to deliver exercises for the WHO and for Viet Nam. Multi agency exercises are very complex and require detailed planning over several months in order to achieve the desired objectives of testing plans and providing an enjoyable learning experience for those taking part. Systematic arrangements have to be in place to ensure that lessons identified during exercises are learned.

Communicating information to the public both before and during a pandemic is an absolute requirement to minimise plans and social disruption. This is led by DH with HPA input and the HPA maintains scientific information for the public on its internet website.

- *How do wider ethical, social and regulatory issues including those associated with the development of new technologies influence current policy making and future preparedness*

There will be issues over ethical approval of studies necessary at the beginning of the pandemic when there will be an urgency to determine the, at present unknown, characteristics of a novel pandemic influenza virus. These studies need to be defined now and ethical approval for the collection of patient data and samples obtained. The necessary resources, human and monetary, also need to be determined and funding and plans put in place now. The HPA is working with DH to prepare for some of these studies and we are aware that the MRC is looking at mechanisms for pre-funding these studies that can only take place once a new pandemic virus has emerged.

The development of new technologies, for instance, for new rapid tests is held back somewhat because we do not know when a new virus will emerge and manufacturers are probably reluctant to commit large funds now. In addition the validation of tests to achieve the CE marking necessary for marketing are difficult to achieve when the pandemic strain has not yet emerged. The HPA is exploring funding options to enable joint work with The University of Cambridge for the development of new rapid dip-stick tests.

- *How is the scientific evidence (academic, public or commercial) being incorporated into policy making*

The HPA has developed its operational policies for the implementation of the pandemic influenza plan by always examining the evidence base that exists. This is exemplified in its control of infection guidelines, in the medical treatment guidelines and in the algorithms developed and published on the HPA website. The RIVM in the Netherlands has commented that these algorithms are excellent and scientifically soundly based.

There are however some areas where the evidence base is poor or missing, these include the use of masks by the public, the use of screening for the detection of infection in travellers to the UK and and quantitative risk assessment studies. Modelling can help to elucidate some of these problems but in itself is based on assumptions made from previous experience.

Appendix 1

HPA guidance docs available on the website

Main Pandemic Plan

HPA influenza pandemic contingency plan
http://www.hpa.org.uk/infections/topics_az/influenza/pandemic/fluplan.htm

Algorithms

Algorithm for the management of returning travelers and visitors from countries affected by avian influenza (H5N1) presenting with febrile respiratory illness
http://www.hpa.org.uk/infections/topics_az/influenza/avian/algorithm.htm

WHO PANDEMIC ALERT PHASE 3 Draft algorithm: Post-exposure prophylaxis (PEP) for contacts of confirmed human cases of avian influenza (H5N1) in the UK
http://www.hpa.org.uk/infections/topics_az/influenza/avian/documents/PHASE3PEPcontactsofconfirmedcasealgorithm080306DRAFT.pdf

WHO PANDEMIC ALERT PHASE 3 Draft Algorithm: Post-exposure prophylaxis (PEP) for farm workers/residents, SVS staff, and cullers involved in outbreaks of highly pathogenic avian influenza (H5N1) in poultry in the UK
http://www.hpa.org.uk/infections/topics_az/influenza/avian/documents/PHASE3PEPpoultryalgorithm280306DRAFT.pdf

WHO PANDEMIC ALERT PHASE 3 Draft algorithm: Management of human contacts in the event of confirmed highly pathogenic avian influenza [HPAI] (H5N1) in one or more wild birds in the UK
http://www.hpa.org.uk/infections/topics_az/influenza/avian/documents/PHASE3PEPwildbirdsalgorithm080306DRAFT.pdf

Department of Health and HPA Clinical Guidelines

Infection control in hospitals and primary care settings
http://www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4121752&chk=lfHfV7

Clinical guidelines for patients with an influenza-like illness during an influenza pandemic
http://www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4121752&chk=lfHfV7