Medical Research Council Response to the Royal Society and the Academy of Medical Sciences joint study on Pandemic Influenza

Background

MRC's contribution to influenza research

1. The MRC has made a long, sustained and significant contribution to influenza research. The human influenza virus was identified in 1933 at the MRC National Institute for Medical Research (NIMR). In 1948, the World Influenza Centre (WIC) was established at the NIMR at the behest of the then newly-established World Health Organisation (WHO). The Centre, now directed by Dr Alan Hay, has continued to work with a network of collaborating laboratories to detect and characterise the emergence of new influenza viruses anywhere in the world. For instance, the Centre helped detect the avian H5N1 and H9N2 viruses that caused human infections in Hong Kong in 1997, 1999 and 2003. The Centre also has a key role advising WHO on the composition of seasonal influenza vaccine. Sir John Skehel, Dr Hay and colleagues at the NIMR are also at the forefront of international research to discover how molecular changes in the virus affect its ability to infect people and cause disease. They have been instrumental in detecting and tracking H5N1 mutations in the current SE Asian/EU outbreaks.
2. The MRC is committed to sustaining and developing its world-leading influenza research programmes and to galvanizing UK biomedical research to meet the challenges of pandemic influenza. Building on our current investment in influenza research (£1.6 million per annum), we have made available an additional £10M over two years (2006/07) for research in this field. The first awards under this Call for Proposals (see below) will be made in May 2006. The current portfolio is summarised briefly at Annex 1.

Development of research strategy

3. MRC's Council considered in July 2005 the public health threat of pandemic influenza. Council recognised the action being taken by the UK Health Departments and of health protection agencies nationally and internationally to prevent and plan for a pandemic, and the MRC's own contribution in this area. It approved activities for the MRC Infections & Immunity Board, chaired by Professor Andrew McMichael (Director of the MRC Human Immunology Unit, Oxford) to review Council's strategy for emerging infections with epidemic and pandemic potential. To cover the interim period, the MRC issued a Highlight Notice inviting research proposals on emerging infections with epidemic or pandemic potential.
4. In order to inform strategy and priorities in the area, Professor McMichael led an MRC scientific mission to South-East Asia in October 2005. This was followed in December 2005 by the hosting of an international expert & stakeholders' meeting in London entitled "Pandemic Influenza- Maximising the potential of research". Having identified its scientific priorities, MRC then issued the Call for Proposals in December 2005 (Annex 2)
5. The MRC is keen to stimulate new research, and welcomes collaborative proposals, including proposals with overseas or industry partners. As an innovation, the Infections & Immunity Board is willing to consider in principle funding for "readiness protocols." These will be to support research that can be put into effect only in the early stages of an epidemic – for example, clinical work on a newly circulating strain. In addition, the MRC will consider requests for putting other MRC grants that applicants hold in abeyance in order that urgent influenza research may be undertaken.

6. MRC is working with BBSRC, the Wellcome Trust, the Health Departments and the Health Protection Agency to survey the UK's main influenza research programmes. The survey will be resource for all the partners and contribute to MRC's ongoing strategy development in influenza. We anticipate the survey will be published.

Coordination of research

7. The Department of Health published a National Pandemic Influenza Contingency Plan in March 2005. It subsequently established a Scientific Advisory Group on Pandemic Influenza, on which MRC is represented. MRC officials are in regular informal contact with counterparts from the Health Departments, the Department for International Development, the Department for Food, Environment & Rural Affairs, the Health Protection Agency, the BBSRC, the OST, the Wellcome Trust, the Academy of Medical Sciences, and other Research Councils. Following on from a series of such meetings on fostering international collaboration in influenza research, a joint agency/funders' forum is being established to take this work forward.
8. Research issues in the field are also reviewed by Heads of International biomedical Research Organisations (HIROs). This informal grouping, which meets six-monthly, brings together the Heads of MRC, the USA National Institutes of Health, counterparts from Canada, Australia, New Zealand, several European national funders, and China (represented by a Vice-President of the Chinese Academy of Sciences).
9. I have regular contact with senior officials of the Chinese Academy of Sciences. The MRC has played a key role in fostering UK scientific collaborations in SE Asia and China.

Specific questions raised by the study

1. What does the scientific understanding (basic research to clinical application) of avian and pandemic influenza, in the short and the long term imply for:

a. Treatment: the use of existing, and development of new drugs and vaccines

Research is required across the board both in relation to questions needing answers in the short term, and longer term issues.

- Biological mechanisms – as a basis for new and better drugs and vaccines. From what we now know, the ability of currently available drugs and vaccines to stem a pandemic is extremely precarious. Better drugs and vaccines are also required for seasonal influenza.
- Better delivery of vaccines – e.g. more rapid scale-up of strain-specific vaccines in response to the emergence of dangerous novel strains; antigen-sparing strategies; novel adjuvants.
- Industry has a crucial role in vaccine research and development, but is likely to do so only with the right incentive structures. MRC welcomes research proposals from industry in partnership with UK academic institutions, although is not able to fund industry directly. There may be room for further European and national action to strengthen the market in Europe for seasonal flu vaccines.

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

Clinical and translational research is needed to understand the respective host and virus-mediated contributions to clinical disease and outcome.

- Currently, determinants of the clinical course are poorly understood, as are the most effective clinical care programmes.
- Epidemiology – to support risk assessment and effective intervention. Mathematical and epidemiological modelling to underpin prevention and control strategies.
- Development and evaluation of public health intervention strategies and technologies – for application in healthcare and community settings.

Some of this clinical research can only be undertaken where and when human cases arise (hence, most data to date have come from Vietnam and China); other studies can use seasonal influenza as a model.

c. Strategies and preparedness for an outbreak: modelling and surveillance

The WHO works closely with individual countries and the international community to monitor and verify the emergence of new flu strains and suspected human cases of zoonotic strains. It coordinates the WHO Global Influenza Surveillance Network[1], established in 1952, which now links four international WHO Collaborating Centres (of which the WIC at NIMR is one, see para.1) with 112 National Influenza Centres. The Network makes recommendations to the WHO on influenza vaccine formulation and acts as a global alert mechanism for new and dangerous influenza strains. The rapid control of Severe Acute Respiratory Syndrome virus (SARS) in 2003/4 owes much to the effectiveness of the WHO Network.

Strong surveillance and reporting systems in affected countries are crucial. The WHO reports that some affected countries do not yet have the requisite laboratory and epidemiological capacity. International collaborative support for affected countries in strengthening their capacity for national and local surveillance, active case finding and rapid response is a critical investment for the world.

- Collaboration with South-East Asian partners to maximise the rapid collection and analysis of high quality clinical data and samples in the pre- and early pandemic periods is crucial. International efforts must support rather than compete with national research aspirations and development of capacity in surveillance and research. The international community must take every opportunity to promote strong science and health protection strategies, and every effort must be taken to mitigate conflicts that arise between international and local interests.
- Reliable and rapid diagnostic tests that are robust under field conditions could be especially valuable in SE Asia. The OST's Foresight Project on the Detection & Identification of Infectious Disease may provide valuable insights into smart, adaptable technologies: the Project is due to report later in 2006. The potential value of testing at home ("self-tests") and in healthcare settings needs to be considered also in the context of a UK epidemic.

2. What lessons can be learnt from other disease outbreaks and more general public emergencies, and the associated emergency planning responses

The containment of SARS, despite its rapid intercontinental spread, offers some comfort as well as lessons. However, influenza is more transmissible than SARS and is considered less likely to be contained by public health measures than was SARS.

Contingency planning is led by the UK Health Departments. The Research Councils have a role in underpinning those plans with scientific advice (e.g. through the DH Scientific Advisory Group on Pandemic Influenza) and generating new knowledge and in developing and evaluating new technologies. It is crucial to build a strong evidential base to public health interventions – whether medical or non-medical.

UK mathematical modelling of outbreaks is at the international forefront. Professor Neil Ferguson (Imperial College) and others have pinpointed the importance of rapid (within days) recognition of small clusters of cases and intervention with antiviral drugs and other measures. It is less clear how effective these strategies would be in the face of a gradual evolution of strains with more efficient human-to-human transmission, and/or diffuse emergence on a widely dispersed geographic front in remote districts with poor communications.

However, much remains uncertain about the biology, clinical characteristics and epidemiology on which risk estimates are based. Consequently, while experts believe that a pandemic will occur, parameters such as timing, spread and scale are unpredictable. Furthermore, despite the current focus on avian H5N1, there is no guarantee that the next pandemic challenge will be from either avian H5N1 or indeed an H5 strain.

The WHO is coordinating action to strengthen surveillance systems regionally in SE Asia and its advice to countries is readily accessible. In relation to the zoonotic threat to human health, the WHO works with the World Organisation for Animal Health (OIE) and the Food and Agriculture Organisation (FAO). The OIE and FAO have in the recent years been assisting countries in South-East Asia with the control the severe avian influenza epidemic poultry. The culling in 1997 of the entire national poultry flock of 1.5 million birds of the Hong Kong Special Administrative Region is considered by the WHO to have averted a human pandemic. Effective surveillance of bird populations, outbreak and panzootic prevention and response are all essential to the protection of human health. This work needs to be underpinned by strong research that fully exploits the opportunities for collaboration between human and veterinary research.

3. How do wider ethical, social and regulatory issues, including those associated with the development of new technologies or treatments, influence current policy making and future preparedness?

There is no doubt that major ethical issues are raised by undertaking clinical research in a pandemic scenario, for instance getting informed consent from the critically ill or next of kin, collection and storage of clinical samples, and undertaking clinical treatment trials with novel therapies or regimes. While some of these issues are adequately covered by current legislation, others will require further discussion and clarification. However, ethics committees are, in principle, able to grant approval for proleptic "readiness" research studies. Licensing of novel vaccines and antivirals will also need to be addressed by the relevant authorities, in particular whether current guidelines are modified in this scenario.

The social implications of a pandemic are far-reaching, and how the public reacts in the face of a pandemic may pay scant regard to legal and regulatory issues (for instance, willingness to take risks which would, in normal day-to-day life, usually be unacceptable). The MRC has ongoing discussions with DH and relevant bodies concerning such issues.

4. How is the scientific evidence (academic, public or commercial) being incorporated into policy making?

There are significant questions about the appropriate intervention strategies at different stages of an outbreak and pandemic. For instance, would antiviral drugs be more effectively used as a prophylactic, or for early treatment (allowing a

degree of exposure to the virus and potentially engagement of the immune system) – and under what circumstances? UK expertise could contribute to answering such questions through collaborative research with clinical teams in SE Asia.

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Annex 1

Current MRC Programmes in Influenza

1. The MRC currently invests £1.6 million per annum on influenza research.
2. The MRC's principal investment in influenza research is at the National Institute for Medical Research (NIMR). The NIMR programme was recognised as being internationally outstanding in a recent a quinquennial review.
3. Sir John Skehel's programme focuses on the structural and functional characteristics of the virus surface that enable it to infect cells; and on the mechanism by which anti-haemagglutinin antibodies neutralise viral infectivity. His team recently explained how the haemagglutinin (HA) of the 1918 virus both retained receptor binding site amino acids characteristic of an avian precursor HA, and was able to bind to human receptors and how, as a consequence, the virus was able to spread in the human population. The programme has produced other major insights into the molecular basis of host range, pathogenicity and human-to-human transmission and into the pandemic potential of different influenza subtypes.
4. Dr Alan Hay leads the World Influenza Centre at the NIMR, monitoring changes in the virus that have significance for human health and protection as those changes occur: this work makes an important contribution to public health internationally. Dr Hay works closely with the HPA and with WHO Collaborating Centres in the USA, Japan and Australia and the global network of National Influenza Centres. Dr Hay also leads a programme of basic research on the mechanisms of action of resistance to anti-viral drugs, including the structural basis of M2-channel activity. Dr Hay also participates in international and EU networks concerned with viral drug resistance.
5. The NIMR has containment facilities that meet the HSE/DEFRA regulatory requirements and the Council is keenly aware of the need to make appropriate high containment arrangements in renewing the Institute in partnership with UCL. The renewal and partnership strategy offer significant advantages over current arrangements at Mill Hill in terms of strengthening translational research and integration with world class physical sciences.
6. The Council also funds a programme of research at the University of Oxford (Professor George Brownlee) to study transcription and regulation of influenza A virus. This is fine grained, basic molecular work on how the segmented RNA viral genome is copied in a regulated manner, and has the potential to lead in the longer term to production of novel influenza antivirals and vaccines.

A**NNEX 2**

MRC Call for Proposals in Pandemic Influenza

Scientific Priorities

- Little is known about the specific risk factors posed by avian flu for the human population. For instance, what are the specific modes of transmission? What can ecology, epidemiology and clinical research reveal about the critical points for preventive (pre-pandemic) or responsive (pandemic) action? There is a need to strengthen the scientific inputs to, and value of, epidemiological and public health modelling and risk assessment.
- A number of viral genes and host cell receptors have been shown to play a role in influenza host range, tissue tropism and pathogenicity. However, the need remains to understand the molecular and cellular mechanisms involved and to identify targets for intervention.
- The clinical consequences of human infection with H5N1 influenza are particularly serious. But what is the full spectrum of illness? What viral and host characteristics determine clinical outcome? What are the molecular and cellular mechanisms that determine virulence and pathogenicity?
- Neutralising antibodies are known to be important in the protective response to influenza. But what is the role of cellular immunity and of immune modulators? What affects the quality of the immune response – which mechanisms are protective and which may cause harm? What are the opportunities for modulating the immune response in favour of protection?
- Current vaccines for seasonal flu are strain-specific and need to be reformulated frequently. There are crucial uncertainties about the correlates of immunity and about the potential effectiveness of a human vaccine to new avian influenza strains. Research is needed to underpin the improvement of the effectiveness and efficiency of current vaccines and to create better vaccines for both seasonal and pandemic influenza in the longer term.
- There are few effective antiviral drugs and resistance is a real threat. In a pandemic, antivirals may be in short supply and they will need to be used efficiently as well as effectively. The most effective dose and duration of treatment for H5N1 needs to be determined both now and in the event of a circulating pandemic strain. Research is needed on different prophylactic and treatment strategies with the currently available drugs. In addition, new targets need to be identified and evaluated.
- In the event of efficient human-to-human transmission, the window of opportunity to intervene could be very small. Effective surveillance requires accurate, predictive and rapid, near-patient diagnostic tests that are robust, affordable and readily interpreted in field settings. There is a need for research to underpin the development and interpretation of such tests.
- Rapid response and effective infection control in healthcare and community settings will require a number of public health intervention strategies. These need to be underpinned by research on the efficacy and effectiveness of barrier and behavioural approaches to infection control.

Research Strategies:

- MRCs remit and capacity is such that its most effective contribution is likely to be to basic biomedical and health research on aetiology and mechanisms; and generalisable clinical, behavioural, public health and field research.
- Nevertheless, a broad range of disciplines and technologies need to be brought to bear on many of the scientific priorities, with the involvement of research teams that do not usually identify themselves with the MRC.
- Some questions can be addressed effectively through research on seasonal flu. Others require research on prevailing emergent strains.
- Some crucial research questions can be addressed only in the narrow window of opportunity when a serious outbreak occurs – in which case a research protocol needs to be in place and enacted then, without delay. The MRC will consider proposals for proleptic "readiness protocols".
- Avian influenza is a zoonosis and some aspects of epidemiology and intervention research require coordinated and complementary human and veterinary research strategies.
- Access to specialised models, reagents, expertise, containment facilities and other infrastructure is often critical. The MRC would welcome Collaboration Grant proposals to facilitate access and share valuable research resources.
- Large and small scale research have important roles to play: some questions will be best addressed through goal-oriented, research networks, collaborations or consortia; and others through focused, individual programmes and projects.
- The outputs of the programme developed through this call for proposals need to be translated efficiently into implementable clinical and public health benefits.
- There is strong rationale for international collaboration, especially with countries at high endemic risk from emerging virulent infections.
- Academic collaboration with industry has an important role in translating discoveries into new diagnostics, antiviral drugs and vaccines.

Research Collaboration

The MRC is willing to consider and fund UK-led proposals that involve a substantial component of collaborative work outside the UK, where the study has the capacity to make an impact nationally (UK) and globally; the non-UK work is supported by robust governance and management, and by the appropriate research infrastructure; and where it is not more appropriate for the work to be funded by another organisation.

The MRC awards funds to UK research organisations. Where non-UK work is involved, the UK organisation must accept responsibility for research, regulatory, project and financial management of the non-UK component. The expectation is that the UK organisation will be awarded the funds and manage them. Any proposed alternative arrangement, involving payments to organisations not normally eligible (such as those outside the UK), must be discussed with the MRC in advance.

In encouraging proposals, and developing its research strategy, the MRC is working closely with other organisations that either commission, fund or conduct research, such as the UK Health Departments, the national Health Protection Agencies, the BBSRC and other Research Councils, the Wellcome Trust and the Department for International Development.