Urgent strategic research into influenza to inform health policy and protect the public

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ABSTRACT

- The *Australian management plan for pandemic influenza* (2005) highlighted a number of areas where more information may yield better plans for protecting Australia.
- In 2005, the National Health and Medical Research Council (NHMRC) developed a special "urgent research" funding program to meet those information needs as quickly as possible.
- The funding program resulted in grants totalling $6.5 million being awarded for 33 research projects, in five broad areas:
  - Detection and identification of the virus;
  - Vaccine development and evaluation;
  - Antiviral medication use and effectiveness;
  - Public health interventions; and
  - Understanding behavioural responses to achieve effective communication and staged implementation of public health strategies.
- Outcomes of the program will be evaluated formally in 2007.

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In the past 100 years, Australians have been at the forefront of influenza containment, research and prevention. During the "Spanish flu" pandemic in 1918, Australia developed successful containment strategies (Box 1).

Research into the influenza virus has been a particular strength in Australian virology (Box 2), having been pioneered in the 1930s by Sir MacFarlane Burnet and his group at the Walter and Eliza Hall Institute, Melbourne. Eminent Australians who subsequently made major discoveries in a range of areas (Box 2) include Laver, Webster and Ada at the John Curtin School of Medical Research, Colman and Ward at the Commonwealth Scientific and Industrial Research Organisation (CSIRO) in Canberra, and White and his group at the University of Melbourne (for complete list see Fenner[4]).

The Australian World Health Organization Collaborating Centre for Reference and Research on Influenza was established at CSL (then the Commonwealth Serum Laboratories) in Melbourne in 1951, and will move to collocate with the Victorian Infectious Diseases Reference Laboratory (VIDRL) in 2007. The WHO Centre has been instrumental in providing timely information on the epidemiology of circulating strains of influenza virus to allow preparation of effective vaccines, based on isolates sent from the WHO National Influenza Centres in Sydney (Institute of Clinical Pathology and Medical Research, Westmead), Melbourne (VIDRL) and Perth (PathWest), and other laboratories in the Public Health Laboratory Network and in the Asia-Pacific region.

Impetus for enhancement of influenza research

It has long been recognised that pandemics of influenza occur in Australia about every 30 years, and that the next one is overdue. The advent and spread of highly pathogenic avian influenza A/H5N1 in Asia and parts of Europe in the past decade, and the recent increase in human cases linked to infected birds have heightened awareness and concern that the virus may cross the species barrier and spread rapidly among humans. This concern has resulted in major planning to protect Australia and Australians from the most serious consequences of a pandemic and to inform policy through substantial investment in research.

Research gaps

The *Australian health management plan for pandemic influenza*[1,2] provides the framework and focus for action to reduce the impact of a pandemic in Australia. The process of drafting and refining the plan revealed gaps in knowledge about influenza, including avian influenza, as well as gaps in infrastructure that must be redressed if Australia is to be well prepared to respond to a pandemic.

Targeting research and the role of the NHMRC

As the principal provider of Australian public health and medical research funding, the National Health and Medical Research Council (NHMRC) in 2005 awarded about $450 million in grants across a broad range of research areas and groups. The research expertise this supports is often drawn on by governments to provide advice on policy, and has been a source of ongoing assistance in pandemic planning. During 2005, research into influenza and other viral infections received $4.3 million through investigator-initiated grant proposals.

A set of strict criteria for "urgent research" was developed by the then Strategic Research Development Committee of the NHMRC in 1999. Severe acute respiratory syndrome was the first subject to meet these criteria and to receive research funding. The NHMRC definition of urgent research was relaxed in 2005, when it was recognised that potentially high-impact problems such as avian influenza did not meet the original criteria. A special program of urgent research around planning for pandemic influenza was then initiated.

A new process for identification and implementation of urgent research by the NHMRC

Responsiveness to research regarded as urgent required the NHMRC to develop a new definition of urgent research (Box 3), to identify the research targets, advertise grants, set up rigorous peer review of applications, and allocate funds, all within a short time frame.

Defining the research topics

Step 1: The NHMRC and the Australian Department of Health and Ageing sponsored the April 2005 Symposium on Pandemic Influenza. This was attended by medical and social research experts,

with the aim of mapping Australian and international research that could be of assistance in planning for pandemic influenza.[5] Key areas for urgent research to inform the Australian management plan were identified.

Step 2: Parameters for funding of up to $7.5 million for urgent research into influenza were proposed by the Research Committee of the NHMRC and accepted by the NHMRC, based on the outcomes of the symposium.

Step 3: Within 1 month, the Urgent Research Working Party, a subgroup of the Strategic Initiatives Working Committee of the Research Committee, with representatives co-opted from the National Security Division of the Department of Prime Minister and Cabinet and the Division of Health Protection of the Australian Department of Health and Ageing, met to decide the targets of the research, avoiding overlap with other government-funded pandemic research. It was agreed that the funding program should encompass research that would be directly relevant to preparing our region for an avian influenza-induced pandemic, and likely to produce results of importance within a short time frame. Five key areas were targeted.

- *Detection and identification of the virus.* This included development of rapid diagnostics and point-of-care tests, and rapid serological tests that indicate immunity to influenza, or development of immunity following infection or vaccination.
- *Vaccine development and evaluation.* This included accelerated antigen and adjuvant dose optimisation of existing vaccines using current techniques in animals or humans with a high probability of favourable outcomes; development of a detailed protocol for assessing the effectiveness of vaccines that could be immediately implemented in the early stages of vaccine use in a pandemic; alternative or new vaccines and vaccine approaches capable of being developed rapidly and which have a high probability of success in providing protection superior to that achieved with existing technology; and optimum vaccine delivery and efficacy in particular at-risk populations.
- *Antiviral medication use and effectiveness.* This included assessment of the probability and likely clinical significance of the development of resistance to neuraminidase inhibitors, ideally in the H5N1 virus strain; and a detailed protocol for assessing the effectiveness of therapeutic and prophylactic use of antiviral agents that could be immediately implemented in the early stages of a pandemic.
- *Public health interventions*. This involved modelling and testing effects of public health interventions that are proposed in response to the threat of an avian influenza-induced pandemic. This includes, but is not restricted to, modelling of proposed border, quarantine and infection controls, and would identify their effects on individuals, families, communities and organisations.
- *Understanding behavioural responses to achieve effective communication and staged implementation of public health strategies.* Such research could focus on the risk perception, trigger points and likely responses of individuals, age groups, families, cultural groups, communities, the health system and other organisations vital to minimising the national health impacts of a pandemic, and may consider which strategies are effective in different community and health care (hospital and non-hospital) groups.

It was also agreed that applicants had to demonstrate a high probability of providing important findings or research breakthroughs within 6 months (although the research might continue

1 Containment of pandemic influenza: World War I (1918)[1,2]

- May 1918: France — mild influenza appears in Australian troops.
- October 1918: "second wave" — severe influenza in Australian troops in Europe; 15 million deaths overseas within 12 months (estimated 50 million overall[3]).
- October 1918 to April 1919: Dr J H Cumpston, then Acting Federal Director of Quarantine, quarantines all ships entering Australia and prevents entry of severe influenza.
- January 1919: less severe influenza enters Australia through Melbourne. ◆

2 Australian contributions to international research into influenza

- Development of a method to grow the virus in chick embryos.
- Chemistry of neuraminidase.
- Replication and genetics of the virus.
- Recognition of antigenic shift and antigenic drift.
- Vaccines and immunisation.
- Pathogenesis and immunology of infection. ◆

3 What constitutes "urgent research"?

- Research must be undertaken rapidly in response to a threat to public health.
- The threat may be generalised or specific to particular groups of individuals.
- The threat may be a current major problem, a potential major problem, or a problem which is expected to increase in the future.
- The main catalysts for urgent research will be:
  - ➢ a disease or illness or its variant(s) is previously unknown or unidentified;
  - ➢ it has a high morbidity or mortality rate; and
  - ➢ public or government concern about the disease/illness is high.
- The National Health and Medical Research Council (NHMRC) prioritises requests for urgent research against the following criteria:
  - ➢ immediate threat to public health;
  - ➢ potential to spread, population at risk;
  - ➢ unfamiliarity with the disease;
  - ➢ high morbidity or mortality; and
  - ➢ broad economic impact of the threat.

More on this topic can be found at: http://www.nhmrc.gov.au/funding/policy/urgent.htm. ◆

4 Funded grants according to research project category

Category	Number funded
Detection and identification of the virus	5
Vaccine development and evaluation	11
Antiviral medication use and effectiveness	6
Public health interventions	6
Understanding behavioural responses	3
Other*	2

* Applications that did not fit clearly into the five designated research categories, but were assessed as directly relevant to the goals of the program and of high quality. ◆

beyond this time). Preference would be given to proposals likely to provide the maximum potential effect in the shortest possible time.

Step 4: On 21 October 2005, the funding program was advertised. Research groups were given a short turnaround time to submit grant applications and a rapid peer review and administrative process was developed and implemented to ensure that successful applicants could be informed of the outcomes by Christmas 2005.

Results

The funding program built a $6.5 million portfolio from the available $7.5 million. Thirty-three applications were successful.[6] Unsuccessful applications did not reach the standard considered fundable or were judged to be outside the scope of the urgent research program. The distribution of funded grants by areas designated in the call for applications is summarised in Box 4. Despite the short lead time for submission of applications and an expectation that successful projects would be implemented immediately, the NHMRC's call for urgent research was met with considerable effort and goodwill from researchers and administrators in university research offices and research institutions across Australia, who worked together to develop and dispatch some excellent proposals in a short period.

Discussion

The NHMRC was able to develop and fund a portfolio of tightly targeted research within a short period in 2005. This research is expected to yield new treatments and strengthen preventive measures and interventions as part of an integrated national response, including:

- Increased understanding of the avian influenza virus and host responses;
- Advanced technology for detection and identification;
- Advanced vaccine production and efficacy; and
- Better informed models and plans for Australian public health and community interventions, including communication strategies and a checklist for business interests.

Integration of research outcomes into national policies and practice will depend on continued close collaboration and communication between the NHMRC, researchers, practitioners and the relevant government departments.

The strong response to this call for urgent research reflects in part the impressive intellectual lineages in Australian influenza research,[4] and would not have been possible had Australia not made significant, long-term investment in research in the fields of immunology, microbiology, vaccine development and public health research in the preceding decades.

The NHMRC's capacity to marshal research resources in response to the risk of an avian influenza pandemic compares favourably with that of other countries. For example, the European Commission, the Canadian Institutes of Health Research and the Medical Research Council of the United Kingdom did not call for policy-oriented research on avian influenza until early 2006, and will not be in a position to fund grants in this area until late 2006 or early 2007. The legislation that governs the operations of the NHMRC has recently been revised, and the changes will further assist the organisation to respond to priority, urgent and emergent issues of national concern to the health and research sectors.

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Competing interests

Tania Sorrell has received travel expenses and sitting fees from the NHMRC for attending meetings. Carey Lonsdale is employed by the NHMRC and received travel expenses.

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