



Report on the Pandemic Preparedness Research Initiative

**Institute of Infection and Immunity
Canadian Institutes of Health Research**



Executive Summary

Influenza is an infectious disease that generally causes fever, sore throat, muscle pain, headache and malaise, but infections can be severe and result in several thousand deaths worldwide each year. New strains of influenza virus occasionally emerge to cause an influenza pandemic that, in the past, has resulted in several million deaths. Most experts agree that the next pandemic is overdue. An influenza pandemic could have severe health, economic and social consequences. Worldwide, between 2 million and 7.4 million people could die including 11,000 to 58,000 Canadians. It is estimated that 4.5 to 10.6 million Canadians could become ill.

Surprisingly, given the potentially devastating health, economic and social consequences of a pandemic, there are severe gaps in knowledge concerning influenza. To effectively meet the challenges of a highly virulent strain of influenza, it is critical to perform research in order to develop new healthcare strategies, policies and products that could be used to prevent or respond to a pandemic. Many countries are conducting influenza research, but it is essential to develop research capacity in Canada to meet the unique needs of this country and to have local experts to call on in the event of a pandemic. New research knowledge will be an essential component of an effective national annual and pandemic influenza response plan.

Recognizing the need to develop a coordinated and focused research effort and to build research capacity in pandemic influenza in Canada, the Canadian Institutes of Health Research Institute of Infection and Immunity (CIHR-III) has established the Pandemic Preparedness Research Initiative (PPRI). The mandate of the Initiative is to identify strategic research priorities and support pandemic preparedness research. PPRI is guided by the Pandemic Preparedness Research Task Group with representatives who carry out pandemic research as well as members who will apply the new research knowledge. The PPRI is supported by the Canadian federal government which announced in May 2006 that it will provide \$21.5 million over five years to support pandemic influenza research.

The purpose of this report is to provide background information about the Initiative and to summarize the activities, accomplishments and future plans of the PPRI. Significant progress has already been made. In September 2005, CIHR-III in collaboration with the Public Health Agency of Canada organized an Influenza Research Priorities Workshop to identify areas of influenza research requiring support. In June 2006, CHIR-III launched a Request for Applications for pandemic preparedness research operating grants with emphasis on the priority areas identified at the Workshop. A strong response to the request was received with 62 letters of registration submitted by researchers. The deadline for full applications is October 2006, and the start date for the grants is March 2007.

To direct the future activities of the PPRI, the Task Group has refined, developed and further prioritized the research areas first identified during the Workshop. These draft priorities have been sent to stakeholders for feedback. Their comments were used to revise the priorities, which will form the basis of future rounds of Requests for Applications that will start in fall 2006. The key areas identified are: i) vaccines and immunization programs ii) the influenza virus, iii) prevention and treatment, and iv) ethics, legal and social research.

In addition, CIHR and partners plan to establish a network of influenza researchers in Canada to enhance research collaboration and build research capacity. Members of the network will include successful recipients of pandemic preparedness research grants awarded by CIHR and partners.

Introduction

Canadian Institutes of Health Research Institute of Infection and Immunity (CIHR-III) is leading the Pandemic Preparedness Research Initiative (PPRI) to develop a coordinated and focused research effort and to build influenza and pandemic preparedness research capacity in Canada. This includes identifying current gaps in knowledge and supporting research training, operating grants, teams and multidisciplinary approaches to pandemic preparedness. The ultimate goal is that the new knowledge will allow Canada and others around the world to prevent or mitigate an influenza pandemic or to be better prepared to respond to a pandemic should one arise. The purpose of this report is to provide background information about the Initiative and to summarize the activities, accomplishments and future plans of the PPRI.

Background

Influenza is an infectious viral disease that generally causes fever, sore throat, muscle pain, headache and malaise, but infections can be severe and result in several thousand deaths worldwide each year. Occasionally, a new strain of influenza virus emerges to cause an influenza pandemic that has resulted in several million deaths. There were three pandemics in the last century. The worst was the Spanish flu in 1918-1919 that killed 20 to 40 million people worldwide. The last pandemic occurred in 1968-69.

It is difficult to predict the timing of the next influenza pandemic, but most experts agree that one is overdue. An additional cause of concern is the human deaths caused by a new highly pathogenic strain of influenza A virus (H5N1) that emerged in south-east Asia in recent years, which has spread widely in birds, the natural reservoir for the virus. By August 2006, the World Health Organization had confirmed 241 cases of human H5N1 infection and 141 deaths. It is not known whether H5N1, or some other strain, will be the cause of the next pandemic.

The Public Health Agency of Canada has estimated that, in the event of an influenza pandemic, 4.5 to 10.6 million Canadians will become clinically ill, 2 to 5 million will require outpatient care, 34,000 to 138,000 will require hospitalization and that 11,000 to 58,000 Canadians will die. The World Health Organization has suggested that worldwide between 2 million and 7.4 million people could die from a global influenza pandemic.

The World Health Organization and public health agencies in many countries have developed plans to prevent and prepare for a pandemic. Canada was one of the first countries to develop a preparedness and response strategy in the form of the Canadian Pandemic Influenza Plan. The Plan was developed to assist with the main components of planning, including surveillance, vaccine programs, use of antivirals, health services, emergency services, public health measures and communications.

Surprisingly, considering the scope of the potential health, economic and social consequences of pandemic influenza, there are severe gaps in knowledge about the virus, the prevention and treatment of influenza as well as a lack of discussion and consensus concerning ethical and social issues, such as the allocation of scarce resources during a pandemic. Acquiring knowledge in these and other areas will allow for the development of new health system strategies, policies and products for pandemic preparedness. Therefore, in addition to public health planning, it is critical to mount a comprehensive influenza research initiative. Ultimately this knowledge will be an essential component of an effective national annual influenza and pandemic influenza response plan.

Other countries have, and continue to develop, research responses to pandemic influenza. In the USA, for example, influenza pandemic preparedness research is a priority of the American government. Critical research includes the National Institutes of Health (NIH) vaccine treatment and evaluation units that are running H5N1 vaccine clinical trials; the National Institute of Allergy and Infectious Diseases (NIAID) influenza genome project and the NIH and NIAID Cooperative Research Partnership for Influenza Product Development, which supports research leading to the discovery and development of therapeutics, diagnostics and vaccines for influenza.

The Medical Research Council in the United Kingdom is also supporting research in several identified priority areas. These include the modes of transmission of avian flu to humans, the molecular and cellular mechanisms of virulence and pathogenicity, mechanisms of immune protection, creation of improved vaccines, effective use of antivirals, development of rapid diagnostics and determination of methods to prevent the spread of infection.

In Canada, CIHR-III has led the way in developing and supporting pandemic influenza preparedness research. CHIR-III established the Pandemic Preparedness Research Initiative (PPRI) to support research that will improve Canada's ability to prevent and/or respond to an influenza pandemic. It is essential to build a network of researchers in Canada, to address issues unique to this country and so that local experts and knowledge will be available in the event of a pandemic. In addition, Canada's healthcare system and expertise make researchers in this country ideally suited to address specific research questions concerning pandemic influenza.

The Initiative is funded by the Canadian federal government which announced in May 2006 that it would provide \$21.5 million over five years to CIHR to support pandemic preparedness activities.

Report on Activities

Influenza Research Priorities Workshop

CIHR-III collaborated with the Public Health Agency of Canada (PHAC) to organize the Influenza Research Priorities Workshop in Ottawa in September 2005. Ten research areas were identified by national and international influenza experts attending the Workshop. Pandemic influenza was recommended as a major research focus in the short term. Participants discussed gaps in knowledge, research activities to help bridge the gaps and infrastructure and capacity requirements that are currently lacking. See the Institute website at <http://www.cihr-irsc.gc.ca/e/30967.html> for the Workshop report.

Request for Applications for Pandemic Preparedness Operating Grants

In June 2006, in response to the recommendations made during the Influenza Research Priorities Workshop, CIHR-III launched a Request for Applications for operating grants (<http://www.cihr-irsc.gc.ca/e/31297.html>) to support pandemic preparedness research. The purpose of the Request for Applications was to further strengthen Canadian influenza research in preparation for a potential pandemic outbreak by funding two-year projects to conduct critical research on disease control, prevention measures and health system preparedness. It is expected that this targeted investment will lead to new diagnostic methodologies, evaluation of vaccines, new antivirals, mechanisms to control disease spread, outbreak modelling and design, assessment of optimal health system strategies and an understanding of ethical issues pertaining to a pandemic and how they should be addressed. In August 2006, CIHR-III received a strong response to the request with 62 letters of registration submitted by researchers. The deadline for full applications is October 2006, and the start date for the grants is March 2007.

Pandemic Preparedness Research Task Group

To develop and guide the Pandemic Preparedness Initiative, CIHR-III formed the Pandemic Preparedness Research Task Group (PPRTG). It has members carrying out pandemic research as well as members who will apply the new research knowledge to help Canada prepare for a pandemic (see Appendix 1 for a list of members and their expertise). The mandate of the Task Group is to make recommendations on strategic research priorities and mechanisms to support these areas; to develop outcome indicators/measures for research; to facilitate research linkages; to identify national and international experts to act as peer reviewers; and to identify partners and obtain funding to support necessary research activities.

Draft Pandemic Preparedness Strategic Research Priorities

To support the Initiative and direct its future activities, the Task Group refined, developed and further prioritized the research areas first identified during the Influenza Research Priorities Workshop. The Task Group's objective was to identify areas in which Canadian researchers could obtain results that would have a significant impact on the ability to prevent and/or respond to an influenza pandemic. The Group considered current pandemic and annual influenza research that is taking place in Canada and internationally and identified gaps in research that Canadian researchers are well positioned to fill. The implications of potential research results in specific areas were also considered.

The Task Group felt that vaccine research should form the cornerstone of an influenza pandemic preparedness research effort, because an effective vaccine will be key to stopping a pandemic. To develop vaccines and assist in the prevention of infection and treatment of influenza, fundamental knowledge about the influenza virus and molecular mechanisms of transmission is needed. In the event that a vaccine for a new strain of influenza is not available at the start of a pandemic, methods to prevent the spread of the virus and to treat affected individuals will be critical. Preparing for and responding to a pandemic raises many ethical, legal, social and societal issues, many of which relate to the other broad research areas. The research carried out under the influenza pandemic Initiative will also impact and inform future responses to annual influenza outbreaks.

The research priorities reflect areas which currently need addressing through strategic initiatives such as targeted requests for applications. The priorities are not intended to lessen the importance of other areas of influenza and infectious disease research which remain eligible for funding through the CIHR regular grant programs and other targeted initiatives.

Consultation Process with Stakeholders

The draft of the Pandemic Preparedness Strategic Research Priorities was sent to the Canadian Rapid Research Response Team and additional stakeholders in pandemic-related fields. For a list of those who received the document, see Appendix 2. The purpose of the consultation was to give stakeholders an opportunity to review and provide feedback to further develop the priorities. Another objective of the consultation was to facilitate the creation of linkages with organizations working in areas related to pandemic preparedness and users of research knowledge nationally and internationally.

A total of 16 responses were received to the consultation request. The overwhelming majority agreed that each of the draft areas identified by the Task Group were a priority for Canadian research. The comments were incorporated and are presented below in a summary of the strategic research priority areas. The following organizations indicated they would like to partner in supporting one or more of the research areas:

- American Red Cross
- Canadian Food Inspection Agency
- Canadian Foundation for Infectious Diseases
- Canadian International Development Agency
- Emerging Infectious Disease Research Network
- First Nations and Inuit Health Branch, Health Canada
- Rx&D (an association of Canada's research-based pharmaceutical companies) Health Research Foundation
- International Development Research Centre
- Public Health Agency of Canada

Summary of Pandemic Preparedness Strategic Research Priorities

The following is a summary of the Pandemic Preparedness Strategic Research Priorities that were developed by the Task Group in consultation with stakeholders. These priorities will direct future activities of the Initiative.

Capacity Building

An overarching theme is the need to build capacity in pandemic influenza research in Canada. It is essential for Canada to build research expertise now so that it will have expert researchers to call on during a pandemic outbreak. The Task Group felt that the best way to achieve this is to support training in influenza research, such as doctoral and fellowship support, as a component of operating and team grants.

Vaccines and immunization programs: optimal use and efficiency of existing vaccines and development of new pandemic vaccines

Research is needed to further our understanding of immune response and protection as well as to devise new vaccine technologies. Effective vaccination strategies would greatly reduce the impact of a new strain of influenza. Research is required to help optimize existing vaccination programs, aid in the discovery of novel means of vaccine delivery, examine scheduling and dosing and address issues of safety. Research is also needed to study human and animal immune responses to immunization and indicators of protective immunity, assess the carry-over and cross-protection by vaccines, develop cross-protective vaccines, study the effectiveness of human vaccines to prevent reassortment of animal and human influenza, and develop novel

influenza virus vaccine technologies and new vaccine platforms. In addition, assessment of the potential benefits and short- and long-term safety of influenza vaccines in specific populations, studies to measure the economic benefits of immunization, the development of methodologies and capacity for annual assessment of program effectiveness are required.

The virus: biology of the influenza virus and rapid diagnostics

Much more information is needed about the influenza virus, and reliable and rapid diagnostic tests for influenza are currently not available. Therefore, research is needed on the biology of the influenza virus, the human and animal host response to infection such as the innate and acquired immune response, the role of mucosal immunity and correlates (predictors) of protection. Examples of the required research include studies to investigate the genetics of influenza, analysis of influenza evolution in avian and mammalian species and assessment of disease production and immune response using animal and human models. Research is required to develop and evaluate rapid diagnostic tests for hospital laboratories and “point-of-care” applications and to evaluate the utility and impact of optimized diagnostic testing.

Prevention and treatment: modes of transmission, use of antivirals and alternate strategies for prevention

In the event of a pandemic, knowledge of ways to prevent the spread of the virus and to treat infected individuals will be critical. Further knowledge is needed on how influenza spreads in different settings. Therefore, research is required to study the molecular basis for transmission of the influenza virus between humans as well as from animals, the mechanisms involved in pathogenesis; the mode of transmission including influenza shedding patterns and the risk factors for infection. Research is also required to determine the optimal methods to prevent transmission at the individual, institutional and community level. Research areas include comparison of protective equipment such as masks, the utility of vaccination of specific populations, and the value of increasing social distancing and containment.

There is a need for new antivirals in light of the limited number that are currently available, but discovery of new drug targets and development of new antivirals are a long-term project. In a pandemic, it will be critical to optimally use existing limited supplies of antiviral drugs such as Tamiflu. Research is needed to determine the optimal dosing, effects on various influenza strains, usage in a variety of settings and degree of development of viral resistance to antivirals. Research might also include discovery of innovative uses of existing antivirals and existing drugs that have an antiviral effect.

Ethics, legal and social contract: research in risk communication, prioritization and the regulatory approval process

It is essential that research and discussions that aid in the planning of how to prevent and respond to a pandemic are in place before a pandemic starts. Research is needed to develop and optimize communication strategies, determine effective means to educate health care providers

in the application of care guidelines and to identify effective protective measures in the Canadian context. There is a need for research to address the issues of surge capacity in pandemic situations. Research into prioritization and resource allocation could address global, hospital, and bedside requirements, fairness of distribution of limited resources and would take into account ethical issues. Ethics research is needed to examine the perceptions among health care providers and the public on the scope and extent of obligations and duty to care during a pandemic. Research is needed to understand the social, economic, cultural and secondary impact of such measures and examine the needs of vulnerable populations and children in pandemic outbreaks.

In the event of a pandemic, new therapeutics and diagnostics will require expeditious approval in a manner that protects human subjects. Research is needed into ways to improve efficiency of the ethics review process. This would include development of models, processes, guidelines and standard operating procedures to allow the research community and research ethics review boards to submit and process applications related to public health threats quickly.

There are opportunities to learn from the research work carried out in this area during the Severe Acute Respiratory Syndrome (SARS) outbreak. As a starting point, research could take the form of analysis of funded SARS research and lessons learned from that research.

Next Steps

An immediate goal of the PPRI is to launch a second round of requests for applications to support pandemic research areas that have been identified by the Task Group and refined through consultation. Given the time frame for the flow of funds for the pandemic Initiative, it is critical to aim for a December 2006 launch for these requests for applications.

CIHR-III and partners plan to establish a network of influenza researchers as part of its Pandemic Preparedness Initiative. The Institute believes that it is essential for Canada to have this network in place and ready to respond to an influenza pandemic should one occur. The network will also help to build collaboration amongst influenza researchers and enhance research capacity in Canada. Members of the network will include successful recipients of pandemic preparedness research grants awarded by the CIHR and partners.

Appendix 1: CIHR Pandemic Preparedness Task Group

Mark Loeb (Chair), CIHR-III Advisory Board, Professor McMaster University
Expertise: Influenza epidemiology, Randomized controlled trials, Health services research, Population health, Influenza surveillance, Observational epidemiology, Pneumonia, Cohort studies

Earl Brown, Professor, University of Ottawa
Expertise: Influenza virus, Viral pathogenesis, Viral pneumonia, Viral genetics, Mouse models, Interferon response, Fusion, Receptor specificity, Influenza virus, RNA viruses, Molecular biology, Reovirus.

Robert Brunham, Director, Centre for Disease Control, University of British Columbia
Expertise: Epidemiology, Immunology of infectious diseases, Public health, Population biology, Mathematical modeling

Theresa Tam, Director, PHAC Centre for Infectious Disease Prevention and Control
Expertise: Influenza virus, Immunization, Vaccines, Epidemiology, Paediatrics, Vaccine preventable diseases, Infectious diseases, Influenza pandemic, Surveillance, Outbreak response, Emergency Preparedness.

Ross Upshur, Director Primary Care Research Unit, Sunnybrook Health Sciences Centre
Expertise: Respiratory disease epidemiology, Primary care research, Public health ethics, Clinical ethics, Qualitative methodologies, Philosophy of medicine

Bhagirath Singh, (Ex Officio) CIHR Institute of Infection and Immunity (CIHR-III), Scientific Director

Appendix 2: Stakeholders Consulted to Finalize the PPRI Priorities

Canadian Rapid Research Response Team (C3RT) Members

Lorne Babiuk, Chair, Institute Advisory Board, CIHR Institute of Infection and Immunity

Alan Bernstein, President, Canadian Institutes of Health Research (CIHR)

Judith Bossé, Vice-President, Science, Canadian Food Inspection Agency

Colleen Flood, Scientific Director, CIHR Institute of Health Services and Policy Research

John Frank, Scientific Director, CIHR Institute of Population and Public Health

Jean Marion, Director, Scientific Affairs, Rx&D (Canada's Research Based Pharmaceutical Companies)

Frank Plummer, Director General, Public Health Agency of Canada

Bhagirath Singh, Scientific Director, CIHR Institute of Infection and Immunity

Isaac Sobol, Chief Medical Officer of Health, Council of Chief Medical Officers of Health

Ernest T. Takafuji, Director, Office of Biodefense Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health

Aubrey Tingle, President, Michael Smith Foundation for Health Research

Michael Vandergrift, Director, Health Science Policy Division, Health Canada

C3RT Ad Hoc Members

Sandra Black, Senior Advisor Pandemic Influenza, Canadian International Development Agency

Dominique Charron, Director, International Development Research Centre, International Development Research Centre

Arlene King, Director General for Pandemic Preparedness, Public Health Agency of Canada

Roland Levandowski, Section Chief, Influenza, SARS, and Related Viral Respiratory Diseases Section, Respiratory Diseases Branch, National Institute of Allergy and Infectious Diseases, National Institutes of Health

Michael Mackey, Biomedical Sector Theme Leader, Mathematics of Information Technology and Complex Systems (MITACS) Network of Centres of Excellence

Earl Nowgesic, Assistant Director, CIHR Institute of Aboriginal Peoples' Health

Susan Richardson, Past President, Association of Medical Microbiology and Infectious Disease Canada

Elizabeth Stirling, KT Sector Specialist, CIHR Knowledge Translation Branch

Burleigh Trevor-Deutsch, Director, CIHR Ethics Office

Others

Althea House and Jennifer Gray, First Nations and Inuit Health Branch, Health Canada

Ben Schwartz, U.S. Center for Disease Control and Prevention

Harpreet S. Kochhar, Canadian Food Inspection Agency

Paul Gully, World Health Organization

Philip Schwab, BioteCanada

Ray Saginur and Tom Wong, Canadian Foundation for Infectious Diseases and Emerging Infectious Disease Research Network

Robert Pascal, Industry Canada

Shimian Zou, University of Ottawa and American Red Cross

Veronika von Messling, INRS-Institut Armand-Frappier