



# Pandemic Preparedness Strategic Research Initiative

**Report on Activities & Outcomes**

**June 2006 - June 2008**

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



**CIHR IRSC**

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# 1. Highlights of the Pandemic Preparedness Strategic Research Initiative

The recent emergence of avian influenza (bird flu) has heightened concerns that an influenza pandemic is close at hand. It is estimated that up to 7 million people could die in the next pandemic, including 58,000 Canadians.

In May 2006, the Government of Canada announced a \$21.5 million, five-year investment in pandemic preparedness research. These funds helped the Canadian Institutes of Health Research-Institute of Infection and Immunity (CIHR-III) create the Pandemic Preparedness Strategic Research Initiative (PPSRI). CIHR-III moved quickly to develop partnerships with other agencies, who invested an additional \$18.5 million and worked with CIHR-III to coordinate strategies, stimulate new research and build capacity in priority areas identified by a PPSRI Task Group. Highlights of PPSRI's progress include:

## **Funding essential pre-pandemic research**

In consultation with researchers and stakeholders, PPSRI identified and began supporting research in four priority areas: vaccines and immunization, the virus, prevention and treatment, and ethical, legal and social issues. Examples of funded research include developing diagnostics, antiviral drugs and vaccines; understanding and preventing disease transmission; and identifying ethical ways to use limited resources during a pandemic.

## **Building research capacity**

PPSRI's directed funding encourages researchers to undertake influenza and pandemic research, thereby building the national expertise that will be needed during a pandemic outbreak. Also, PPSRI grant recipients are required to include trainees in their research programs, increasing the number of highly qualified personnel in this area.

## **Preparing for outbreak research**

To ensure that the research community is poised to act immediately in the event of a pandemic, PPSRI is helping researchers prepare for outbreak research. For example, PPSRI offers application development funds, so that, in the event of an outbreak, research teams will be able to submit abbreviated applications for expedited peer review and funding.

## **Fostering collaborations and networks**

Through the International Opportunities Program, PPSRI supports research collaborations between Canadian researchers and researchers in China, Thailand, Peru, India, Europe, and the United States. As well, CIHR-III is working with the Public Health Agency of Canada (PHAC) to establish an Influenza Research Network comprised of Canadian researchers who will develop methodologies to evaluate influenza vaccines and implement immunization programs.

### **Enhancing communication and knowledge translation**

Fostering communication is a central part of PPSRI's goal. For example, PPSRI research teams must collaborate with research users, such as public health practitioners and policy makers, throughout the research project. In addition, CIHR-III, PHAC and the Canadian Food Inspection Agency (CFIA) will host a meeting in November 2008 featuring presentations by Canadian and international authorities on pandemic and influenza research.

### **Impact**

PPSRI has already increased research capacity and strengthened linkages and partnerships for enhanced pandemic influenza planning and control. Knowledge from PPSRI-funded research will lead to improved methods to prevent and treat seasonal influenza and will enhance our ability to respond to other infectious disease outbreaks. Canada must remain committed to the intense, organized and sustained effort required to be ready to rapidly respond to the next pandemic.



## **2. Executive Summary**

Influenza is an infectious viral disease that generally causes fever, sore throat, muscle pain, headache and fatigue. But, infections can be severe and result in several thousand deaths worldwide each year. Occasionally, a new strain of the influenza virus emerges 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 large gaps in knowledge concerning influenza. More research is needed to effectively meet the challenges of a highly virulent strain of influenza. This research will help develop new health-care 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 available 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 Strategic Research Initiative (PPSRI). The mandate of the PPSRI is to identify strategic research priorities and support pandemic preparedness research. PPSRI is guided by the Pandemic Preparedness Strategic Research Initiative Task Group. The Task Group has representatives who carry out pandemic research, as well as members who apply new research knowledge. The PPSRI 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 PPSRI and to summarize its activities, accomplishments and future plans. Significant progress has already been made. In September 2005, CIHR-III and the Public Health Agency of Canada (PHAC) organized an Influenza Research Priorities Workshop to identify areas of seasonal and pandemic influenza research requiring support. To direct the activities of the PPSRI, the Task Group refined, developed and further prioritized the research areas first identified during the Workshop. These draft priorities were sent to stakeholders for feedback, and the comments were used to revise the priorities. 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.

It is critical that research that addresses the strategic priorities is funded in a timely manner. To this end, CIHR-III has taken a lead role and has also collaborated with other CIHR Institutes and organizations to launch funding opportunities to build capacity in pandemic preparedness research



and to support research before an outbreak. For example, in June 2006, CIHR-III launched a funding opportunity for pandemic preparedness research operating grants with emphasis on disease control, prevention measures and the health-care system. Twenty-six of the sixty applications that were received were funded. The funded research is wide-ranging and innovative. Highlights of the proposed projects include studies to discover novel antiviral drugs, to develop vaccines that would protect individuals from multiple strains of the virus, to determine the best methods to respond to a pandemic, and to identify ethical issues pertaining to a pandemic and to determine how they should be addressed.

In July 2006, CIHR-III and the CIHR International Relations Branch, as part of the International Opportunity Program, launched funding opportunities for seed and collaborative research grants to encourage and support international research collaborations in the area of pandemic preparedness research. Results of the competition were announced in March 2007. The eight researchers who received grants plan to engage in international research in areas such as determining risk factors for emerging diseases, understanding the genetic changes in influenza viruses that take place in children in different countries, determining the factors that protect individuals against influenza and the development of broad spectrum antivirals.

To continue to build research capacity and support research before a pandemic, a major round of funding opportunities was launched in December 2006. These included requests for applications for operating grants to support research that addresses influenza diagnostics, transmission, ethics review and antiviral medication, as well as team grants in influenza biology, vaccines, ethics, legal and social research or in influenza transmission and prevention research. To support individuals with an interest in applying for these grants and to foster collaborations among them, an application development workshop was held in Ottawa in March 2007. One team grant was awarded in October 2007 to Dr. Mark Loeb who will examine influenza transmission and prevention in a model community. In March 2008, five researchers received awards under this operating grant opportunity. It is expected that the funded research will lead to rapid diagnostics, better methods for controlling disease spread and new ways to treat affected individuals.

Late in 2007, the PPSRI moved into an important second phase. The goal of this phase is to support the research community to prepare for outbreak research. To this end, CIHR-III and PHAC announced two innovative catalyst grant opportunities. One is for individual researchers or small teams to start the preparatory phase of outbreak research projects. Five researchers received grants under this funding opportunity in March 2008. The other funding opportunity is for application development funds to team leaders who can bring together a research team in a key area that will require a response when an outbreak occurs. This preparation will allow for an immediate response during an influenza pandemic because team leaders, research protocols and tools will have been identified ahead of time.

In addition to the catalyst grants, PHAC and CIHR-III have collaborated to establish an Influenza Research Network with the overall objective to develop and test methodologies to evaluate the safety, immunogenicity and effectiveness of influenza vaccines and to establish methods for



vaccine program implementation. The network will ensure surge capacity and mechanisms for rapid data collection, analysis and evaluation of vaccines before and during a pandemic. It will also assemble a critical mass of experience and talent by linking individual researchers and research centres involved in vaccine evaluation, building on their core competencies and coordinating their efforts. An application development workshop was held in Ottawa in February 2008 to assist researchers with an interest in applying to this funding opportunity and to provide an opportunity for them to meet each other, exchange information and begin preparation of an application. In addition to these activities, CIHR and partners plan to organize annual meetings of pandemic and influenza researchers and end-users of the knowledge created. The first meeting will be held in Winnipeg in November 2008. The meetings will provide an overview of the current state of pandemic and influenza research, build collaboration amongst researchers and linkages to end-users, and support knowledge translation of research findings.

It is anticipated that research and activities supported through these and other initiatives will help to identify strategies to prevent or mitigate a pandemic outbreak, as well as methods and procedures to control disease spread (both human-to-human and from animals to humans) and to treat affected individuals should an outbreak occur. In addition, the international research collaborations established and supported through the International Opportunities Program, Team Grants and the PPSRI Annual Meeting will enhance linkages amongst Canadian and international researchers. This is important because the threat of an influenza pandemic is global.



### **3. Introduction**

CIHR-III is leading the PPSRI to develop a coordinated and focused research effort and to build influenza and pandemic preparedness research capacity in Canada. Work includes identifying current gaps in knowledge and supporting research training, operating grants, teams and multidisciplinary approaches to pandemic preparedness. The PPSRI also supports knowledge translation activities to ensure that research results are rapidly taken up by end users. 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 PPSRI.



## **4. Background**

Influenza is an infectious viral disease that generally causes fever, sore throat, muscle pain, headache and fatigue. 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 June 2008, the World Health Organization had confirmed 385 cases of human H5N1 infection and 243 deaths. It is not known whether H5N1, or some other strain, will be the cause of the next pandemic.

PHAC 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 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, the Canadian Pandemic Influenza Plan for the Health Sector. 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. For example, questions remain about the prevention of influenza transmission and treatment of the disease. There has also been 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 facilitate development of new health-care 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. Examples of current research projects include H5N1 vaccine clinical trials being run

by the National Institutes of Health (NIH) vaccine treatment and evaluation units, as well as the National Institute of Allergy and Infectious Diseases' (NIAID) influenza genome project. Additionally, the NIH and NIAID Cooperative Research Partnership for Influenza Product Development supports research leading to the discovery and development of therapeutics, diagnostics and vaccines for influenza.

The Medical Research Council (MRC) 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. CIHR-III established the PPSRI to support research that will improve Canada's ability to prevent and/or respond to an influenza pandemic. Another goal is to facilitate collaboration and linkages amongst researchers and end-users of the new research knowledge in order to ensure that research results are translated in a timely fashion. It is essential to build a network of researchers and end-users 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.

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.



## **5. Report on Activities**

### **5.1 Influenza Research Priorities Workshop**

CIHR-III and PHAC organized 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 ([www.cihr-irsc.gc.ca/e/30967.html](http://www.cihr-irsc.gc.ca/e/30967.html)) for the Workshop report.

### **5.2 Pandemic Preparedness Strategic Research Initiative Task Group**

To develop and guide the PPSRI, CIHR-III formed the PPSRI Task Group. The Task Group includes 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 encompasses the following objectives: 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.

### **5.3 Draft Pandemic Preparedness Strategic Research Priorities**

To support the PPSRI 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 objective of the Task Group 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 Task Group considered current pandemic and annual influenza research in progress 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. And, 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 also be critical. The Task Group determined that 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. They also noted that research carried out under the PPSRI will impact and inform future responses to annual influenza outbreaks. Detailed descriptions of each priority are contained in the next section of the report.

The research priorities identified by the Task Group reflect areas that require investment through strategic initiatives such as targeted funding opportunities. The priorities are not intended to lessen the importance of other areas of influenza and infectious disease research, which remain eligible for funding through regular grant programs and other targeted initiatives offered by CIHR and other funding agencies.

## **5.4 Consultation Process with Stakeholders**

The draft pandemic preparedness strategic research priorities were sent to the Canadian Rapid Research Response Team and additional stakeholders in pandemic-related fields. For a list of those who were consulted, see Appendix 2. The purpose of the consultation was to give stakeholders an opportunity to review the draft priorities and provide feedback. The consultation also helped to create linkages with organizations working in areas related to pandemic preparedness, as well as users of research knowledge nationally and internationally.

The PPSRI received 16 responses to the consultation request. The overwhelming majority agreed that each of the draft areas identified by the Task Group was a priority for Canadian research. The comments were incorporated, and the finalized priorities 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
- Association of Medical Microbiology and Infectious Disease Canada / 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

## **5.5 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 direct the activities of the PPSRI.

### *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: optimize existing vaccination programs; aid in the discovery of novel means of vaccine delivery; examine scheduling and dosing; and address issues of safety.

Proposed projects to further our understanding of immune response and protection would: 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.

Research is also needed to: develop better assessments of the potential benefits and short- and long-term safety of influenza vaccines in specific populations; study and measure the economic benefits of immunization; and develop methodologies and capacity for annual assessment of program effectiveness.

*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.

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; and the role of mucosal immunity and correlates (predictors) of protection. Recommended research would also 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 which, at the present time, are not available. Research would also 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.

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 optimal methods of preventing 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 long-term projects. 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, as well as discovery of 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.

## **5.6 Funding Opportunities and Research Supported**

It is critical that the strategic research priorities identified during the Influenza Research Priorities Workshop and by the PPSRI Task Group are funded in a timely manner. To this end, CIHR-III has taken a lead role and has also collaborated with other CIHR Institutes and organizations to launch several funding opportunities to support pandemic preparedness research. The applications have

been peer-reviewed, grants have been awarded to successful applicants and research is underway. These funding opportunities and the research supported are summarized in section 5.6.1. The PPSRI has also supported pandemic preparedness research by providing funds to successful applicants to other programs or initiatives, providing the research proposed addresses one or more of the PPSRI strategic priorities. These funding opportunities and the research supported are described in section 5.6.2.

## 5.6.1 Funding Opportunities Led by the PPSRI and Summary of the Research Supported

### *Operating Grants: Pandemic Preparedness*

*Funding Opportunity:* [www.cihr-irsc.gc.ca/e/31297.html](http://www.cihr-irsc.gc.ca/e/31297.html)

*Funding Decision:* [www.cihr-irsc.gc.ca/e/33490.html](http://www.cihr-irsc.gc.ca/e/33490.html)

In June 2006, CIHR-III, PHAC and Mathematics of Information Technology and Complex Systems (MITACS; a Network of Centres of Excellence) launched this first funding opportunity to address the recommendations made at the Influenza Research Priorities Workshop. The purpose is 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-care system preparedness. In August 2006, CIHR-III received a strong response to this opportunity with the receipt of 60 applications, and 26 were funded in February 2007 (Table 5.6.1.1). The research proposed is wide-ranging and innovative, and will be vital to help Canada and the rest of the world prepare for a potential pandemic outbreak. For example, it is anticipated that the research will lead to novel methods to detect pandemic strains of influenza, to a universal influenza vaccine that would protect against multiple strains of influenza, to new ways to prevent the spread of the virus and to treat people with influenza infections, to improved health-care strategies and to a better understanding of ethical issues pertaining to a pandemic and how they should be addressed. The funding also supports and helps to build influenza research capacity in Canada, which is essential to meet the unique needs of this country and to ensure that local experts are available in the event of a pandemic. See Appendix 3.1 for project summaries.

**Table 5.6.1.1 - Projects Funded under the Operating Grants: Pandemic Preparedness Funding Opportunity**

Principal Investigator	Host Institution	Project Title
Boivin, Guy	Université Laval	Mechanisms of resistance of influenza to antiviral agents and evaluation of new therapeutic modalities
Buckeridge, David	McGill University	Understanding epidemics in special populations: Guiding intervention and planning
Coombs, Kevin	University of Manitoba	Proteomics of influenza virus-infected human cells
Dasal, André	Sir Mortimer B. Davis Jewish General Hospital (Montreal)	Ability and willingness of health care workers to report for work in an influenza pandemic
Day, Robert	Université de Sherbrooke	Antiviral inhibitors of furin and related convertases

Principal Investigator	Host Institution	Project Title
Earn, David	McMaster University	Consequences of evolution for pandemic preparedness
Gutfreund, Klaus	University of Alberta	Immunotargeting with CD154 to induce antiviral immunity to avian influenza
Kelvin, David	University Health Network (Toronto)	The role of complement cascades in pathogenesis of H5N1 disease
Kenny, Nuala	Dalhousie University	Pandemic planning and foundational ethical questions of justice, the common good and the public interest
King, Malcolm	University of Alberta	Cough and bioaerosol in influenza pandemic containment
Kobinger, Gary	University of Manitoba	In vivo evaluation of conventional and experimental avian influenza A (H5N1) virus vaccines
Lapointe, Réjean	Centre hospitalier de l'Université de Montréal	Development of a pan-specific cellular immune response to influenza
Leclerc, Denis	Université Laval	Development of a universal influenza vaccine candidate
Magor, Katherine	University of Alberta	Antiviral responses to influenza in the natural host
Maunder, Robert	Mount Sinai Hospital	Education and support to increase the resilience of health-care workers facing pandemic influenza: What is the minimum effective dose?
Nicholas, David	Hospital for Sick Children (Toronto)	Pandemic planning for paediatric care
Pante, Nelly	University of British Columbia	Toward the development of novel anti-influenza drugs that block nuclear import of influenza
Predy, Gerald	Capital Health Region (Edmonton)	Feasibility and effectiveness of a community triage centre to manage influenza-like illness in an urban setting
Skowronski, Danuta	University of British Columbia	Influenza vaccine effectiveness against serious outcomes
Skowronski, Danuta	University of British Columbia	From genotype to phenotype: Early detection of influenza variants and correlation with variation in vaccine effectiveness
Suresh, Mavanur	University of Alberta	Targeted dendritic cell vaccines for influenza: Providing a vaccine to all 33M Canadians
Tellier, Raymond	Hospital for Sick Children (Toronto)	Early detection of avian influenza isolates with increased affinity for the human sialic acid receptor
Upshur, Ross	University of Toronto	Ethics and pandemic planning: Engaging the voices of the public
von Messling, Veronika	Institut national de la recherche scientifique (Québec)	Pandemic potential assessment of recent animal influenza isolates
Watts, Tania	University of Toronto	Mouse models for evaluating the protective value of increased costimulation of CD8 T cell responses in the lung
Zhou, Yan	University of Saskatchewan	The role of PI3K/Akt pathway in modulating chemokine IP-10/CXCL10 production by influenza A virus infection in human airway epithelial cells

**CIHR International Opportunity Program: Seed and Other Grants**

*Funding Opportunity:* [www.cihr-irsc.gc.ca/e/32585.html](http://www.cihr-irsc.gc.ca/e/32585.html)

*Funding Decision:* [www.cihr-irsc.gc.ca/e/34273.html](http://www.cihr-irsc.gc.ca/e/34273.html)

CIHR-III and the CIHR International Relations Branch issued a joint call for applications to the International Opportunity Program for both seed and collaborative research project grants that are relevant to pandemic preparedness in July 2006. The purpose of the seed grants is to assist Canadian researchers to explore, develop and establish new international collaborations with foreign researchers. These one-time grants support Canadian participation in the pre-research stages that will lead to new international research collaborations. The Other Collaborative Research Grant enables Canadian researchers to participate in international research projects approved for funding by foreign entities in which the Canadian participants must secure their own funding.

The importance that CIHR-III places on establishing international collaborations is evidenced by its participation in a re-launch of the funding opportunity for International Opportunity Program Seed Grants ([www.cihr-irsc.gc.ca/e/30812.html](http://www.cihr-irsc.gc.ca/e/30812.html)) in October 2006.

Eight grants were awarded under the program in March 2007 (Table 5.6.1.2). It is anticipated that the results of the research will improve our ability to prevent and treat pandemic influenza and will foster necessary international research linkages in this important area. See Appendix 3.2 for project summaries.

**Table 5.6.1.2 - Projects Funded under the CIHR International Opportunity Program**

Seed Grants		
Principal Investigator	Host Institution	Project Title
Brewer, Timothy	McGill University Health Centre	Risk factors for emerging diseases
Brown, Earl	University of Ottawa	Evolution of interferon resistance of avian and human influenza viruses
Fish, Eleanor	University Health Network (Toronto)	Canada-EU collaboration: Development of broad-spectrum antivirals
McElhaney, Janet	Vancouver Coastal Health Research Institute	The roadmap to improved correlates of protection against influenza
O'Callaghan, Christopher	Queen's University (Kingston, Ontario)	Building global capacity for evidence-based research in communicable diseases
Pourbohloul, Babak	University of British Columbia	Pandemic preparedness: An international modeling exchange
Tran, Dat	Hospital for Sick Children (Toronto)	Genetic epidemiology of influenza: A multinational pediatric initiative
Other Collaborative Research Grants		
Principal Investigator	Host Institution	Project Title
von Messling, Veronika	Institut national de la recherche scientifique (Québec)	Characterizing the potential and mechanism of type I interferons as influenza treatment

**Team Grants: Influenza Transmission and Prevention**

*Funding Opportunity:* <http://www.researchnet-recherchenet.ca/rnr16/viewOpportunityDetails.do?prog=177&view=browseArchive&browseArc=true&sponsor=CIHR-10&type=AND&resultCount=25&sort=program&next=2>

*Funding Decision:* [www.cihr-irsc.gc.ca/e/35209.html](http://www.cihr-irsc.gc.ca/e/35209.html)

In December 2006, CIHR-III and CIHR/Rx&D Collaborative Research Program launched this funding opportunity in partnership with Canada's Research-Based Pharmaceutical Companies (Rx&D) Health Research Foundation 2006, the Canadian Food Inspection Agency, CIHR Institute of Aboriginal Peoples' Health and the International Development Research Centre. The objective of the CIHR Team Grant program is to strengthen Canadian health research by supporting teams of talented and experienced researchers conducting high-quality research and providing superior research training and mentorship. It is anticipated that the results will be realized more rapidly and more efficiently through the CIHR Team Grant program than if the components were to be funded as a series of separate operating grants.

The goal of this funding opportunity was to fund three-year team grants to study the modes of transmission of the influenza virus and alternative strategies for prevention of infections. Dr. Mark Loeb from McMaster University and his team were awarded a grant in October 2007 to examine influenza transmission and prevention in a model community (Table 5.6.1.3). The results of this research will form the basis of policy decisions on how best to prevent the spread of annual and pandemic influenza. See Appendix 3.3 for a project summary.

**Table 5.6.1.3 - Project Funded under the Team Grants: Influenza Transmission and Prevention Funding Opportunity**

Principal Investigator	Host Institution	Project Title
Loeb, Mark	McMaster University	HRF/CIHR/CFIA Team in Influenza –Transmission and prevention of influenza among Hutterites: A model for pandemic preparedness

**Operating Grants: Influenza Diagnostics, Transmission, Ethics Review and Antivirals**

*Funding Opportunity:* <http://www.researchnet-recherchenet.ca/rnr16/viewOpportunityDetails.do?prog=179&view=browseArchive&browseArc=true&sponsor=CIHR-10&type=AND&resultCount=25&sort=program&next=2>

*Funding Decision:* <http://www.cihr-irsc.gc.ca/e/36101.html>

CIHR-III launched this funding opportunity in collaboration with the PHAC, CIHR Institute of Aboriginal Peoples' Health, Canadian Foundation for Infectious Diseases and Association of Medical Microbiology and Infectious Disease Canada in December 2006. The purpose is to fund three-year research projects that will examine the optimal use of existing antivirals, disease transmission, rapid diagnostics and the ethics review process. Funding decisions were made in March 2008. Of the nine applications that were received, five were funded (Table 5.6.1.4). It is expected that the funded research will lead to rapid diagnostics, better methods for controlling disease spread and new ways to treat affected individuals. See Appendix 3.4 for project summaries.

**Table 5.6.1.4 - Projects Funded under the Operating Grants: Influenza Diagnostics, Transmission, Ethics Review and Antivirals Funding Opportunity**

Principal Investigator	Host Institution	Project Title
Boivin, Guy	Université Laval	Mechanisms of influenza resistance to neuraminidase inhibitors and evaluation of new therapeutic modalities
Borgeat, Pierre	Université Laval	A rationale approach towards alternative pharmacological interventions in the treatment of influenza virus infection
Krahn, Murray	University Health Network (Toronto)	The cost-effectiveness of pandemic influenza Mitigation strategies using a stochastic, agent- based transmission model
Richter, Martin	Université de Sherbrooke	Targeting host cell mechanisms: A novel approach to anti-influenza prophylaxis and therapy, and the study of the subsequent host immune response
Smieja, Marek	McMaster University	Rapid molecular diagnostics for influenza

**Team Grants: Influenza Biology, Vaccines, Ethics, Legal and Social Research**

Funding Opportunity: [www.cihr-irsc.gc.ca/e/32804.html](http://www.cihr-irsc.gc.ca/e/32804.html)

Funding Opportunity: <http://www.researchnet-recherchenet.ca/rnr16/viewOpportunityDetails.do?prog=180&view=browseArchive&browseArc=true&sponsor=CIHR-10&type=AND&resultCount=25&sort=program&next=2>

Funding Decision: [www.cihr-irsc.gc.ca/e/36353.html](http://www.cihr-irsc.gc.ca/e/36353.html)

Also in December 2006, CIHR-III launched this funding opportunity in collaboration with the PHAC, CIHR Institute of Aboriginal Peoples' Health, Ethics Office of CIHR and the Canadian Food Inspection Agency. The purpose is to fund three-year team grants on vaccines, the biology of the influenza virus, including the animal-human interface, and the social, ethical and legal issues related to preventing and responding to a pandemic. Expected outcomes of funded research are the identification of strategies to prevent or mitigate a pandemic outbreak, as well as methods and procedures to control disease spread between humans and from animals to humans, and to treat affected individuals. See Appendix 3.5 for project summaries

**Table 5.6.1.5 - Projects Funded under the Team Grants: Influenza Biology, Vaccines, Ethics, Legal and Social Research Funding Opportunity**

Principal Investigator	Host Institution	Project Title
Agrawal, Babita	University of Alberta	Investigation of Novel Vaccine Strategies for Influenza: Targeting Innate and Adaptive Immunity for Cross-protective Vaccines
Boivin, Guy	Université Laval	Optimization of influenza vaccines for human and avian influenza strains
Brown, Earl	University of Ottawa	Natural and Experimental Models of Evolution of Influenza A Viruses



Principal Investigator	Host Institution	Project Title
Feldmann, Heinz	University of Manitoba	Comparison and basis of efficacy in commercial conventional vaccines against the H5N1 influenza virus
Jean, François	University of British Columbia	CIHR Team Grant in the Functional Infectomics of H5/H7 Influenza A virus
McCarthy, Anne	Ottawa Health Research Institute	Optimizing Health Care Worker Interpandemic Vaccine Uptake in Acute and Long Term
Skowronski, Danuta	University of British Columbia	Sentinel Network to Monitor Influenza Vaccine Effectiveness During Annual Outbreaks and Pandemics
Upshur, Ross	University of Toronto	Canadian Program of Research on Ethics in a Pandemic (CanPREP): Whose risks, whose duties, and what priorities?
Watts, Tania	University of Toronto	Correlates of Protection Against Influenza Illness: From Mouse Models to Older Adults

**Research Syntheses: Knowledge Translation**

*Funding Opportunity:* <http://www.researchnet-recherchenet.ca/rnr16/viewOpportunityDetails.do?prog=157&view=browseArchive&browseArc=true&sponsor=CIHR-10&type=AND&resultCount=25&sort=program&next=2>

CIHR-III launched this funding opportunity in December 2006 in partnership with the CIHR Knowledge Translation Branch. The purpose is to strengthen knowledge translation by funding research syntheses related to preparing for and responding to an influenza pandemic. There are opportunities to learn from research work carried out during the Severe Acute Respiratory Syndrome (SARS) and other disease outbreaks. No applications related to pandemic preparedness were received.

**Workshop/Symposia Support in collaboration with Knowledge Translation Branch**

*Funding Opportunity:* [www.cihr-irsc.gc.ca/e/24244.html](http://www.cihr-irsc.gc.ca/e/24244.html)

*Funding Decision:* [http://webapps.cihr-irsc.gc.ca/funding/detail\\_e?pResearchId=1513270&p\\_version=CIHR&p\\_language=E&p\\_session\\_id=568681](http://webapps.cihr-irsc.gc.ca/funding/detail_e?pResearchId=1513270&p_version=CIHR&p_language=E&p_session_id=568681)

CIHR-III and the CIHR Knowledge Translation Branch announced in December 2006 that they will provide partial support of workshops and symposia that either support knowledge translation research and/or contribute to building networks relevant to pandemic research in order to assist in pandemic preparedness planning and pandemic control. Dr. Thomas Coleman and his colleagues were awarded a grant in February 2008 to support a symposium he is organizing in Toronto entitled: Pandemic Preparedness: Strategies and Tools. Experts in quantitative methods for pandemic planning and in public health will discuss methods to enhance pandemic preparedness and to develop the most appropriate response plan. See Appendix 3.6 for a project summary.



**Table 5.6.1.6 - Projects Funded under the Workshop/Symposia Support in collaboration with Knowledge Translation Branch Funding Opportunity**

Principal Investigator	Host Institution	Project Title
Coleman, Thomas	University of Waterloo	Pandemic Preparedness: Strategies and Tools

***Application Development Workshop***

[www.cihr-irsc.gc.ca/e/33173.html](http://www.cihr-irsc.gc.ca/e/33173.html)

An application development workshop for researchers with an interest in submitting applications to the December 2006 funding opportunities was held in Ottawa in March 2007. Over twenty individuals, including researchers with expertise in influenza and vaccine evaluation, participated in the workshop. The purpose of the workshop was to assist researchers in the application process by providing a review of the relevant research areas in the funding opportunity, a description of the goals of the organizations collaborating to fund this research and information about writing a successful grant application. The workshop also allowed researchers to meet each other to discuss areas of common interest. Participants stated that the meeting was effective in enhancing linkages and helping them begin to plan an application.

***Catalyst Grant: Mobilization of the Research Community for Outbreak Response***

*Funding Opportunity:* <http://www.researchnet-recherchenet.ca/rnr16/viewOpportunityDetails.do?prog=312&view=browseArchive&browseArc=true&progType=CIHR-1&type=AND&resultCount=25>

*Funding Decision:* <http://www.cihr-irsc.gc.ca/e/35881.html>

At the PPSRI Application Development Workshop held in March 2007, participants highlighted a need for research planning and preparation before an outbreak occurs to enable the research community to be poised to act immediately in the event of a pandemic. This funding opportunity, launched by CIHR-III and PHAC in September 2007, will support researchers by funding catalyst grants for individual researchers or small teams to start the planning and preparatory phase of research projects that will be essential for pandemic control during an outbreak, and to gather data for analysis in order to develop recommendations to prevent or mitigate future outbreaks. A total of fourteen applications were received, and five were funded in March 2008 (Table 5.6.1.7). See Appendix 3.7 for project summaries.

**Table 5.6.1.7 - Projects Funded under the Catalyst Grant: Mobilization of the Research Community for Outbreak Response Funding Opportunity**

Principal Investigator	Host Institution	Project Title
Bisaillon, Martin	Université de Sherbrooke	Development of a SOFA-ribozyme-based strategy to control the propagation of the influenza virus
Buckeridge, David	McGill University	Evaluating the population effect of a new vaccination policy: An international comparison

Principal Investigator	Host Institution	Project Title
Christian, Michael	Mount Sinai Hospital (Toronto)	Prognostic scoring for patients with severe disease due to influenza
McGeer, Allison	Mount Sinai Hospital (Toronto)	Pandemic research priorities in influenza transmission and its prevention
Tran, Dat	Hospital for Sick Children (Toronto)	Genetic determinants of influenza severity in children: A pre-pandemic community-based feasibility study

**Operating Grant: Priority Announcement (Pandemic Preparedness)**

*Funding Opportunity:* <http://www.researchnet-recherchenet.ca/rnr16/viewOpportunityDetails.do?prog=378&&view=currentOpps&org=CIHR&type=AND&resultCount=25&sort=program&all=1&masterList=true>

In December 2007, CIHR-III and PHAC launched this priority announcement to fund three-year operating grants to address questions of influenza transmission, the effectiveness of public health control measures and the fostering of compliance with public health control measures. It is anticipated that this research will lead to the identification of effective public health control measures for responding to an influenza pandemic and controlling disease spread, and the identification of effective strategies for improving compliance with such measures.

**Catalyst Grant: Pandemic Outbreak Team Leader**

*Funding Opportunity:* <http://www.researchnet-recherchenet.ca/rnr16/viewOpportunityDetails.do?prog=352&view=browseActive&progType=CIHR-1&type=AND&resultCount=25>

*Funding Decision:* <http://www.cihr-irsc.gc.ca/e/38676.html>

CIHR-III and PHAC launched this program in December 2007 with the goal to provide application development funds to team leaders with expertise in the areas of influenza and pandemic who can bring together a research team in key areas that will require a research response when an outbreak occurs. Through peer review, the top team leaders will be identified in each of the relevant research areas including: characterizing human infection with novel influenza strains, study of the mode of transmission of the virus in hospitals and in the community; evaluation and use of vaccines, evaluation and use of antivirals, assessment of the implementation of pandemic plans, identification of determinants of at-risk Inuit and First Nations communities, and assessment of the impact of a pandemic on the health care system, society and the economy. When an outbreak occurs, it is anticipated that additional research funding will be available and the identified team leaders will be asked to describe the members of their team, their research plan and a budget in an abbreviated application for expedited peer review and funding. Developing research teams before a pandemic via this funding opportunity will ensure that teams of qualified researchers are in place to rapidly respond to an outbreak, and that essential research is funded in a timely manner.

**Influenza Research Network**

*Funding Opportunity:* <http://www.researchnet-recherchenet.ca/rnr16/viewOpportunityDetails.do?prog=360&view=browseActive&progType=CIHR-13&type=AND&resultCount=25>

Through this funding opportunity that was launched in December 2007, CIHR-III is working with the PHAC to establish an Influenza Research Network with the overall objective to develop and test methodologies to evaluate the safety, immunogenicity and effectiveness of influenza vaccines and to establish methods for vaccine program implementation. The network will consist of a network leader who must be a researcher with proven leadership capabilities and experience and at least five additional independent investigators who have an established research track record in areas related to the collaborative project. It is anticipated that this targeted investment will ensure surge capacity and mechanisms for rapid data collection, analysis and evaluation of vaccines before and during a pandemic. It will also assemble a critical mass of experience and talent by linking individual researchers and/or research centres involved in vaccine evaluation, building on their core competencies and coordinating their efforts. Collectively, the researchers in the network will be positioned to achieve more than the sum of their individual efforts.

#### ***Influenza Research Network Application Development Workshop***

*<http://www.cihr-irsc.gc.ca/e/38537.html>*

An application development workshop for researchers with an interest in submitting an application to the Influenza Research Network funding opportunity was held in Ottawa in February 2008. The purpose of the workshop was to assist researchers in gaining an understanding of the application process and the expectations of the sponsoring organizations. The workshop also provided an opportunity for researchers to meet each other, exchange information and begin preparation of an application.

### **5.6.2 Funding Opportunities Initiated by Others and Summary of Research Supported by the PPSRI**

#### ***Operating Grants: Partnerships for Health System Improvement***

*Funding Opportunity: [http://www.researchnet-](http://www.researchnet-recherchenet.ca/rnr16/viewOpportunityDetails.do?prog=242&view=browseArchive&browseArc=true&progType=CIHR-14&type=AND&resultCount=25)*

*[recherchenet.ca/rnr16/viewOpportunityDetails.do?prog=242&view=browseArchive&browseArc=true&progType=CIHR-14&type=AND&resultCount=25](http://www.researchnet-recherchenet.ca/rnr16/viewOpportunityDetails.do?prog=242&view=browseArchive&browseArc=true&progType=CIHR-14&type=AND&resultCount=25)*

In the event of a pandemic, many issues will arise that relate to health systems and services. Research is needed to create new knowledge for informed decision making in pandemic planning and policies. To encourage this research, CIHR-III partnered with the CIHR Institutes of Health Services and Policy Research and Population and Public Health to launch this funding opportunity in March 2008. The purpose is to support teams of researchers and decision-makers interested in conducting applied health research in the area of pandemic preparedness useful to health system managers and/or policy makers.

#### ***Bridge Funding: Pandemic Preparedness Strategic Research Initiative***

*Funding Decision: [www.cihr-irsc.gc.ca/e/33462.html](http://www.cihr-irsc.gc.ca/e/33462.html)*

Bridge funding offers support to researchers who submit excellent research operating grant applications that are not funded through the regular CIHR competition. Three researchers in areas

relevant to the PPSRI were awarded bridge funding operating grants in February 2007 (see Table 5.6.2.1). The research that is supported will examine the risk of infection attributable to emergency ward visits, the role of cytokines in the pathogenesis of influenza and the mechanisms involved in long-term protection against influenza infection.

**Table 5.6.2.1 - Projects Funded under the Bridge Funding: Pandemic Preparedness Strategic Research Initiative**

Principal Investigator	Host Institution	Project Title
Kelvin, David	University Health Network (Toronto)	The role of chemokines and chemokine receptors in the development of host response and immunopathogenesis during H5N1 influenza infections
Quach-Thanh, Caroline	Montreal Children's Hospital	Transmission of infections in health-care settings: determining the risk of infection in elderly after a visit to the emergency room
Watts, Tania	University of Toronto	Co-stimulation and maintenance of T cell memory

***China-Canada Joint Health Research Initiative - Grants Program***

*Funding Decision:* <http://www.cihr-irsc.gc.ca/e/35047.html>

The program is jointly managed and funded by CIHR and the National Natural Science Foundation of China (NSFC). Its aim is to promote the development of Canadian-Chinese scientific co-operation between universities, hospitals, research institutes or affiliated research organizations in Canada and China through the support of collaborative research grants. One of the twenty successful grants awarded in October 2007 under this program is directly relevant to the strategic priorities of the PPSRI and was supported by the Initiative (Table 5.6.2.2). The successful applicants, Dr. Jingxin Cao and Dr. George Gao, plan to examine why certain forms of avian influenza are highly pathogenic in humans. Their research results will be useful in helping to contain the spread of influenza and in treating humans infected with highly pathogenic forms of the virus. See Appendix 4.1 for a project summary.

**Table 5.6.2.2 - Project Funded under the China-Canada Joint Health Research Initiative – Grants Program Funding Opportunity**

Principal Investigator	Host Institution	Project Title
Cao, Jingxin and Gao, George	University of Manitoba Chinese Academy of Medical Sciences (Beijing)	Studies on roles of NS1 protein of avian influenza H5N1 virus in evasion of innate and adaptive immunities using an interferon sensitive vaccinia virus recombinant system

### **Applied Public Health Chairs**

*Funding opportunity:* <http://www.cihr-irsc.gc.ca/e/31329.html>

*Funding decision:* <http://www.cihr-irsc.gc.ca/e/35106.html>

CIHR Institute of Population and Public Health manages and supports this program in partnership with the PHAC. The goal is to support research in policy and program intervention that has national relevance to public health, to foster links with the public health system, and to educate and mentor public health researchers. Two of the ten successful grants awarded in the July 2007 competition have direct relevance to pandemic preparedness and, therefore, were partially supported by the PPSRI (Table 5.6.2.3). Dr. Manuel plans to evaluate the impact of Ontario’s Universal Immunization Program on population health and to create tools that will enable public health planners at all governmental levels estimate the potential of intervention strategies on population health. Dr. Sargeant plans to investigate population-level risk factors and intervention strategies for zoonotic disease by bringing together networks of animal and human health researchers, practitioners and decision makers. This research and the networks established will be essential for pandemic planning and response because pandemic influenza is a zoonotic disease that initially spreads from animal reservoirs, such as birds, to humans. See Appendix 4.2 for project summaries.

**Table 5.6.2.3 - Project Funded under the Applied Public Health Chairs Funding Opportunity**

<b>Principal Investigator</b>	<b>Host Institution</b>	<b>Project Title</b>
Manuel, Douglas	Sunnybrook Health Sciences Centre	Population health impact intervention assessment tools (PHIAT)
Sargeant, Janice	University of Guelph	Meeting the zoonotic disease public health challenge: integrated methodologies for research and application

### **5.7 PPSRI Annual Meeting of Researchers and End-Users**

CIHR and partners plan to organize annual meetings of pandemic and influenza researchers and end-users of the knowledge created. The first meeting will be held in Winnipeg in November 2008. Participants will include researchers funded through the PPSRI, other national and international researchers from university, hospital, government and private research laboratories, health-care and public health practitioners, program administrators, policy and decision makers and representatives from sponsoring organizations. The meetings will provide an overview of the current state of pandemic and influenza research, build collaboration amongst researchers and linkages to end-users, and support knowledge translation of research findings.



## 6. Summary

Significant progress has been made by CIHR-III and partners in developing a research initiative to build research capacity and to prepare for pandemic influenza. Successful applicants to the first funding opportunity for pandemic preparedness operating grants in June 2006 were announced in February 2007, and critical research projects are underway. The PPSRI Task Group worked with stakeholders over the summer of 2006 to quickly set strategic research priorities that have formed the basis of a second major round of funding opportunities for pandemic preparedness research in December 2006. To enhance the funding available for these grants, the CIHR-III approached and reached agreements with partners that have a mutual interest in influenza pandemic preparedness. Collaboration with the PHAC led to the launch of a third major set of funding opportunities in the fall of 2007, and has allowed the PPSRI to enter a second important phase. This funding is targeted at identifying research projects that will be conducted during a pandemic outbreak, and will identify and support team leaders and individuals in their preparations for outbreak research. CIHR-III and PHAC are also establishing an influenza research network consisting of researchers from across the country that will develop and test methodologies to evaluate the safety, immunogenicity and effectiveness of influenza vaccines and to establish methods for vaccine program implementation. In addition, the international research collaborations supported through the International Opportunities Program, Team Grants and the PPSRI Annual Meetings will enhance linkages between Canadian and international researchers. This is important because the threat of an influenza pandemic is global. It is anticipated that the results from research that has been fostered and supported by the PPSRI and the continued activities of the Initiative will have significant outcomes that will help Canada and the rest of the world prepare for influenza outbreaks and a future pandemic.

## Appendix 1: CIHR Pandemic Preparedness Strategic Research Initiative 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), Scientific Director, CIHR Institute of Infection and Immunity (CIHR-III).



## **Appendix 2: Stakeholders Consulted to Finalize the Pandemic Preparedness Strategic Research 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

**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

**Raphael 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

## Appendix 3: Research Summaries of Projects Supported by Funding Opportunities Led by the PPSRI

### 3.1 Operating Grants: Pandemic Preparedness Project Summaries

#### **Antiviral resistance and new antiviral treatments**

*PI: Guy Boivin, Université Laval*

Currently, there are limited classes of antiviral drugs with activity against influenza. In addition, the use of antiviral drugs is associated with significant side-effects and with the emergence of resistant viruses. Dr. Boivin and his colleagues will examine mechanisms involved in antiviral drug resistance by mutating selected genetic regions in influenza viruses, and then examining which mutant viruses become resistant to antivirals. They also intend to evaluate new antiviral treatment regimens for influenza by testing new antiviral drugs and immunomodulatory compounds alone or in combination. It is anticipated that their research will result in improved management of severe influenza pulmonary infections including those caused by viruses that are resistant to current antiviral drugs.

#### **Controlling the spread of epidemics**

*PI: David Buckeridge, McGill University*

Epidemics often move quickly through a population because certain susceptible groups help to spread the disease. Children, for example, often play a key role in influenza epidemics, but, other groups, such as people with chronic disease or people living in crowded settings, may also play an important role in spreading influenza. To control an influenza pandemic effectively, public health authorities will have to target these groups strategically. Dr. Buckeridge and his team from the Clinical and Health Informatics Research Group at McGill University and the Children's Hospital Informatics Program at Harvard Medical School will study data from previous flu epidemics to learn more about how infections spread through these populations and the best way of controlling the risk of infection in different populations.

#### **Virus to cell – You've been hijacked**

*PI: Kevin Coombs, University of Manitoba*

On its own, a virus is powerless. It must invade a cell in the body of a host (such as a human) in order to replicate and cause illness. Researchers already have some idea of how viruses interfere with the activity of genes in the cells they infect, but little is known about how the viruses affect proteins, the real workhorses in any cell and organism. Dr. Coombs and his team are now studying how flu viruses alter the process by which cells make proteins. By changing a cell's proteins, a virus can hijack the cell's normal functions and begin to replicate itself. Identifying which proteins are affected and how they change will give scientists a greater understanding of how viruses work. This information could lead to the development of new vaccines or antiviral medications.

### **It's a pandemic – help wanted**

*PI: Andre Dascal, Sir Mortimer B. Davis Jewish General Hospital*

What if you had a pandemic, but no one came to help? Although this sounds dramatic, recent surveys suggest that just over 50% of health-care workers would stay away from work in the event of a pandemic. Current pandemic preparedness plans, however, do not take this possibility into account. Dr. Dascal and his team at the Jewish General Hospital in Montreal and the Direction de la Santé Publique de Montréal will survey Montreal-area health-care workers to learn more about how they would react to a pandemic. What would make them feel that the situation is too risky for them to report to work and on what would they base this decision? The team will work with health-care administrators to make sure they know about survey findings and help them ensure that they address the concerns of health-care workers in the event of a pandemic.

### **Inhibiting human proteins to prevent and treat influenza**

*PI: Robert Day, Université de Sherbrooke*

New antiviral drugs are needed for both the prevention and treatment of influenza infections. Dr. Day and his colleagues intend to develop a new class of antiviral drugs that target the human proprotein convertases, furin and PC5/6. Furin and PC5/6 are essential for the activation of multiple pathogens including influenza A viruses. The researchers intend to identify molecules that specifically inhibit the activity of furin and PC5/6. The efficacy of the most promising inhibitors will be tested to determine whether they protect isolated human cells against viral infection. The identification of the inhibitory molecules could eventually lead to important clinically relevant antiviral drugs that would be used not only for the treatment of influenza, but for many other types of viral infections.

### **Modelling viral evolution**

*PIs: David Earn, McMaster University and Troy Day, Queen's University*

During previous influenza pandemics, multiple waves of disease incidence occur at the start of a pandemic and new sub-types of influenza typically replace preexisting subtypes. This suggests that the virus rapidly evolves or changes, but the mechanisms underlying these observations are not understood. Dr. Earn and Dr. Day will use mathematical analysis and agent-based computer simulations in order to try to explain these observations. They will also determine how the use of both vaccines and antiviral drugs are expected to alter these evolutionary processes, and how they will alter the outcome of influenza pandemics. The results of their research promise to provide insights into behaviour of the virus during a pandemic, the effect of medical management, and will assist in the preparation and planning for an influenza pandemic.

### **Giving genetic influenza vaccines a boost**

*PI: Klaus Gutfreund, University of Alberta*

Genetic vaccines (DNA or viral-vector based) can be generated rapidly, are safe and immunogenic, and therefore, hold great promise for controlling the spread of emerging influenza viruses with pandemic potential. A strategy to improve these genetic vaccines is the inclusion of immunostimulatory molecules such as CD154. CD154 is critically important in many types of

immune responses to infection or vaccination. Dr. Gutfreund and his colleagues intend to determine whether immunization of mice with a genetic vaccine coding for a component of the influenza virus (hemagglutinin) and mouse CD154 will enhance immunity to influenza in comparison to vaccines coding for hemagglutinin alone. He predicts that CD154 will accelerate and enhance protective immune responses. If successful, these strategies can be adapted to develop protective vaccines for humans and livestock.

### **The role of complement cascades in the pathogenesis of H5N1 disease**

*PI: David Kelvin, University Health Network (Toronto)*

Infection of humans with the highly pathogenic bird flu or H5N1 influenza A virus leads to a severe illness resulting in a mortality rate of just greater than 60%. At present, little is known about the host responses in humans and mammals infected with H5N1. Dr Kelvin and his colleagues have previously discovered that the complement cascade is deregulated during H5N1 infection, which may explain the severity of symptoms and high degree of mortality observed. In their current studies, the researchers plan to explore this possibility in greater depth. They will determine whether changing levels of certain complement proteins has any effect on H5N1 infection or pathogenesis. The role played by influenza factors known to activate the complement pathway will also be examined. These studies will provide additional insight into host immune responses regulating infection and pathogenesis. They may also lead to the development of unique therapies to combat influenza infections during early and late stages of disease.

### **Questions of justice, the common good and the public interest in pandemics**

*PI: Nuala Kenny, Dalhousie University*

An influenza pandemic will have an impact upon virtually every aspect of society. Underlying the scientific and health policy challenges are important ethical issues of justice, care, and protection of the public. The fear, uncertainty, and substantial risks inherent in pandemics raise these ethical concerns to a high level not only for individuals but also for societies. Dr. Kenny believes that pandemic planning work regarding these issues has relied on individual bioethical concepts with insufficient attention to communal values. To remedy this situation, Dr. Kenny and her colleagues intend to develop a robust, coherent and meaningful public health ethics document for Canada that will serve in times of disaster response. The team will also identify and analyze the legal implications of the ethical decision-making framework for pandemic planning, and methods to best involve the general public in various aspects of the ethical decision-making framework.

### **Stopping the virus in its path**

*PI: Malcolm King, University of Alberta*

Infectious respiratory diseases are transmitted when an infected person expels droplets containing viruses or bacteria as aerosol when coughing, sneezing or even talking. Effective methods are needed to interrupt the path from the infected person to others. Dr. King and his colleagues plan to assess in volunteers the effectiveness in preventing aerosol spread with simple methods such as covering the mouth and nose when coughing or sneezing. The ability of currently available physical barriers such as masks that are used to contain aerosol from coughs will also be assessed by measuring aerosol patterns with a laser diffraction analyzer. An innovative approach to

preventing infection spread is to make mucus in the respiratory tract more sticky and therefore, more difficult to expel as aerosol. The effectiveness of this approach will also be examined. Information gained through this research will be useful in helping to prevent the transmission of several diseases including influenza.

### **Modern approaches to influenza vaccines**

*PIs: Gary Kobinger, University of Manitoba and Darwyn Kobasa, National Microbiology Laboratory, Public Health Agency of Canada*

Accumulating data suggest that the H5N1 influenza virus may be adapting for better transmission to humans. Historically, vaccination has been the ideal strategy for protecting against influenza infections and for preventing the occurrence of large epidemics and pandemics. The conventional influenza vaccine, based on egg-grown inactivated virus, has for H5N1 shown low efficacy in clinical trials and remains challenging to produce. The objective of Dr. Kobinger's and Dr. Kobasa's research is to develop an optimized vaccine strategy that is capable of protecting against several H5N1 isolates using newly developed immunization technology. In this approach, DNA and adenovirus-based vaccine technology will be used to vaccinate mice and ferrets against several influenza proteins alone or in combination. The vaccinated animals will be challenged with distinct H5N1 isolates to determine the optimal vaccine strategy.

### **Let's get some help around here!**

*PI: Réjean Lapointe, Centre Hospitalier de l'Université de Montréal*

Despite the fact that vaccination against influenza has been available for decades, no current vaccine induces long-term pan-specific memory responses or is effective against several sub-types of the virus. This is because the current vaccines induce antibody responses to highly variable viral components. Dr. Lapointe and his colleagues believe the challenge now is to develop a new generation of influenza vaccines that will elicit strong and sustained memory responses against highly-conserved viral components. They plan to take an innovative approach by developing an influenza vaccine that will specifically stimulate cytotoxic and helper T cells, which are necessary to control viral attack. The approach promises to complement current influenza vaccines, and greatly increase our ability to combat future pandemics.

### **One for all**

*PI: Denis Leclerc, Infectious Disease Research Centre, Université Laval*

Influenza viruses continually change forcing scientists to select the most prevalent strains each year for new vaccine formulations. An ideal solution is to develop a vaccine that is targeted against influenza proteins that remain very similar from strain to strain. However, the problem with this approach is the lack of immunogenicity of these conserved proteins. Dr. Leclerc and his colleagues have discovered that virus-like particles (VLPs) made of the coat protein of papaya mosaic virus are a powerful adjuvant, that enhances the immune response to a highly conserved influenza A protein. The researchers plan to continue this work by testing vaccine preparations and determining the most efficient combination in a mouse and ferret animal model. If successful, the results will form the basis for the clinical development of a new universal vaccine against all strains of the influenza virus A.

### **Antiviral responses to influenza in ducks**

*PI: Katherine Magor, University of Alberta*

Ducks are a natural host and reservoir for influenza viruses: in most cases they do not become ill following influenza infection. Dr. Magor's research examines the immune responses of ducks to influenza infection and the evasion strategies of the virus in order to explain this phenomenon. One of her objectives is to compare the immune responses to a non-pathogenic strain of H5N1 influenza with responses to an unusual strain of H5N1 that causes influenza-like symptoms. She also plans to determine why chickens are more susceptible to influenza infection. Understanding how ducks clear influenza may identify new ways to combat human infections.

### **Vaccinating health-care workers against stress**

*PI: Robert Maunder, Mount Sinai Hospital*

A severe influenza epidemic in Canada would severely strain the health-care system, not just in terms of increased demand for beds and supplies but also in terms of the stress on health-care workers. Increased stress would decrease the effectiveness of staff and increase the chance of absenteeism – a dangerous scenario in the midst of a pandemic. Dr. Maunder and his team will study ways of “innoculating” health-care workers against stress to maximize the chance they will remain on the job. Through e-learning and in-person workshops, researchers will focus on teaching health-care workers how to increase their skill and confidence in responding to stress since the usual response to stress is automatic and in a crisis often negative.

### **Pandemic planning for paediatric care**

*PI: David Nicholas, Hospital for Sick Children*

The SARS outbreaks in Canada in 2003 highlighted that paediatric populations are uniquely and dramatically affected by such a health emergency. Despite milder illness in children with SARS, chronically ill children with other conditions and their families reported significant stress and challenges accessing hospital services. Hospital staff faced ethical dilemmas related to the burden of restrictions. Dr. Nicholas and his colleagues will engage in research with the aim to provide recommendations in the development of an influenza pandemic plan that includes strategies to support young people, their families and their health care providers, and contains protocols that incorporate prevailing paediatric ethical principles. On-line surveys and interviews with key stakeholders will be used to identify needs, gaps and best practices. A panel of recognized experts in health and policy planning will use the information to draw conclusions and make specific recommendations.

### **No nuclear entry allowed!**

*PI: Nelly Pante, University of British Columbia*

Antiviral drugs against the influenza virus play an important role in the treatment and prevention of human influenza infection. These drugs are recommended for the control of seasonal influenza, and until suitable vaccines are produced, would be the first line of defense against a future pandemic. In recent years, influenza viral strains have developed resistance against available antiviral drugs. Therefore, it is imperative that new drugs be developed that work at different stages of the life cycle



of the influenza virus. One of these stages is the entry of the viral genome into the nucleus of the host cell. Dr. Pante and her research team plan to study genome entry into the nucleus and to identify peptides or antibodies that block this process. Their discoveries may ultimately lead to the development of a novel class of antiviral drugs.

### **Community triage and treatment centres**

*PI: Gerald Predy, Capital Health Region (Edmonton)*

It is likely that conventional methods of health care delivery will be overwhelmed in the event of a pandemic, and it is essential that new methods are developed now to build health-care capacity. Dr. Predy and his team have conceived of an innovative approach to this problem, namely the use of mobile community triage and treatment centres that will be adjacent to emergency departments. The typical winter influenza season will be used to test the centres for safety, acceptance, and effectiveness in the management of influenza-like illnesses. If the centres do increase capacity in the management of influenza, the procedures and methods used could be employed in the case of a pandemic.

### **Rapid detection of new influenza viruses and their impact on vaccine protection**

*PI: Danuta Skowronski, University of British Columbia*

Scientists usually identify new viral strains by examining the proteins on a virus's surface. They use a test known as a hemmagglutination inhibition (HAI) assay, which can detect changes in the structure of one of the surface proteins of the virus. But it can take a long time to conduct HAI assays. Dr. Skowronski and her team have developed a much faster technique that looks for changes in the genetic material of viruses – samples are sent in by a province-wide network of clinics. For the past two years, the team has been using this approach and has been able to predict important new strains of the influenza virus and correlate these with how well vaccines work much earlier than HAI assays. The project will be expanded to include influenza viruses and vaccine effectiveness data collected in other provinces of Canada, including Alberta and Quebec.

### **Making more vaccine with less**

*PI: Mavanur Suresh, University of Alberta*

In the event of a pandemic, current vaccine stocks will be insufficient to protect everyone. This simple fact is driving efforts to find new ways of developing vaccines that can deliver the same protection but in smaller doses so that more people can be helped. Dr. Suresh from the University of Alberta in Edmonton in collaboration with Dr. Kobasa from the National Microbiology Laboratory in Winnipeg and their team will study new ways of making vaccines using powerful immune cells known as dendritic cells. Dendritic cells are like sentinels, constantly on the lookout for new pathogens. Once found, these cells process antigens and help mobilize the body's immune response. Current approaches to vaccine manufacturing require a large amount of the virus antigen to stimulate an immune response and offer protection against future exposure to the same virus. Early results suggest that, with a vaccine that is delivered to dendritic cells, one needs 500 times less vaccine and hence a much smaller dose to give the same protection as a traditional vaccine.

### **Back from the future**

*PI: Robert Tellier, Hospital for Sick Children*

The highly pathogenic strains of influenza A (H5N1) circulating many parts of the world are the most feared candidates for giving rise to a strain of influenza that will trigger the next pandemic. Fortunately, current H5N1 strains are not easily transmitted from human to human. Dr. Tellier and his team have taken advantage of the predicted small one to two amino acid changes in current H5N1 proteins that could generate a pandemic strain to develop a rapid, convenient and powerful method to detect influenza strains with these changes. The test will allow for the early detection of avian influenza viruses with enhanced ability to be transmitted from human to human.

### **Ethics and pandemic planning: engaging the voices of the public**

*PI: Ross Upshur, University of Toronto*

The research proposed by Dr. Upshur and his colleagues builds on a report entitled “Stand On Guard for Thee: Ethical considerations in preparedness planning for pandemic influenza” produced by the Joint Centre for Bioethics at the University of Toronto. The report outlined a framework of values for inclusion in pandemic planning and illustrated their application. Dr. Upshur and colleagues intend to solicit public perspectives via innovative public engagement technologies and traditional survey methods on the four ethical challenges identified in the report (i.e. health workers’ duty to care; restrictive measures to protect the public good; priority setting and allocation of scarce resources; and global governance implications) and to refine the framework in light of these findings. The outcomes will be of interest to public health policy makers at all levels of government and will help inform pandemic planning efforts internationally.

### **Assessing the pandemic potential of influenza subtypes**

*PI: Veronika von Messling, Institut national de la recherche scientifique (Québec)*

Currently, it is very difficult to predict which influenza strain(s) will emerge to cause the next epidemic or pandemic. Dr. von Messling and her colleagues plan to develop a computer algorithm to predict the pandemic potential of newly isolated animal influenza viruses. To do this, they will infect ferrets with a number of influenza viral subtypes from livestock and wild animals, assess the ability of the subtypes to spread and cause disease, and then compare the genetic sequences of the subtypes to determine which sequences are associated with greater ability to cause disease. The sequence-based computer algorithm that the researchers develop will enable a more accurate risk assessment and targeted control strategies of viruses with pandemic potential.

### **A novel influenza vaccine strategy—Co-stimulation of cytotoxic T cells**

*PI: Tania Watts, University of Toronto*

Current influenza vaccines are only about 60% effective and are highly strain-specific requiring yearly changes to vaccine formulations. The development of a vaccine that leads to increased and long-lived cytotoxic T cell immunity offers the possibility of improved cross-protective immunity. Dr. Watts and her research team have recently found that two co-stimulators of cytotoxic T cells can enhance cytotoxic T cell responses to influenza virus in culture. The researchers plan to use this information to test this vaccination strategy in mice by examining viral clearance, lung pathology and lung function following vaccination and challenge of the mice with a strain of influenza virus

that would otherwise be lethal in unvaccinated mice. Results of the research will potentially form the basis of novel vaccine strategies that could be applied to humans.

### **Too much of a good thing**

*PI: Yan Zhou, University of Saskatchewan*

A highly pathogenic avian influenza virus (H5N1) first infected humans in 1997, and while human-to-human transmission has been inefficient to date, the severity of the disease is exceptional and the mortality rates are high. Patients with H5N1 have unusually high levels of chemokines such as interferon-gamma-inducible protein 10 (IP-10), which is released from epithelial cells of the airway upon infection and activates the immune system. Instead of helping the infected individual; the excess production of IP-10 may contribute to the pathogenesis, such as pulmonary inflammation, that is seen with H5N1 infection. Dr. Zhou and her colleagues plan to investigate the cellular mechanisms underlying the enhanced secretion of IP-10. The investigators hope that this knowledge will lead to novel strategies to reduce the severity of influenza and aid in the recovery from illness.

## **3.2 CIHR International Opportunity Program: Seed and Other Grants Project Summaries**

### **Risk factors for emerging diseases**

*PI: Timothy Brewer, McGill University Health Centre*

The prevention of the next pandemic is recognized as one of the greatest challenges confronting health today. Though pandemics can occur at any time and place, populations living in poverty, overcrowding or lacking adequate sanitation are more vulnerable to communicable diseases. Social and environmental factors are clearly associated with illness and death from infectious diseases; however, the relative contribution of these and other factors to the development of pandemics are not well known, complicating any rational attempt to prevent their occurrence. Areas most prone to emerging diseases are least likely to have the trained personnel and public health infrastructures to efficiently recognize and control outbreaks. While low-income countries such as Peru bear the brunt of communicable diseases, rapid globalization makes all countries vulnerable to pandemic and emerging diseases regardless of where epidemics originate. It is essential that we have a better understanding of the causes for the development and spread of pandemics and emerging diseases. The goals of the collaboration led by Dr. Brewer are to build outbreak control capacity in Peru through workshops presenting the current understanding of the social, environmental and health factors associated with emerging pandemics, as well as to identify areas for new research. The discussions will encourage international collaborations between Canadian and Peruvian researchers to build capacity in the identification, prevention and control of potential pandemics and emerging diseases throughout Peru and the Amazon Basin region.

### **Evolution of interferon resistance of avian and human influenza viruses**

*PI: Earl Brown, University of Ottawa*

Avian influenza is a continuing threat in both the veterinary and human public health settings. It is important to understand the molecular epidemiology and pathogenesis of human and avian

influenza viruses in order to meet future challenges presented by novel forms of influenza. The University of Ottawa and the China Agricultural University have both demonstrated success in research in the field of influenza. Studies in Ottawa have focused on modeling human influenza virus evolution to high virulence in the mouse, while researchers at the China Agricultural University are studying natural evolution and experimental evolution of influenza in wild birds and poultry. The researchers in both countries will mutually analyze influenza biology using data collected from both avian and mammalian influenza viruses. In particular they have found that highly virulent mouse-adapted human influenza viruses, which cause pneumonia in mice, have mutations in the NS1 gene that are identical to mutations that have been independently selected in pathogenic avian influenza strains including the pathogenic H5N1 viruses. The research team will initially study the NS1 genes of pathogenic H9N2 viruses that are related to those of H5N1 but are less dangerous to study. They will then produce synthetic versions of the avian strain that have mutations in common with the virulent mouse-adapted viruses to identify the changes that affect the severity of disease. The ultimate goal is to understand the biology of influenza viruses through analysis of viral gene sequences.

#### **Canada-EU collaboration: Development of broad-spectrum antivirals**

*PI: Eleanor Fish, University Health Network (Toronto)*

Pandemic preparedness involves both management of populations in terms of quarantine measures and hospital isolation procedures, and the use of antiviral drugs. Influenza viruses mutate very rapidly, therefore vaccine development requires the isolation and characterization of the specific pandemic strain before an effective vaccine may be manufactured. In the intervening months, antiviral drugs will be the first line of defense. Notably, drug-resistant and drug-dependent strains of the avian flu, H5N1, have emerged against the currently available and licensed anti-influenza drugs. Dr. Fish plans to focus on the human host, not the virus, to develop novel broad spectrum antiviral drugs. The research will integrate the activities of her antiviral research group with that of a European Network of Excellence, VIRGIL, in an EC-funded cooperation programme. In addition to working together on the development of novel anti-influenza antivirals, this collaborative will also consider resource-saving management opportunities, important for Canada and Europe. Therefore, besides the establishment of this research collaborative, learning from the respective health systems and practices in the field of pandemic planning will be of significant added value.

#### **The roadmap to improved correlates of protection against influenza**

*PI: Janet McElhaney, Vancouver Coastal Health Research Institute*

The immune response to the influenza vaccination in specific age-groups such as young children and older adults is insufficient. Consequently, these groups remain vulnerable to serious disease despite vaccination. Thus, the development of an influenza vaccine based on induction of antibody responses in young healthy adults may result in an insufficient and unpredictable level of protection in these at risk age groups. Recently, Dr. McElhaney, along with investigators from the CANVAC project, identified additional and improved indicators of protective immune responses such as granzyme B and IFN $\gamma$ /IL-10. The use of these markers is a significant step in the ability to practically measure the cell-mediated immune response to influenza in older adults and in high-risk

populations. The goal of the research project is to identify additional new or improved correlates of protection for influenza, which are applicable to immunity for avian types of influenza and valid in multiple age groups, i.e. infants/children, adults and older adults. Dr. McElhaney will collaborate with investigators in the European FluSecure project to develop test systems based on high-throughput analysis to enable large-scale analyses necessary for vaccine trials in high-risk populations.

### **Building global capacity for evidence-based research in communicable diseases**

*PI: Christopher O’Callaghan, Queen’s University*

Researchers at Queen’s University and the Sri Ramasamy Memorial (SRM) Institute of Science and Technology in India have established a research partnership in population and public health to address global issues in the area of infectious diseases. In India, populations are vulnerable to infectious disease due to poor sanitation and hygiene, unsafe water, etc., but data is needed to develop informed interventions to reduce the incidence of sickness and death. The team plans to develop and test a Regional Population Health Registry (RPHR) that will allow for data collection and analysis, monitoring of community health over time and space, and will link trends to individual and household demography, health behaviours and environmental risks. In order to illustrate the power of the RPHR, their initial research will focus on community-acquired multi-drug resistant *Staphylococcus aureus* (CA-MRSA), a disease that is spreading at an alarming rate in North American communities, whose high incidence rate in India provides a robust sample size. Results of this research are expected to inform health-care decision making, not only in India, but also in Canada. Once established, the RPHR will enable regional surveillance of pathogens like H5N1 and other infectious diseases, building "early-warning" capability as the RPHR can track transmission dynamics.

### **Pandemic preparedness: An international modeling exchange**

*PI: Babak Pourbohloul, University of British Columbia*

Protecting public health means planning for unpredictable eventualities, and given its very complex nature, infectious disease transmission within and between populations often manifests unforeseen outcomes. Concern regarding the natural emergence or deliberate release of biological agents has been rising since the terrorism of 9/11, followed by the threat of SARS on global safety and the possibility of an influenza pandemic threatening all human societies. As a result, pandemic preparedness planning and the pressing need to proactively evaluate pandemic influenza intervention strategies has become a priority for public health-policy makers worldwide. Dr. Pourbohloul will bring together and integrate international mathematical modeling expertise to create a unique network that is otherwise unlikely to be attainable in an individual institution. The initial meetings supported by the funding will help the participants to develop new partnerships and offer new solutions to the pressing issue of pandemic preparedness planning through continuous and shared access to advanced decision-making technologies. Many of these techniques have evolved independently within various participating groups and in order to maximize this collective gain for policy recommendation, it is urgent to facilitate dialogue between these leading international groups to ensure optimal benefit for Canadians and all our global neighbours. The

group's members will undertake cross-validation of various methodologies and applications of statistically robust models of infectious diseases with available data, to effectively inform public health policy.

### **Genetic epidemiology of influenza: A multinational pediatric initiative**

*PI: Dat Tran, Hospital for Sick Children (Toronto)*

Influenza is a major cause of illness and death worldwide. The emergence of aggressive bird flu viruses has raised international concern of an imminent pandemic, which is expected to kill up to 4,000 children in Canada and up to 50 million people worldwide. As with seasonal influenza, some healthy children may be at greater risk in a pandemic. Common genetic differences in healthy children's immune responses to the virus may explain why some get sicker with influenza than others. This initiative brings together researchers in four pediatric medical centres from Canada (SickKids), the U.S., Thailand, and Hong Kong in order to plan a study, involving all four centres, to look for common differences in genes of the immune system that are linked to more severe influenza. The goal is to increase understanding of how influenza causes disease and ultimately to speed development of new treatments for seasonal and pandemic influenza. The ability to predict the healthy children at highest risk may also help public health agencies to better prepare drugs, equipment and personnel for a pandemic.

### **Characterizing the potential and mechanism of type I interferons as influenza treatment**

*PI: Veronika von Messling, Institut de la recherche scientifique (Québec)*

Influenza is one of the most important human viral infections. The virus is constantly changing, and a global outbreak of a new variant would result in many deaths and severe economic damage. The goal of this international study is to determine if a treatment with interferon could be used to prevent or inhibit influenza infection. Interferons are normally produced by our cells in response to an infection. Members of the research team have previously observed that cells treated with interferon produce a protein called Mx that protects them from influenza infection. They have also shown that mice that express this protein are resistant to influenza infection, and are currently studying the underlying mechanism of action. The goal of the research is to expand these studies to ferrets, which are naturally susceptible to influenza and develop the same signs of disease as humans. Because of these characteristics, ferrets have long been used to study the efficacy of vaccines and treatments. The team anticipates that this international research effort will provide an additional treatment option for influenza, and will thus contribute to the ongoing research effort to prevent future influenza outbreaks.

## **3.3 Team Grants: Influenza Transmission and Prevention Project Summary**

### **Transmission and prevention of influenza among Hutterites: A model for pandemic preparedness**

*PI: Mark Loeb, McMaster University*

*Co-applicants: David Earn, Julie Fox, Julia Keenlside, Margaret Russell, Marek Smieja, Stephen Walter*

In the past, it has been a challenge to examine transmission of influenza within a community,



because repeated contact with infected individuals outside the community makes the analysis difficult. Dr. Mark Loeb and his research team are now studying a Canadian community of Hutterites to gain new understanding about influenza transmission and its prevention. The majority of Hutterites live in Alberta, Saskatchewan, and Manitoba where they practice communal farming on small colonies relatively isolated from towns and cities. Within these homogeneous, moderately sized colonies, regular influenza transmission is facilitated by a communal lifestyle; however, isolation from the outside community limits re-introduction of the virus. Additionally, Hutterites are active swine farmers. This is important because, in the past, strains of influenza with the ability to infect humans have originated in pigs. The Hutterite community, therefore, offers a unique opportunity to determine if swine-to-human and human-to-swine transmission of influenza is occurring and also to gain a better understanding of human to human influenza transmission. Dr. Loeb and his team plan to detect the virus in samples from humans and pigs, and use this information to examine transmission of the virus by mathematical modeling and spatial analysis. One of the novel aspects of the research is to assess genetic determinants of influenza vaccine response. The effect of repeated immunization on immune responses to influenza will also be examined, along with any adverse effects of vaccination. The results of this research will form the basis of policy decisions on how best to prevent the spread of annual and pandemic influenza.

### **3.4 Operating Grants: Influenza Diagnostics, Transmission, Ethics Review and Antivirals Project Summaries**

#### **Viral resistance to neuraminidase inhibitors and evaluation of new therapies**

*PI: Guy Boivin, Université Laval*

Existing anti-influenza agents, including neuraminidase inhibitors and adamantanes, are important for the control of influenza infections. These antivirals, however, can become ineffective if drug-resistant viruses emerge. Viral strains that are resistant to adamantanes retain their ability to spread and cause disease, but little is known about viral strains that are resistant to neuraminidase inhibitors. The objectives of the research led by Dr. Boivin are to better understand the mechanisms of influenza resistance to existing and investigational neuraminidase inhibitors, to determine, via mathematical modelling, the ability of neuraminidase-resistant strains to spread and cause infection and to evaluate new therapeutic modalities, including combination treatments for the control of influenza infections. Their results will increase our knowledge of resistance mechanisms to anti-influenza compounds and validate novel therapeutic strategies, allowing for improvements in the treatment of both seasonal and pandemic influenza infections.

#### **Modifying lipid mediators of inflammation for the treatment of influenza**

*PIs: Pierre Borgeat and Louis Flamand, Université Laval*

When we are infected with a virus, such as the influenza virus, our body releases a number of compounds that stimulate our immune system, thereby helping to fight the infection. These compounds are usually beneficial, but sometimes they cause an exaggerated response that contributes to the pathology seen during infection. Drs. Borgeat and Flamand will investigate if viral infection in the lungs triggers the formation of a group of these compounds called “lipid mediators of inflammation”. If so, they will determine, through the use of various inhibitors or

antagonists of the lipid mediators, which ones exert beneficial or detrimental effects on the outcome of infection. These studies will provide important information that could rapidly lead to improved treatments, using already available drugs, of influenza and other airway infections such as those caused by the SARS coronavirus, bacteria and fungi.

### **Targeting host cells to prevent and treat influenza**

*PI: Martin Richter, Université de Sherbrooke*

Currently available antivirals and vaccines may not be in sufficient supply and/or may not be efficient in controlling the spread of an emerging highly pathogenic strain of influenza virus, because the virus evolves over time and can become resistant to the treatments. The team led by Dr. Richter will investigate a novel approach to the treatment of influenza that targets the host cell. They plan to disrupt host cell mechanisms needed by the virus for entry, replication and spread, thereby, minimizing the possibility for the virus to adapt to the treatments. An acidic pH is required within the cell to allow the virus to enter and infect the cell. As well, host enzymes known as proteases are required to process viral proteins for the formation of new infectious viruses. The team will test whether drugs, which either decrease the acidity of airway cells or inhibit proteases, will inhibit the ability of the influenza virus to infect and replicate in cultured cells and in a mouse model. The study will allow for the rapid assessment of the efficacy of known, well-tolerated drugs with worldwide availability against influenza, thus contributing to pandemic preparedness. If successful, this approach will be useful against all influenza strains, even ones that have not yet emerged, because all influenza viruses require the same host cell mechanisms for infection and replication.

### **Rapid molecular diagnostics for influenza**

*PIs: Marek Smieja and Astrid Petrich, McMaster University*

Highly sensitive and rapid tests are urgently needed to help prepare Canada for all phases of an influenza pandemic. Molecular diagnostics such as reverse-transcriptase polymerase chain reaction (RT-PCR) have the advantage of speed, high throughput, and high sensitivity and specificity, but are not currently widely available. The goal of the research team led by Drs. Smieja and Petrich is to develop and implement molecular diagnostics for seasonal influenza and for pandemic influenza. They plan to: develop an assay capable of detecting all 16 hemagglutinin (H) and 9 neuraminidase viral genes; develop an assay to quantify H3 (seasonal influenza strain) and H5 (potential pandemic influenza strain) in respiratory specimens; and to develop a rapid molecular sequencing to determine the nosocomial spread of influenza viruses, as a tool for infection control and transmission studies. Such tests will help physicians and public health personnel to make individual and community decisions on preventative or therapeutic use of antivirals, hospitalization, quarantining, school closures, or other control measures.

### **Cost effectiveness of pandemic influenza prevention and treatment strategies**

*PI: Murray Krahn, University Health Network (Toronto)*

It is important for policy makers to have information about the usefulness and cost-effectiveness of various influenza intervention strategies so that they can make informed decisions in the event of a pandemic. Dr. Krahn and his team plan to develop a mathematical model that simulates pandemic

influenza transmission in representative Ontario communities in order to estimate the cost-effectiveness of preventive and therapeutic pandemic influenza mitigation strategies. A two-stage process will be used. First, an agent-based model will be developed, simulating pandemic influenza transmission in Toronto and another, smaller Ontario community. The model will predict the number of influenza cases under a variety of interventions. Second, the model will be extended to evaluate the burden of pandemic influenza in the absence of any intervention and to incorporate a cost-effectiveness analysis of prevention and treatment strategies (vaccines, targeted antiviral prophylaxis, antiviral treatment, and social distancing measures) from the perspectives of the healthcare payer and society. The results will assist in the development recommendations for the most appropriate use of influenza vaccines and antivirals, and will aid in the prediction of the demand for vaccines and antivirals in different circumstances. As well, the proposed model could be used in the future to support public health decision making regarding influenza prevention and treatment.

### **3.5 Team Grants: Influenza Biology, Vaccines, Ethics, Legal and Social Research Project Summaries**

#### **Novel vaccine strategies for influenza: towards cross-protective vaccines**

*PIs: Babita Agrawal, University of Alberta,*

*Rakesh Kumar, University of Alberta,*

*Christopher Richardson, Dalhousie University (Nova Scotia)*

*Co-Applicants: Jackie Katz, James Kellner, Darwyn Kobasa, John Smit*

Vaccination will be the best method to prevent the spread of disease and reduce the severity of infection during a widespread influenza pandemic. There are several limitations, however, with current vaccines including the large amount of antigen that is needed per dose, the need to produce a new version of the vaccine each year and current egg-based production methods. Dr. Agrawal and the rest of the research team will investigate ways to optimize current influenza vaccines and develop new cross-protective vaccines. They first plan to boost immune responses to current vaccines by adding synthetic toll-like receptor (TLR) agonists, which are known to stimulate both innate and adaptive immunity. They will then combine the TLR agonists with influenza antigens (HA, NP and M2e) in an egg-free system. The team will test the vaccines that they develop in animal models to determine whether they provoke strong immune responses and prevent infection caused by several strains of influenza virus. The results of the studies will help in the development of innovative vaccine technologies, generate new influenza vaccine candidates, optimize current vaccines and contribute to our understanding of the types of immune responses that afford protection against influenza infection.

#### **Optimization of influenza vaccines for human and avian influenza strains**

*PIs: Guy Boivin, Université Laval,*

*Barbara Papadopoulou, Université Laval,*

*Brian Ward, McGill University*

*Co-Applicants: David Burt*

Annual vaccination is the cornerstone of management of influenza epidemics. However, despite their proven efficacy in reducing influenza-related mortality and morbidity, some important problems remain with the current inactivated vaccines. For instance, their efficacy is considerably lower in elderly individuals and when there is not a good match with the circulating influenza strain. In addition, the occurrence of a new pandemic would result in extraordinary challenges to the existing immunization program. The team intends to optimize existing inactivated influenza vaccines in order to generate stronger, more durable and broader immune responses. They plan to test a series of adjuvants, which are added to vaccines to enhance immune responses, and different routes of administration combined with an existing inactivated human influenza A/H3N2 vaccine and a prototype avian influenza A/H5N1 vaccine developed by their industrial partner GlaxoSmithKline. To evaluate these vaccines, animal models (mouse and ferret) will be vaccinated. Antibody and cellular immune responses will be then be examined, as well as protection following challenge with various influenza strains. The results will facilitate the selection of the best adjuvant(s), route and immunization schedule for future human trials.

### **Natural and experimental models of evolution of influenza A viruses**

*PI: Earl Brown, University of Ottawa*

*Co-Applicants: Lorne Babiuk, Manjeet Sethi, Hana Weingartl, Hana Weingartl, Yan Zhou*

Human influenza A strains with pandemic potential usually originate from animal reservoirs including birds and pigs. Therefore, it is critical to understand the animal-human interface of influenza infections. Dr. Brown and his research team plan to develop biological tests and define genetic markers for potential pandemic viruses so that they can be identified as they emerge from natural animal populations. Specifically, they will identify the genetic properties of influenza virus mutants and/or reassortants (genetic mixtures) that control host switching and transmission from avian to mammalian hosts. Recombinant and mutant viruses with combinations of genes from avian, swine, or human influenza viruses, including the highly pathogenic avian influenza (H5N1), will be generated and tested for their ability to replicate and infect mice, pigs, ferrets and guinea pigs. The newly developed guinea pig model is included with the swine model to assess the roles of adaptive mutations on transmission of modified swine viruses. These studies will identify both general and host-specific genetic determinants of infection and virulence. The proposed studies have a strong training component involving various animal and biochemical models. Dr. Sethi of the Canadian Food Inspection Agency of Canada is a member of the research team. He directs research activity within the agency and ensures that new knowledge is used for policy development. Therefore, the research results will have a direct and immediate impact on surveillance and control of influenza virus transmission among animals, as well as from animals to humans.

### **Comparison and basis of efficacy in commercial conventional vaccines against the H5N1 influenza virus.**

*PI: Heinz Feldmann, University of Manitoba*

*Co-Applicants: Shawn Babiuk, Darwyn Kobasa, Gary Kobinger, Veronika von Messling*

Since 1997, a highly virulent avian H5N1 virus has become established in domestic and wild bird populations. In turn, the virus has been transmitted from birds to humans causing 190 deaths in 312

cases. The virus is not transmitted between people but the cases of human disease have raised the concern that the virus may adapt to easy transmission between people and trigger a new pandemic of a virus capable of causing serious disease in people. In response to the threat of an influenza pandemic much effort has been dedicated to producing vaccines that could be used to limit the impact of the pandemic. Several vaccine companies have approved conventional vaccines that utilize an inactivated egg-grown virus. These vaccines differ in their ability to provide efficient protection against H5N1 viruses that is dependent on the strain of virus used for generating the vaccine, as well as formulations, or adjuvants, designed to enhance the strength of the immune response. The team led by Dr. Heinz Feldmann will test the effectiveness of each commercially available vaccine, in animal models of influenza disease, against several circulating strains of H5N1 virus. Further, the team will study the specific immune responses generated by each vaccine with the goal of identifying the types of responses that are correlated with the best levels of protection. Finally, it is known that vaccines may offer only limited protection against viruses that are too different from the vaccine virus and this mismatch may select mutations in the virus that reduce the effectiveness of the vaccine for future use. The team will examine how this problem may contribute to the spread of viruses that cannot be controlled with currently available vaccines. Overall, this research will help pandemic planners select the best vaccine to use, as well as enhance understanding of how to best design and use vaccines.

### **Functional infectomics of H5/H7 influenza A virus**

*PI: François Jean, University of British Columbia*

*Co-Applicants: Robert Ernest Hancock, John Pasick, Joseph Sriyal Peiris, Suryaprakash Sambhara, Craig Stephen, Natalie Strynadka, Patrick Tang, Stephen Withers,*

The World Health Organization predicts that we will witness three to four influenza pandemics each century. Bird flu, also known as avian influenza virus A, is thought to be the next likely cause of a pandemic. The virus consists of 15 strains or subtypes. In 1997, the first human died from subtype H5N1, and from 2003-07, 216 deaths were attributed to H5N1. In February 2004, the H7 subtype of the virus was detected on a chicken farm, one hour east of Vancouver, Canada. The virus spread rapidly such that the area was quarantined and 19 million birds were destroyed. This outbreak included Canada's first human case of avian influenza A infection and demonstrated the extreme economic loss to the rural farming community. Incidents of outbreak continued in 2007: Saskatchewan (loss of birds, no human loss) and Indonesia (36 people died). Much about the H5N1 and H7N3 strains of the avian influenza A virus remains unknown. Dr. François Jean, Scientific Director of the UBC Facility for Infectious Disease and Epidemic Research (FINDER), has coordinated a team of world-class researchers to work together to study the genetics of the virus, gain an understanding of how the disease manifests both in birds and humans and to understand the animal-human interface. Outcomes of this research include: (1) a better understanding of the biology of influenza virus, including the human and animal response and interface; (2) superiorly trained young faculty and students; (3) enhanced pandemic research capacity in both human and animal research fields; (4) improved translation of research findings to stakeholders (hospitals, governments, associations) so that they can better respond to future outbreaks; and (5) enhanced working relationships with national and international agencies who will integrate the findings for pandemic preparedness.



### **Optimizing health-care worker interpandemic vaccine uptake in acute and long-term care**

*PIs: Anne McCarthy, Ottawa Health Research Institute,*

*Larry Chambers, Elisabeth Bruyère Research Institute,*

*Co-Applicants: Paula Arnold, Sherry Bowman, Donna Gallant, Po-Po Lam, Shelly McNeil, Annette O'Connor, Virginia Roth, Kathryn Suh, Jane Sutherland*

Keeping nurses and doctors working during a flu pandemic is essential. A key to protecting health workers is the yearly influenza (flu) shot, particularly until a new vaccine can be made against the new pandemic strain. The number of health workers taking the flu shot is below the public health target of 90%, even though it is known the flu shot can decrease the effect of flu on society, in hospitals, on staff and patients. Studies show that if high numbers of staff take the flu shot, fewer patients die. So, why don't all health-care workers get the flu shot each year? The biggest roadblock seems to be their beliefs and opinions about the flu shot. To address health workers concerns such as the fear of side effects, doubt about it preventing the flu, as well as lack of information about national guidelines, the Ottawa Influenza Decision Aid was developed. The Decision Aid, available in French and English, takes individuals through the steps of decision-making. It takes research and presents it in a balanced, clear, easy to read manner for all staff. It asks them to think about their values and beliefs related to this topic. Managers and occupational health will use the related Implementation Guide to fit the Decision Aid into their yearly campaign. It will help them use the Decision Aid to meet the culture of their facility. Over the three-year study, these tools will be used in facilities across the country, to see if they increase the number of staff taking the flu shot each year. At the same time, information about different programs will be collected. The methods used by these programs, especially those with success, will be shared between organizations, through a cooperative web-based national network. The study results will help to improve the number of staff taking a flu shot each year. It is hoped that this will also help frontline staff stay healthy and improve the level of overall pandemic preparedness.

### **Sentinel network to monitor influenza vaccine effectiveness during annual outbreaks and pandemics**

*PIs: Danuta Skowronski, University of British Columbia,*

*Natasha Crowcroft, Ontario Ministry of Health & Long Term Care (Toronto),*

*Gaston de Serres, Université Laval,*

*Yan Li, Public Health Agency of Canada,*

*Martin Petric, BC Centre For Disease Control*

*Co-applicants: Erika Bontovics, Hugues Charest, James Dickinson, Naomi Dove, Steven Drews, Josée Dubuque, Kevin Fonseca, Karen Grimsrud, Perry Kendall, Monique Landry, Anu Rebbapragada, Marsha Taylor, Anne Winter*

Influenza is a constantly changing virus. It can change in small ways from year to year, causing winter outbreaks. Periodically, it can change in a big way, causing pandemics. The main strategy for reducing influenza illness, during winter outbreaks or pandemics, is immunization. Currently, influenza immunization is offered to >12 million Canadians every year. The influenza virus changes quickly, therefore, the vaccine must also change each year to keep up. Because of the rapid change in influenza viruses, potential vaccine mismatch, and the large investment made in



immunization each year, it is important to measure the degree of protection. An annual monitoring system also helps to build the tools needed during a pandemic. British Columbia (BC) has developed a unique approach to measure how well the influenza vaccine protects each year. A special network of doctors (called sentinels) submits specimens from patients who come to see them with influenza-like illness and collects some basic information from the patients. From this, how well the vaccine works and whether this varies with factors such as age or health status, can be determined. To improve the power of this approach, the research team led by Dr. Skowronski will expand the project to include Canada's four largest provinces: BC, Alberta, Ontario and Quebec. The greater participation will provide better information about how influenza viruses change. This will aid in making better decisions about vaccine components each year and improve understanding about how well immunization programs protect against influenza illness in the population. It will forge ongoing interactions between clinicians, epidemiologists and laboratories that are critical in monitoring and managing emerging new disease threats generally. It will also build critical capacity to evaluate viruses and vaccines during a pandemic. This unique project puts Canada at the very forefront of tracking new influenza viruses and their impact on how well the vaccine works each year.

**Canadian Program of Research on Ethics in a Pandemic (CanPREP): Whose risks, whose duties, and what priorities?**

*PI: Ross Upshur, University of Toronto*

*Co-Applicants: Karen Faith, Rory Fisher, Barbara Gibson, Alejandro(Alex) Jadad, Tiffany Jay, Douglas Martin, Sioban Nelson, Paul Ritvo, Ann Robertson, Alison Thompson, Kumanan Wilson, Randi Zlotnik-Shaul*

As pandemic planning progresses, ethical, legal, and social issues have come into greater focus. Likewise, unanswered questions relevant to an effective national and global pandemic response are becoming clear. These questions include: 1) what are the obligations of health workers in a pandemic crisis and what are the obligations of the health-care system to health workers? 2) how should limited resources be used most fairly in a pandemic? and 3) how should information be communicated to the public during a pandemic and who should lead the public dialogue? Dr. Upshur and his research team based at the Joint Centre for Bioethics at the University of Toronto will expand on work that started with a study of the ethical problems that were raised by the SARS crisis in 2003. More recently, they produced a report entitled "Stand on Guard for Thee" that outlines the major ethical issues that are central to pandemic planning and preparedness. The report was influential in framing the World Health Organization guidelines and has been incorporated into pandemic plans both here in Canada and abroad. Building upon this foundation, the team will conduct an innovative program of research comprised of three interlinked working groups devoted to addressing the three questions outlined above. Cutting across these issues are broader themes such as building and maintaining public trust, devising strategies to engage the public, and protecting vulnerable populations. The three interlinked collaborative working groups--each comprised of researchers, end-users, community partners, and research trainees--will address these critical issues and help to build an ethical, legal and social framework for pandemic planning and response.

### **Correlates of protection against influenza illness: from mouse models to older adults**

*PIs: Tania Watts, University of Toronto,*

*Robert Bleackley, University of Alberta,*

*Kevin Kane, University of Alberta*

*Janet McElhaney, University of British Columbia*

*Co-applicants: Theo Moraes, Jim Tartaglia*

Influenza infection causes significant illness and death, particularly in older adults and the very young. In persons over 65, complications of influenza infection include pneumonia, heart attacks and strokes and are a major cause of catastrophic disability, resulting in irreversible loss of independence. Influenza viruses change rapidly and vaccines made against a particular strain do not provide protection against infection with another strain. T cells are a kind of white blood cell that fight viral infections. The parts of influenza virus recognized by T cells do not change as much as the parts recognized by antibodies, so vaccines that induce strong and broad T cell responses could protect people from severe effects of new strains of influenza, a critical issue during a pandemic. At the same time, inducing too much or the wrong kind of T cell response can cause tissue damage and worsen disease. A key issue in developing new vaccines against influenza virus is to determine the kind of immune response that prevents severe disease following exposure to influenza and to determine ways of inducing such responses in vulnerable populations. The team, led by Dr. Watts, will use mouse models of influenza infection to ask what kinds of T cell response can protect against severe disease. They will extend these results to humans by analyzing T cell responses in older adults to determine which immune parameters correlate with a good outcome during the flu season. They will also test influenza-specific T cells in blood samples from older people for their responses to the stimulation strategies identified in the mouse models. These studies will help to determine better ways of evaluating and measuring immune responses to influenza virus and provide new insights into the parameters that correlate with protective immunity to influenza virus, key information required for developing and testing pandemic influenza vaccines.

### **3.6 Workshop/Symposia Support in collaboration with Knowledge Translation Branch Project Summary**

#### **Pandemic Preparedness: Strategies and Tools**

*PI: Coleman, Thomas, University of Waterloo*

Yearly influenza outbreaks and the recent outbreaks of avian influenza and Severe Acute Respiratory Syndrome (SARS) have highlighted the need for quantitative methods to determine whether a pandemic will occur and to develop optimal intervention strategies. Dr. Coleman and his colleagues are organizing a symposium in Toronto entitled: Pandemic Preparedness: Strategies and Tools. The invited speakers will include experts in quantitative methods for pandemic planning and public health. The Symposium will bring together 60-70 health-care providers, emergency planners, policy makers and academics to discuss how mathematical modeling, statistical estimation, and computing and simulation can be used to enhance pandemic preparedness and to develop the most appropriate response plan.

### 3.7 Catalyst Grant: Mobilization of the Research Community for Outbreak Response Project Summaries

#### **Ribozymes to the rescue!**

*PI: Martin Bisaillon, Université de Sherbrooke*

Ribozymes are RNA molecules that can act like enzymes, modifying target molecules to which they specifically bind. Dr. Martin Bisaillon and his research team plan to use ribozymes to bind to and cleave the RNA copies of the influenza virus, thereby inhibiting the replication of the virus and preventing viral spread. They will first generate specific ribozymes against the influenza virus and will test them in cell culture for their ability to inhibit viral replication. They will then investigate different strategies to deliver the inhibitory ribozymes to the respiratory tract of ferrets. Ferrets are a good animal model of human influenza infection because they are naturally susceptible to the influenza virus and have a similar clinical course of infection. If successful, the research will lead to a novel strategy to control the propagation of the influenza virus. Moreover, the research project provides an opportunity for researchers from multiple disciplines to work together as a team, thereby building research capacity in the area of influenza research.

#### **Evaluating the Population Effect of a New Vaccination Policy: An International Comparison**

*PIs: David Buckeridge, McGill University*

*John Brownstein, Harvard University*

Influenza is a significant cause of illness and death each year. Annual vaccination is the primary method recommended to reduce the impact of influenza. Since the 2004-2005 flu season, it has been recommended that infants and toddlers (6-23 months) receive publicly-funded influenza vaccine in North America, because of their high rates of influenza-related hospitalization. Based in part on previous work by members of the research team, the US Advisory Committee on Immunization Practice (ACIP) extended universal influenza vaccination to include all children under five beginning in the 2006-2007 season. In Canada, no changes in recommendations regarding pediatric influenza immunization have been made. This divergence in vaccination policy creates an extraordinary opportunity to evaluate whether targeting children in the older age group slows the spread of influenza, and whether it prevents illness and death for specific ages and overall. Drs. Buckeridge and Brownstein will use health-care use and mortality data from Canada and the United States, collected before and after the change in vaccination policy in the United States, to evaluate the population-level impact of the policy change. Results of their research will provide a basis for future immunization recommendations.

#### **Prognostic scoring for patients with severe disease due to influenza**

*PI: Michael Christian, Mount Sinai Hospital (Toronto)*

During the next pandemic, health care resources may be stretched to the point where it is necessary to triage patients, and ration care. If this circumstance occurs, it is important that we have adequate tools to identify which patients will benefit the most from treatment. Dr. Christian and his team plan to use a variety of scoring systems to assess the outcome of ill patients with seasonal influenza

and will determine which of these systems will work best during the pandemic. The results will provide clinicians and public health officials with the tools they will need to make choices for rationing care during a pandemic.

### **Pandemic research priorities in influenza transmission and its prevention**

*PI: Allison McGeer, Mount Sinai Hospital (Toronto)*

In the event of an influenza pandemic, authoritative advice on infection control will be necessary across a wide range of settings from healthcare to general household. The evidence base on influenza transmission is both limited and hotly debated, especially in relation to the possible effectiveness of respiratory protective equipment such as surgical face masks and higher grade respirators. While studies are underway to address some of these issues, we will not have definitive answers to all of the important questions before the next pandemic. Dr. McGeer and her colleagues plan to hold expert workshops to debate and agree on priorities for questions that can be pragmatically addressed during a pandemic, to identify researchers able to participate in such research, to create research protocols, and to define a process for performing the research. Having these plans in place before a pandemic will greatly facilitate essential studies that will be needed during a pandemic.

### **Genetic determinants of influenza severity in children: A pre-pandemic feasibility study**

*PI: Dat Tran, Hospital for Sick Children (Toronto)*

As with seasonal influenza, some healthy children may be at greater risk of developing serious infections in a pandemic. Common genetic differences may explain why some healthy children get sicker than others. Dr. Tran's long-term objective is to find these common differences in human genes that are linked to more severe influenza in healthy children. He plans to establish a research team that will carry out a community-based study to examine the genetic risk factors for severe disease during a pandemic. To prepare for the study, his team will perform a "dry run" from November 2008 to April 2009 at a paediatrician's office. The team will recruit healthy children seen for influenza and their families. Participants will be asked to provide spit samples for DNA. The ability to predict which healthy children are at highest risk for serious influenza infections will help public health agencies better prepare drugs, equipment and personnel for a pandemic. Identifying susceptibility genes will also assist in understanding how influenza causes disease, and ultimately, will speed the development of new treatments for seasonal and pandemic influenza.

## Appendix 4: Research Summaries of Projects Supported by the PPSRI but Led by Others

### 4.1 China-Canada Joint Health Research Initiative - Grants Program

#### **Does the viral protein NS1 contribute to pathogenesis in human cases on avian influenza?**

*Principal Applicants: Jingxin Cao, University of Manitoba and George Gao, Chinese Academy of Medical Sciences (Beijing)*

Bird (avian) influenza viruses are a threat to public health, because they have the potential to cause a worldwide outbreak of human influenza. Raising concerns are the several hundred human deaths due to avian influenza that have been reported over the past few years. To prevent the occurrence of this type of devastating infectious disease, it is extremely important to understand how avian influenza viruses cause fatal infections in humans. Drs. Cao and Gao speculate that a viral protein called NS1 contributes to the pathogenesis of avian influenza in humans. They will study whether NS1 suppresses the human immune system, in particular anti-viral activity regulated by interferon. One part of the study involves examining whether NS1 contributes to viral virulence in mice and determining whether specific immune responses are altered. The results of the research will be valuable in containing and treating human infections with avian influenza.

### 4.2 Applied Public Health Chairs

#### **Population health impact intervention assessment tools (PHIAT)**

*Principal Applicant: Douglas Manuel, Sunnybrook Health Sciences Centre*

The overall goal of Dr. Manuel's research is to integrate health intervention research into public health practice. A key intervention that will be studied is Ontario's Universal Influenza Immunization Program, in which the flu vaccine is free to all individuals, and its impact on population health. To evaluate this program, Dr. Manuel and his collaborators in public health will examine health administrative data over a four-year period. The research team also plans to create tools that will enable public health planners at the federal, provincial and local levels estimate the potential of intervention strategies on population health. These tools will bring together research evidence on the effectiveness of interventions using existing data that describe disease risk in a target population. The knowledge gained will guide future influenza immunization programs. The tools that are developed will be made available to public health authorities and policy makers at all levels of government to help them make informed decisions concerning public health intervention measures.

#### **Meeting the zoonotic disease public health challenge: Integrated methodologies for research and application**

*Principal Applicant: Janice Sargeant, University of Guelph*

Over 75% of emerging infectious diseases of humans are zoonotic, meaning that they arise from animals or their products. The spectrum of zoonotic disease is immense and includes emerging



pathogens with catastrophic potential such as pandemic influenza and SARS. These diseases involve complex pathways from the animal host to humans. Currently, there is a lack of integration between animal and human health research methodologies, educational approaches and knowledge translation activities. This integration is essential to better protect the Canadian public from zoonotic illness such as pandemic influenza. Dr. Sargeant intends to address this need by developing integrated networks of animal and human public health researchers, practitioners, and decision makers. The assembled team will investigate population-level risk factors and intervention strategies for zoonotic disease; identify effective knowledge translation strategies in order to develop communities of practice and knowledge networks between all individuals in the animal and human health communities, and provide graduate level research training in population-level intervention methodologies for zoonotic disease. This approach will not only answer important public health questions and train the next generation of public health researchers and practitioners, but also will form powerful knowledge networks and communities of practice that will work together to improve and protect the health of Canadians.

