

# Research preparedness paves the way to respond to pandemic H1N1 2009 influenza virus

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The international community has been preparing for an influenza pandemic because of the threat posed by H5N1 avian influenza. Over the past several years, Canada has dedicated funding to boost capacity for research, and public health and health care system readiness and response in the event of a pandemic. The current H1N1/09 influenza pandemic is now testing our readiness. From a research perspective, the present commentary discusses how have we prepared, along with the research gaps. We conclude that: sources of pandemics are not always predictable; investment in the past few years has paid off in a rapid response to pandemic H1N1/09 virus in Canada; and research to meet the challenges of infectious diseases has to be done on an ongoing long-term basis, and its funding has to be flexible, available and predictable to maintain capacity and expertise. In addition, new vaccine technologies are needed to develop and produce vaccines for public health emergencies in a timely fashion.

**Key Words:** *Influenza; Pandemic H1N1/09 influenza virus; Pandemic preparedness; Pandemic research*

In the 21st century, one anticipates that research should form the basis for evidence-based policy making when responding to sudden outbreaks of infectious diseases. The novel influenza A (H1N1) virus (now called pandemic H1N1/09 influenza virus) that appeared in Mexico in March 2009 has spread to over 170 countries and territories including the United States and Canada (1). As of mid-August, over 1400 laboratory-confirmed deaths have been reported, and increased numbers of cases with more hospitalizations and deaths are expected. The virus has genes derived from classical and avian-like swine influenza viruses (2). In addition to human-to-human transmission, transmission from humans to pigs has also been observed (3). It is not known if the virus infected humans directly from pigs or through another host. Fortunately, the virus does not appear to be as virulent as originally thought and various isolates of the virus show little genetic variation, but data are still emerging (2). In addition, most isolates of the virus are sensitive to the antiviral agents oseltamivir (Tamiflu, Roche Canada) and zanamivir (Relenza, GlaxoSmithKline Inc, Canada) providing

## La recherche sur l'état de préparation ouvre la voie à la réaction des autorités publiques à la pandémie de grippe A(H1N1) de 2009

La communauté internationale s'est préparée à une pandémie de grippe en raison du risque de grippe aviaire H5N1. Le Canada a affecté, au cours des dernières années, des fonds aux seules fins d'augmentation de la capacité de recherche, de préparation des services de santé publique et du système de soins de santé, et de réaction en cas de pandémie. L'épidémie mondiale de grippe A(H1N1) met maintenant à l'épreuve l'état de préparation du pays. Le présent article expose, d'un point de vue de la recherche, la façon dont les autorités se sont préparées ainsi que les lacunes en matière de recherche. Voici les principales conclusions : les sources de pandémie ne sont pas toujours prévisibles; l'argent investi dans la préparation au cours des dernières années a permis de réagir promptement à la pandémie de grippe A(H1N1), au Canada, en 2009; la recherche, pour être en mesure de faire face aux défis des maladies infectieuses, doit se faire de façon continue et à long terme, et le financement doit être souple, disponible et prévisible afin de pouvoir maintenir le degré actuel de capacité et d'expertise. De plus, il faut concevoir de nouvelles techniques de préparation et de production des vaccins afin de répondre, en peu de temps, aux situations d'urgence en matière de santé publique.

an avenue for treatment of infected individuals, but sporadic cases of oseltamivir resistance have been reported (4,5). The possibilities that further genetic changes in the virus will lead to further antiviral resistance or a more virulent form are concerns (6).

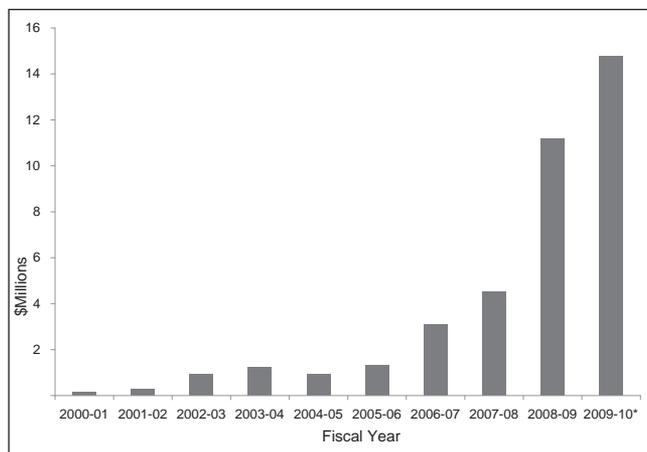
The international community has been preparing for an influenza pandemic because of the previous and ongoing threat posed by H5N1 avian influenza (7,8). Over the past several years, Canada and United States have dedicated funding to boost capacity for research, and public health and health care system pandemic readiness and response (7-10). The H1N1/09 influenza pandemic is now testing our readiness. From a research perspective – how have we prepared and where are the knowledge gaps?

### BUILDING CAPACITY IN PANDEMIC AND INFLUENZA RESEARCH

Although research over the past few years has focussed on H5N1 avian influenza, the effort has built capacity that is

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**Figure 1)** Canadian Institutes of Health Research investment in pandemic and influenza-related research. This includes funds through both the Pandemic Preparedness Strategic Research Initiative and Canadian Institutes of Health Research open grant competitions. \*Estimated funding for 2009-10

being applied to the H1N1/09 pandemic. Canada has shown again, as we did with the outbreak of severe acute respiratory syndrome (SARS), that our genomic platforms are able to rapidly respond to health challenges. In 2003, the BC Genome Centre was first to sequence the SARS virus (11). With the H1N1/09 pandemic, the National Microbiology Laboratory (NML) at the Public Health Agency of Canada (PHAC) was the first to sequence the complete genome of the virus. The NML scientists determined that the virus isolated from Canadian patients was the same as the one isolated in Mexico, illustrating the value of research in pandemic preparedness (12).

The Canadian Institutes of Health Research Institute of Infection and Immunity (CIHR-III) has played a leadership role in both facilitating and supporting influenza and pandemic preparedness research, making Canada better prepared for the current pandemic. In 2006, CIHR-III created the Pandemic Preparedness Strategic Research Initiative (PPSRI) with a five-year \$21.5 million investment made by the Government of Canada (13). CIHR-III moved quickly to develop partnerships with other agencies, including the PHAC, Canada's Research-Based Pharmaceutical Companies Health Research Foundation, the Canadian Food Inspection Agency (CFIA), and the Canadian Foundation for Infectious Diseases, increasing the total funds to \$40 million. The strategic PPSRI funding makes up a significant portion of the overall CIHR funding for influenza and pandemic preparedness research, which also includes funding through open grant competitions (Figure 1).

Under PPSRI, CIHR-III and partners have worked to coordinate strategies, funded and stimulated research, and built capacity in the following strategic priority areas:

- Vaccines and immunization programs;
- Influenza virus biology;
- Prevention and treatment of influenza infections; and
- Ethics, legal and social issues.

These strategic priorities were identified by the PPSRI Task Group (Table 1) in consultation with various funding partners and stakeholders. Over the past three years, more than

**TABLE 1**  
Members of the Pandemic Preparedness Strategic Research Initiative Task Group

Name	Affiliation
Mark Loeb (Chair)	McMaster University, Hamilton, Ontario
Earl Brown	University of Ottawa, Ottawa, Ontario
Robert Brunham	Centre for Disease Control, University of British Columbia, Vancouver, British Columbia
Theresa Tam	Centre for Infectious Disease Prevention and Control, Public Health Agency of Canada
Ross Upshur	University of Toronto Joint Centre for Bioethics, Toronto, Ontario
Bhagirath Singh (ex officio)	Canadian Institutes of Health Research Institute of Infection and Immunity, University of Western Ontario, London, Ontario

**TABLE 2**  
Pandemic Preparedness Strategic Research Initiative by the numbers

Number of identified research priorities	4
Number of partners with formal partnership agreements	4
Amount contributed by partners	\$18 million
Number of funding opportunities launched	30
Number of applications received	149
Number of funded applications	71
Total amount contributed by PPSRI	\$40 million

50 principal investigators have been funded to carry out research in the above priority areas (Table 2). Examples of funded research include developing diagnostics, antiviral drugs and vaccines; understanding and preventing influenza transmission; and identifying ethical ways to use limited resources during a pandemic (13).

## INNOVATIVE APPROACHES TO PREPARE FOR PANDEMIC RESEARCH

The SARS outbreak in 2003 highlighted the challenges in both facilitating and supporting research once an outbreak is underway (14-16). This experience prompted CIHR-III to take a unique approach to enable researchers to prepare for outbreak/pandemic research ahead of time. For example, CIHR-III and PHAC created and funded catalyst grants both for individual researchers to start the preparatory phase of outbreak research projects and for application development funds to team leaders who will bring researchers together to engage in essential outbreak research. Dr Guy Boivin from Laval University (Quebec) is leading a national network for the characterization of influenza virus evolution and antiviral susceptibility, while Dr Babak Pourbohloul from the University of British Columbia is leading a team in mathematical modelling of pandemics. Both these research network teams were funded by CIHR following an expedited peer review of their pandemic research plans and research is presently underway.

In addition to the catalyst grants, PHAC and CIHR-III collaborated to establish the PHAC/CIHR Influenza Research Network. Dr Scott Halperin from Dalhousie University (Nova Scotia) is leading a group of 82 investigators from

30 institutions that make up the network. The overall objectives are to develop and test methodologies to evaluate the safety and effectiveness of influenza vaccines, and to establish methods for vaccine program implementation. The network is also preparing to monitor the safety and efficacy of the new pandemic H1N1/09 vaccine in Canada.

Recognizing the need to establish linkages between researchers and research users before an outbreak or pandemic (14-16), CIHR-III and partners have required that users of research results be included in PPSRI teams. In addition, CIHR-III, PHAC and CFIA organized and sponsored a meeting in Winnipeg, Manitoba, in November 2008 that was attended by over 150 influenza and pandemic researchers and research users. The objectives were to discuss recent research results, foster collaboration and linkages, and to identify research needs and gaps. An informative pre-meeting session was also held in Winnipeg at the Canadian Science Centre for Human and Animal Health, which is home to NML and the CFIA National Centre for Foreign Animal Disease. Participants learned about the facility and the research related to pandemic influenza that is being conducted through presentations by Canadian Science Centre for Human and Animal Health researchers.

### RESPONDING TO THE CURRENT H1N1/09 INFLUENZA PANDEMIC

In light of the outbreak of pandemic H1N1/09 influenza virus in March 2009, the PPSRI Task Group, along with other influenza and pandemic researchers, have intensified their efforts. The Task Group is meeting frequently via teleconference to identify gaps in knowledge and to help coordinate research efforts. The Task Group has been expanded to include representatives from PHAC, NML, CFIA and the private sector. Updates have been received from currently funded pandemic and influenza researchers on the progress of research projects, pandemic research plans and any results that can be communicated to those on the front lines.

Several research areas that require immediate attention have been identified by the Task Group. They are:

- *Epidemiological characteristics of the spread of pandemic H1N1/09 influenza virus and the natural history of infection*: the mode of human-to-human transmission including viral shedding patterns, the risk factors for infection, and optimal methods for preventing transmission.
- *Biology and genetics of the virus and effective use of antivirals*: analysis of viral evolution in humans and animals, influenza genetics, the development of diagnostic tests, and the assessment of efficacy and safety of antiviral drugs.
- *Immune response to pandemic H1N1/09 virus and contributing cofactors*: identification of the responses that reduce/increase the severity of infection; the role of the environment, nutrition and genetics in transmission and disease course; and the role of pre-existing immunity in offering cross-protection.
- *Ethical issues – priority setting, risk communication and research ethics approval*: assessment of the fairness in the distribution of limited clinical material, reagents and resources during a pandemic, identification of the best methods to communicate risk; and the development of

guidelines for the rapid, but thorough, approval of research studies by ethics review boards.

- *Vaccine development and evaluation*: the development of methods for antigen sparing including the use of adjuvants, the assessment of cross-protection from existing vaccines, and studies to assist in decisions regarding optimal influenza vaccine formulations for the upcoming flu season.
- *Health services and policy research*: the identification of health system strategies for treating of those affected, while minimizing untoward effects on others; and the determination of the medical, economic and other costs of possible transmission of pandemic H1N1/09 compared with those associated with practices to avoid transmission (eg, development of a vaccine).

The above areas represent largely new research avenues that have relevance to the current H1N1/09 pandemic. A vaccine against pandemic H1N1/09 influenza virus is also needed to reduce viral spread. It usually takes up to six months to develop such a vaccine. Thus, globally, we have a major research gap in our ability to rapidly develop vaccines to deal with public health emergencies.

To foster collaboration among researchers and promote the uptake of research results during the current H1N1/09 pandemic, CIHR-III, CFIA and Canada's Research-Based Pharmaceutical Companies Health Research Foundation hosted a meeting entitled *Canadian Pandemic Preparedness Meeting: H1N1 Outbreak Research Response* in Toronto, Ontario, on July 8, 2009. More than 180 researchers, stakeholders and knowledge users attended the meeting. The meeting was successful in providing a forum for influenza and pandemic experts to share current research results, develop research strategies and collaborate with partners and end-users.

In July 2009, CIHR announced a new funding opportunity to support networking and collaboration of H1N1 influenza outbreak research teams. The primary objective of the funding opportunity is to catalyze the mobilization of teams focused on pandemic H1N1/09 research by providing seed money for planning and development activities of expert teams to advance research in priority areas determined by the Task Group.

### LESSONS FROM THE H1N1/09 PANDEMIC: LONG-TERM RESEARCH MUST BE SUPPORTED

The eventual outcome of the current H1N1/09 influenza pandemic is uncertain. The influenza season is underway in the southern hemisphere, and pandemic H1N1/09 virus has been or is becoming the predominant strain of influenza virus in this region (1). It is expected that the pandemic H1N1/09 virus will continue to persist during the upcoming influenza season in the northern hemisphere, because of its dominance worldwide. Experts have cause for concern given experiences with previous influenza pandemics. For example, the virus that caused the Spanish flu pandemic of 1918 arose in March of that year and initially caused mild disease, but became more virulent by the fall 1918, causing millions of deaths (17). In addition, the highly pathogenic form of H5N1 avian influenza remains a threat with recent human deaths reported in Egypt, Vietnam and China (18). As well, seasonal influenza continues to be a health concern causing thousands of deaths worldwide each year, and new strains of influenza will continue to emerge.

With air travel, emerging and re-emerging infections can spread rapidly, as was clearly demonstrated by the H1N1/09 pandemic.

To meet the challenges of infectious diseases, research must be undertaken on an ongoing long-term basis, and its funding must be flexible, available and predictable to maintain capacity and expertise (19). Researchers now need additional funds to purchase materials and hire personnel to ramp up research capacity to be able to answer critical questions during the present H1N1/09 pandemic. The immediate support will help to evaluate the safety and efficacy of treatments for pandemic H1N1/09 viral infections and manage disease in vulnerable populations, aboriginal communities and pregnant women. The need is heightened by the large international gatherings that are expected at the upcoming winter Olympics in British Columbia in February 2010. In the medium term, new research in vaccine technology is essential to discover methods to rapidly produce vaccines in sufficient quantities in order to respond to pandemic emergencies in a timely fashion.

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CIHR-III and partners have invested considerable time, effort and funds in building the research capacity, expertise and linkages that have made Canada better prepared than ever to mount an effective research response to the H1N1/09 pandemic. PPSRI funding, however, will end in 2011. The current pandemic reinforces the need for ongoing funding for influenza and pandemic preparedness research in Canada. It also reminds us that collaboration and linkages between researchers, health professionals and policy makers are essential so that research results are rapidly put into practice. We must work to maintain and foster the research capacity, expertise and linkages that we have developed over the past few years. In doing so, we will ensure that sound scientific evidence will form the basis of policy decisions and responses to future outbreaks of infectious diseases.

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