Canadian vaccine research networks: Vaccine safety resources for Canada

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Abstract

The Public Health Agency of Canada / Canadian Institutes of Health Research Influenza Research Network (PCIRN), established in 2009 to undertake evaluative research to inform public health decision making in Canada, is now being replaced by the Canadian Immunization Research Network (CIRN), which will retain the mandate of PCIRN but expand it to all vaccines including influenza vaccine. CIRN is organized as a network of networks focusing on undertaking research in the areas of vaccine safety, adverse events following immunization (AEFIs), vaccine hesitancy, vaccine effectiveness, and vaccine coverage. CIRN’s networks include: a clinical trial network; a laboratory network; a modelling and economics network; a network of social science and humanities researchers; a vaccine safety surveillance network; a hospital-based surveillance network; a clinic network to evaluate serious AEFIs; and a network that links vaccine research capacity in provincial health agencies and departments. PCIRN has contributed to Canada’s vaccine safety surveillance system and has facilitated the translation of safety research into policy. Vaccine safety surveillance and research will remain a focus of the newly formed Canadian Immunization Research Network.

Introduction

The Public Health Agency of Canada (PHAC) / Canadian Institutes of Health Research (CIHR) Influenza Research Network (PCIRN) was designed to consolidate the existing expertise in influenza vaccine evaluation, increase capacity to rapidly test influenza candidate vaccines, develop links between researchers and decision makers, and train influenza researchers. In 2013, PHAC and CIHR announced that they would fund a Canadian Immunization Research Network (CIRN), with a mandate to undertake evaluative vaccine research, including research related to influenza vaccine formerly undertaken by PCIRN. Currently, CIRN represents over 100 investigators from more than 40 Canadian institutions, comprising experts in vaccine-related evaluative research from a wide array of disciplines. The objective of this article is to describe how PCIRN contributed to vaccine safety intelligence in Canada in the past and how CIRN will take over and expand this mandate in the future.

PCIRN overview and research networks

PCIRN was designed as a “network of networks.” From its inception in 2009, PCIRN has addressed important issues related to influenza vaccine programs.
The Clinical Trials Network
The Clinical Trials Network has sites in Vancouver, Calgary, Winnipeg, Sudbury, Hamilton, Toronto, Ottawa, Montréal, Québec City and Halifax, and has the capability to conduct rapid clinical trials in large and specialized groups with a focus on safety, immunogenicity and mechanisms of immunity.

Canadian National Vaccine Safety Network (CANVAS)
The Canadian National Vaccine Safety Network quickly gathers and analyzes safety data on thousands of vaccinated individuals (adults and children) to provide influenza vaccine safety information to public health authorities before the core weeks of the annual influenza vaccination campaign. Participants are recruited from acute care and public health influenza vaccination clinics in five provinces. Participants receive a short electronic survey eight days after their vaccination. The main outcome is the occurrence of any new health problem or the exacerbation of an existing condition that is severe enough to cause work or school absenteeism and/or prevent daily activities or to require a medical consultation. Selected severe reported events are followed up by telephone for additional details. A control group of unvaccinated participants is also recruited each year to determine the frequency of reported events in an unvaccinated group (i.e., the background rate).

Special Immunization Clinics Network
The Special Immunization Clinics Network is a national network of expert clinicians in 13 hospitals across Canada who accept referrals from public health professionals or clinicians for individual patients who have experienced an adverse event following immunization (AEFI) or who have another vaccine safety issue. Its first objective is to standardize clinical care and guide best practice in the management of these patients. The standardization of clinical care provides opportunities for observational research. The second objective is to establish a platform for research studies on vaccine safety issues.

Serious Outcomes Surveillance (SOS) Network
The (SOS) Network, conducts active surveillance for influenza requiring hospitalization in Canadian adults. This surveillance covers more than 18,000 beds in 45 hospitals in seven provinces. The SOS Network is designed to measure disease burden and to assess vaccine effectiveness in the prevention of influenza-related hospitalization and death.

Program Delivery and Evaluation Network
The Program Delivery and Evaluation Network engages in applied public health research related to the delivery of influenza vaccines. This Network will conclude its work at the end of the PCIRN funding period.

Reference Laboratory Network
The Reference Laboratory Network includes five laboratory sites across Canada and is managed by scientists with expertise in microbiology, influenza, and other infectious diseases. Each scientist leads active research programs at his respective institution and also operates within the public health sector. The Network provides influenza-related laboratory testing support for the Network and manages PCIRN’s biorepository.

PCIRN’s record of vaccine safety studies
While PCIRN’s influenza research mandate is broad, vaccine safety research has been a major focus for several of its networks. The Clinical Trials Network has completed eight clinical trials to date, many of which had a vaccine safety focus. The PCIRN clinical trials in 2009 with the adjuvanted pandemic vaccine measured adverse events in different population groups, including healthy adults (1), Aboriginal populations (2), and individuals with human immunodeficiency virus (HIV) infection (3). In 2010, there was concern that previous recipients of the adjuvanted H1N1 pandemic vaccine might have increased rates of injection-site and systemic adverse events when they received the seasonal trivalent inactivated vaccine containing the pandemic strain, because of very high levels of pre-existing antibodies. Two clinical trials, one in adults and one in children, were performed as soon as the vaccine was made available and results were presented to decision makers and program planners in advance of the roll-out of the annual influenza vaccine campaigns (4, 5). The vaccination of egg-allergic individuals with influenza vaccine was also a major safety research focus of PCIRN and provided data that led to a significant change in vaccination recommendations (6, 7). The success of these safety studies led to the development of the Special Immunization Clinics Network, which will continue its work under CIRN.
The Canadian National Vaccine Safety Network also contributed safety information about influenza vaccines over the last several years (8, 9). For the 2013–2014 season, CANVAS reached record recruitment, enrolling over 35,000 adults and parents of children. The response rate was 61% (n=13,127) in the vaccinated group and 50% (n=6,763) in the control group. Parents of children 6 months to 16 years of age accounted for 12% (n=2,314) of participants. The vast majority of participants reported no health events (96% of vaccinees and 93% of controls). In the control group 5% reported an event that caused absenteeism, prevented daily activities, or required a medical consult, while 2.5% of vaccinees reported such events. The remaining events (2% in controls and 1.5% in vaccinees) were reported as uncomfortable or easily tolerable. Regardless of vaccination status, the most frequently reported symptoms in adults and children were respiratory and gastrointestinal symptoms, and these symptoms occurred more frequently in controls than in vaccinees. In children, changes in eating patterns were reported more frequently among vaccinees. No deaths or hospitalizations were reported among vaccinees or controls. Fewer than 1% of vaccinees (0.4%) and 1% of controls reported medical consultation for their symptoms, and among those the rate of emergency department visits was the same in both groups (0.53 per 1,000 participants). With the ability to detect events occurring at a rate of less than 1 in 1,000, we did not find any safety signals associated with 2013–2014 influenza vaccines in adults or children. In the event a signal is detected, CANVAS has the ability to link with public health authorities and conduct additional enhanced follow-up.

Following the release of the adjuvanted pandemic influenza vaccine in Canada in 2009 and during the immunization campaigns of 2010–2011, the SOS Network conducted active surveillance for adverse events of special interest. Surveillance monitors in all participating hospitals reviewed all admissions to medical services, intensive care units, and hematology and neurology services daily to identify patients admitted with Guillain-Barré syndrome, idiopathic thrombocytopenic purpura (ITP), or encephalitis meeting the Brighton Collaboration case definitions and with symptom onset within six weeks of receipt of an influenza vaccine. No cases of AEFIs were identified in participating hospitals during the surveillance period.

**CIRN overview and networks**

Like PCIRN, CIRN will be a “network of networks.” As PCIRN funding ends in 2015, several of its network infrastructures will become part of CIRN and will be joined by several new networks to meet CIRN’s expanded mandate.

The Special Immunization Clinics Network, which was created during PCIRN’s renewal term, will not require any transition into CIRN because it was designed to undertake standardized evaluation of AEFIs related to all vaccines, not just influenza. In its first year, investigators reviewed the literature on the risk of recurrence of AEFIs and prepared a clinical management guide. The Network currently recruits patients for its core study which will evaluate the risk of revaccination in patients previously affected by an AEFI and the risk of administering vaccines in patients with underlying conditions that may constitute an apparent contraindication.

The Clinical Trials Network will transition easily from PCIRN to CIRN since all of the sites have experience with clinical trials unrelated to influenza vaccine.

The SOS Network will transition from PCIRN to CIRN and provide CIRN with hospital-based surveillance and the ability to measure vaccine effectiveness. Although focused primarily on describing the burden of influenza and the effectiveness of influenza vaccine against severe disease, the SOS Network has already leveraged industry funding to measure the burden of invasive meningococcal disease, community-acquired pneumonia, and invasive pneumococcal disease in adults.

While initially created to assess vaccine safety immediately after implementation of annual influenza vaccine campaigns, the Canadian National Vaccine Safety Network will be leveraged for studies related to safety of other vaccines used in these cohorts, evaluation of vaccine hesitancy, and vaccine effectiveness.

The Reference Laboratory Network will transition from PCIRN to CIRN, and will continue to actively manage a sample archive of sera and other biological samples collected through CIRN infrastructures, accessible to investigators for future studies. The Network will also encompass the Immunity of Canadians and Risk of Epidemics (iCARE) Network. The Reference Laboratory Network spans five provinces and coordinates the
matching of laboratory capabilities from participating academic and public health laboratories with CIRN project needs.

**Provincial Collaborative Network**

The Provincial Collaborative Network is a new network created under CIRN that will capitalize on the extensive research capabilities in provincial public health agencies and other provincial departments of health and provide a collaborative platform in which to undertake evaluative, programmatic, applied public health research. The Network will develop common methodologies to assess vaccine safety, effectiveness, and coverage, including the use of aggregate and linkable individual-level data contained in a variety of existing databases within each province (e.g., reportable disease, laboratory, immunization, health care utilization, and vital statistics data). This approach is analogous to the U.S. Vaccine Safety Datalink and the Canadian Network for Observational Drug Effect Studies (10). Current investigators are based in 7 of 13 provinces/territories. We hope to include others in the future and build on the methodology developed in our initial studies.

**Social Sciences and Humanities Network**

CIRN’s new Social Sciences and Humanities Network will link social scientists and humanities researchers across Canada to examine the ethical, legal and social implications of vaccine programs and CIRN-related research. The Network will enhance CIRN’s ability to address societal issues in all proposed projects and will serve as a hub for social science and humanities-focused research generated by CIRN; vaccine hesitancy will be a major focus.

**Modeling and Economics Research Network (ModERN)**

CIRN’s newly created Modeling and Economics Research Network will link modellers/health economists in at least five provinces to undertake epidemiological analyses, mathematical modelling, and economic analysis to study the cost-effectiveness and population-level effectiveness of public health interventions. ModERN can also investigate the likelihood of outbreaks based on coverage; predict the magnitude of impact of emerging pandemics and optimal control strategies in Canada; and examine population-level concerns following introduction of vaccines about shifts in the age at infection, type replacement, and waning efficacy.

**CIRN projects involving vaccine safety**

The Clinical Trials Network of CIRN, arising from PCIRN’s rapid clinical trials network, now has the requisite training and infrastructure to respond to public health issues concerning vaccine-preventable diseases by developing high quality research protocols to evaluate vaccines, implement them quickly and in accordance with regulatory and international standards, and rapidly provide results on vaccine safety at various time points during and after the trial is complete. The trials planned for the 2014–2017 CIRN funding cycle will address two important vaccine-preventable diseases: hepatitis B and invasive meningococcal disease (*Neisseria meningitidis*). One project will determine whether youth immunized with hepatitis B vaccine as infants continue to have serologic evidence of immunity and, if not, whether a booster dose of vaccine will elicit antibodies produced because of anamnestic immune memory. In a second randomized, controlled, double-blind clinical trial, the safety and immunogenicity of an accelerated schedule for a four-component meningitis B vaccine will be evaluated. Outcome measures for vaccine safety will be incorporated into both studies, capturing information on solicited local injection-site and systemic AEFIs, unexpected unsolicited adverse events, as well as tolerability. The Clinical Trials Network will work with other CIRN researchers to test novel tools to measure AEFIs, such as a smartphone application which will facilitate the electronic capture of AEFI data.

The methodology employed by CANVAS for monitoring AEFIs after influenza vaccination is well adapted to monitoring the safety of other vaccines. CIRN protocols are being developed that would adapt CANVAS to safety reporting for new vaccines, such as the new meningococcal B vaccine.

The Special Immunization Clinics Network will act as a platform for multicentre clinical studies relevant to vaccine safety. Within CIRN, the Network’s initial focus will be on vaccination of immunocompromised patients. The first project will enroll children who have completed chemotherapy for acute lymphoblastic leukemia (ALL) or who have received a stem cell transplant (SCT). The objectives are to a) describe institutional immunization practices at pediatric oncology and SCT centres through a survey; b) identify risk factors for low vaccine titres in children treated for ALL; c) identify clinical and immunologic factors that influence vaccine responses in pediatric ALL and post-SCT patients; and d) determine the frequency of AEFIs in both groups. This study will be conducted at the
Special Immunization Clinics Network sites, using similar approaches to patient assessments and follow-up as those developed under PCIRN. The findings will help support the development of immunization guidelines for children with ALL and harmonize immunization practices for pediatric SCT recipients. If successful, the methodology will be expanded to other populations of immunocompromised patients. The Network will continue to build capacity to evaluate new and emerging vaccine safety signals and will thus contribute to pandemic preparedness. Future studies could include selected AEFIs requiring investigation in real time, the study of the biologic mechanisms involved in AEFIs, or the study of the genetic basis of particular events in collaboration with other similar networks.

One of the Provincial Collaborative Network’s initial studies will examine safety issues of relevance to Canada. In the project “Assessing rotavirus vaccine safety in Canada with regard to intussusception using administrative databases,” researchers plan to take a pan-Canadian approach using health administrative data to determine the background rate of intussusception in Canadian infants and examine whether there has been a change in incidence following the introduction of publicly-funded rotavirus vaccination programs. This study will demonstrate the capability of the Network to conduct relevant post-marketing safety studies and provide much needed baseline data within Canada. It will also inform decision making for jurisdictions that have yet to implement vaccination programs and provide information for risk communication for parents.

The SOS Network provides important infrastructure for targeted surveillance for AEFIs and for signal assessment and hypothesis testing. With trained surveillance monitors in all participating hospitals and existing surveillance protocols and agreements in place, the SOS Network has the capacity to respond rapidly to an emerging safety signal through amendments to existing protocols. All surveillance monitors are well trained in the use of the existing SOS Network DACIMA database, and changes to data elements collected for the purpose of AEFI surveillance could be implemented rapidly to allow PHAC and the provinces/territories real-time access to observed AEFIs.

Conclusion

CIRN, like PCIRN before it, provides a national, integrated, collaborative, multidisciplinary research platform to undertake ongoing federally- and provincially-funded evaluative research that will inform public health policy and will provide the infrastructure, capacity and capability for a national research response to new and emerging infections including (but not limited to) pandemics. CIRN will also play a pivotal role in mentoring early-career researchers, providing opportunities for trainees, and delivering meaningful engagement of stakeholders at all research stages.

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Conflict of interest

Scott A. Halperin reports grants from the Canadian Institutes of Health Research (CIHR) and the Public Health Agency of Canada during the conduct of the study and grants from multiple vaccine manufacturers outside the submitted work. He serves on ad hoc advisory panels from multiple vaccine manufacturers. Gaston De Serres reports grants from GlaxoSmithKline outside the submitted work. Joanne M. Langley reports grants from GlaxoSmithKline during the conduct of the study; grants from Sanofi Pasteur outside of the submitted work; and service in a volunteer capacity on immunization/infectious disease advisory committees to the Government of Nova Scotia and the Public Health Agency of Canada. Shelly McNeil reports grants from Pfizer, GlaxoSmithKline, and Sanofi Pasteur. David Scheifele reports grants from Pfizer, Novartis, GlaxoSmithKline, and Sanofi Pasteur outside the submitted work. All other authors have nothing to disclose.

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