Postmarketing Surveillance of Annual Influenza Vaccines: Extended Vaccine Safety

Background
Trivalent inactivated influenza vaccines have been used for decades in Canada and are considered safe and effective. Ontario has a universal influenza immunization program and other jurisdictions in Canada have adopted the expert recommendation of the National Advisory Committee on Immunization (NACI) to immunize individuals at increased risk for influenza-related complications (includes otherwise healthy children aged 6 to <24 months and adults aged 65 years and older), people who may transmit influenza to individuals at high risk of complications (including healthcare workers), and those who provide essential community services. Additionally, based on available evidence, NACI has concluded that influenza vaccine is safe for pregnant women at all stages of pregnancy as well as for breastfeeding women.

Annual immunization against influenza is required for optimal protection because of the continually changing nature of the antigenic makeup of circulating influenza strains. These changes may be small (antigenic drift) or large (antigenic shift). The three influenza strains selected for each year’s vaccine are based on antigenic characteristics of globally circulating and emerging strains of influenza virus. In Canada there has been a good match between the predicted and actual circulating viral strains about 80% of the time based on data gathered from 1982/83 through 1996/97. When there is a good match, laboratory-confirmed influenza will be prevented in 70% or more of otherwise healthy individuals. When there is a mismatch vaccine effectiveness may be as low as 30% to 60% depending, in part, on the degree to which the annual vaccine induces cross-protective immunity against the mismatched strains.

Given the changing nature of circulating influenza strains, each year’s trivalent influenza vaccine is essentially a new product with up to three antigenically different strains from vaccines used in preceding years. As with all vaccines, regulatory authorities require specific testing of new product lots before authorizing release. Since the processes manufacturers use to make the vaccines are highly standardized and the same from year to year, several national regulatory authorities, including the FDA in the United States, do not require human clinical testing of each year’s products prior to giving vaccine manufacturers authorization to market. This was also true for Canada up to the 2000/2001 influenza season. In contrast the European Medicines Evaluation Agency (EMEA) does require clinical evaluation of safety and immunogenicity in a small sample of otherwise healthy adults aged 18 to 60 years and >60 years (60 in each group).

Canada changed their requirements to be in line with those of EMEA following the unexpectedly high frequency of what became known as the oculorespiratory syndrome (ORS) in the 2000/2001 influenza immunization campaign. ORS is defined as the onset, within 24 hours of receiving influenza vaccine, of bilateral red eyes and/or respiratory symptoms and/or facial swelling. The pathogenesis of ORS is still uncertain but it is not thought to be an IgE mediated allergic reaction. In subsequently performed randomized controlled studies the vaccine-attributable risk of ORS was shown to be 2.8% (95% confidence intervals of 0.5% to 5.1%) in individuals who had never had a prior episode and 5% to 34% in those with a prior occurrence of ORS. The symptoms are generally mild, resolve quickly and rarely lead to healthcare utilization. Nevertheless, in 2000/2001 the unexpectedly high rate of ORS raised significant concerns for immunization program providers who were not only observing and reporting the syndrome as an unexpected adverse event but also struggling to properly inform and communicate with the public and...
healthcare professionals in the absence of evidence to support risk management decisions. It is not clear that the clinical testing as required by EMEA would have detected ORS since only 120 subjects are enrolled in those trials. On the other hand, had the enhanced safety surveillance studies as proposed here, been conducted in 2000-2001 it is more likely that there would have been a clear signal detected very early in the influenza immunization campaign that would have facilitated public health communications, decisions and actions. In the absence of an emerging event such as ORS, specific vaccine safety information collected from 900 to 1000 vaccinees early in the annual campaign will provide reassurance that currently used vaccines are behaving as expected in terms of relatively common (1% to 5% of doses) local and systemic reactions.

Another key reason for conducting enhanced vaccine safety surveillance is to improve Canada’s readiness to monitor a vaccine used in the event of an influenza pandemic. Such a vaccine will be, by definition, an entirely new product incorporating a heretofore unknown strain of influenza as well as potentially being a different vaccine type (live attenuated or subunit preparation) with a novel formulation including a new adjuvant. Limited clinical trials for determining immunogenicity and safety will be done prior to the initiation of mass immunization campaigns. It is essential that ongoing timely enhanced postmarketing surveillance be conducted in order to support public health policy and decisions. Currently there is very limited capacity in Canada for collecting, analyzing and disseminating vaccine safety surveillance data in real time during the annual influenza campaign. Further having vaccine manufacturers pay for and conduct postmarketing surveillance given publicly administered immunization programs raises the specter of both real and perceived conflicts of interest. Thus the Public Health Agency of Canada has both a role and a responsibility, as the authority for postmarketing surveillance of vaccines in Canada, to work to ensure that such a capacity is present and employed not only for pandemic but also for mass campaigns such as annual influenza immunization.

**Study Goal**

The immediate purpose of the proposed studies is to gather timely safety data for influenza vaccines used in the annual campaign. Over the longer term the proposed studies are part of pandemic preparedness plans for safety and efficacy monitoring of pandemic influenza vaccines. It is anticipated that similar studies will be conducted during each of the next several years in order to enhance Canada’s capacity to conduct postmarketing field studies of influenza vaccine safety in the initial phases of the annual mass immunization campaign. Such studies will expand the age-related evidence base on local and systemic reactogenicity of each new annual influenza vaccine that can be shared with immunization providers and vaccinees as the campaign progresses. Should any concerns emerge regarding the current vaccine, immediate steps can be taken to gather additional needed information to properly inform public health decisions.

**Detailed Study Objective**

1. To describe the safety of the inactivated, split-virion influenza vaccines used during the annual influenza campaign in adults aged 18 years and older.

**Study Endpoints**

Safety will be evaluated within 21 days following injection of the designated annual influenza vaccine to determine the following specific endpoints:
1. Occurrence, nature, duration, severity and relationship to vaccination of any solicited local or systemic adverse events occurring within 30 minutes, 3 days and 7 days following immunization.

2. Occurrence, nature, time to onset, duration, severity and relationship to immunization of unsolicited, spontaneously reported adverse events up to 21 days after immunization.

**Investigators and Trial Organization**
In order to achieve the study objectives, the protocol will be carried out in several Canadian settings using the same design. The invitation to participate and conduct these studies will be extended to provincial/territorial health departments and other healthcare facilities that routinely conduct annual influenza immunization. Criteria for choosing the participating centres will be:
- ability to get local IRB approval by the end of August
- ability to recruit to the study prior to the week of scheduled immunizations
- ability to enroll and immunize 120 subjects by the end of the first week of October or if there is a delay in provision of the annual influenza vaccine, within three weeks of the release of the first lots (first lots usually released by Sept 15 but can be delayed)
- ability to conduct the protocol as written with the designated funds to be provided based on anticipated recruitment.
- Ability to send a daily update (Mon-Fri) by fax or phone to the Vaccine Safety Section at Public Health Agency of Canada with information on recruitment, degree of subject completion of each study endpoint (day 0, 3, 7 and 21) and summary data re number of subjects with any, as well any serious, local or systemic AEFI (as per appendix 1).
- Ability to courier Public Health Agency copy of completed case report forms for each designated time point (day 0, day 3, day 7, day 21) on a weekly basis.

**Independent Ethics Committee**
The pilot study protocol, conducted in 2006, was approved by Health Canada’s IRB in November 2006. This protocol, with only minor changes from the pilot project, will be reviewed in June 2007 for approval as a continuing project. Each participating site must obtain local IRB approval by the end of August so that any changes in site consent forms and poster can be submitted to the HC IRB for approval prior to starting recruitment in September.

**Detailed Protocol**

**Design:**
- Observational cohort study of adults immunized with influenza vaccine as distributed for use in the annual campaign and followed actively for safety outcomes during the 21 days post-immunization

**Study populations:**
- 600 healthy adults aged 18 to ≤ 60 years (5 sites each enrolling 120 participants)
- 240 adults aged >60 years (2 sites each enrolling 120 participants)

**Study Plan**
Overview

- Study subjects assessed directly on the day of immunization (Day 0) and the subject enrolment form completed (appendix 2)
- Solicited local and systemic events occurring within 7 days of immunization to be recorded by study participants on the subject Diary Card. (appendix 3)
- Unsolicited adverse events occurring within 21 days of immunization to be recorded by study participants on the subject Unsolicited Adverse Event Report Card. (appendix 4)
- Follow-up by phone or return visit at 4, 8 and 22 to 24 days after immunization to review all entries made in the Diary Card and Unsolicited Adverse Event Report Card.
- All data to be recorded in the paper Case Report Forms provided
- All adverse events occurring within 21 days of immunization, that meet current Canadian adverse event reporting criteria, to be submitted to both provincial/territorial health authorities and to the Public Health Agency of Canada using a standard Canadian AEFI report form
- All serious adverse events (fatal, life threatening, requiring hospital admission or prolonging an existing hospital admission, causing residual damage, birth defect or congenital anomaly) occurring within 21 days of immunization to be reported within 24 hours of the event being known.

Specific Activities

Day 0

After explaining the study to subjects and obtaining informed consent, the subject Enrolment and Day 0 Observations Form (Appendix 2) will be completed, inclusion and exclusion criteria carefully reviewed and influenza vaccine administered according to standard immunization practice. Prior to immunization any injection site clinical findings that could impact on the assessment of local injection site reactions will be documented (such as existing rash, bruising and so on). While in the immunization clinic, subjects will be shown how to complete all subject report forms (Appendices 3-5) and taught the correct method for taking an oral temperature daily using a digital thermometer and for using the plastic template (containing five circles of increasing diameter from 1 to 5 cm) to measure the size of any injection side redness, swelling, induration or bruising.

Subjects will be kept under observation for a time period in accordance with local standard of practice. It is preferable that subjects be reexamined 30 minutes after immunization for any local or systemic reactions. In health care situations where employees would normally return to work before the 30 minute time point, phone follow-up to record the 30 minute observations is acceptable but arrangements should be made to examine any who report moderate to severe local or systemic reactions.

Reactogenicity (Solicited Reactions from D0 to D7 after Immunization)

The diary cards for use from Day 0 to Day 3, and Day 4 to Day 7 (will be printed on opposite sides of a single card) are shown in Appendix 3. Oral temperatures will be routinely taken at the same time each day for 7 days following immunization and recorded in the diary card (in degrees Centigrade). In addition, subjects will be instructed to repeat the temperature measurement any time they feel feverish and to record the value and time taken on the diary card. Other
observations to be recorded in the diary card each day for the 7 days following immunization include:

- daily assessment of the presence or absence, and if the former, the maximal severity of pain at the injection site, headache, feeling unwell, muscle aches/pains or chills/shivering. Levels of severity are defined as:
  - mild: present but doesn’t interfere with daily activities
  - moderate: interferes with daily activities
  - severe: unable to do daily activities
- daily measurement of the maximum diameter of any redness, swelling, induration or bruising at the injection site (<1cm; 1to<2cm; 2to<3 cm; 3to<4 cm; 4to<5 cm; ≥5 cm). For this purpose plastic templates with 5 circles of diameters 1, 2, 3, 4 and 5cm will be provided.

Any solicited AEs that are not resolved by Day 7, should be reported on a separate line of the unsolicited events report card (appendix 4) and use that to record the date of the last day the AE was present.

**Adverse Events from D0 to D21 after Immunization**

A separate report card (Appendix 4) should be used to record unsolicited adverse events (ie any adverse events other than those listed on the subject diary card that occur from Day 0 through Day 21 after immunization, or any of the events listed on the subject diary card that occur or persist after day 7). Subjects will record a description of each AE along with a start and stop date, an assessment of severity in terms of maximal impact on daily activities (mild, moderate or severe as defined above) and whatever actions were taken to deal with the adverse event (over the counter medication, prescription medicine, healthcare utilization or other action such as staying home from work). Any new medications (ie not already recorded on the enrollment Daily Medication Log) or changes in the dose or frequency of medications already recorded on the Daily Medication Log for 21 days after immunization should be recorded on the New Medication Log (Appendix 5).

**Post-immunization Follow by Study Centre:**
Follow-up to record diary and report card entries will be done 4 (±1day), 8(±1day) and 22 to 24 days post immunization. This can be done by phone interview or in person, depending on what is most appropriate for the given site. All data are to be captured using the paper case report form. If any adverse events, solicited or otherwise, are ongoing at the time of the call, subjects will be directed to record the last day the adverse event is present. If there are any adverse events ongoing on day 22, the study team will arrange to continue follow-up until resolution or until the condition is considered stable and unlikely to change.

**Diary Card Collection**
The diary cards are provided for the subjects to record observations and for use as a memory aide when talking to or meeting with study staff at each endpoint. These need not be returned to the study site.

**Reporting Procedure for any AEFI Meeting National Reporting Criteria**
If any solicited or unsolicited adverse event meets the national AEFI reporting criteria (1. temporally associated with immunization; 2. no other proven explanation; and 3. meets at least one of the following: requiring urgent medical attention; unusual or unexpected event; serious event [SAE] defined as life-threatening, resulting in hospitalization, permanent disability or fatality) a national AEFI report must be completed and sent to the provincial/territorial jurisdiction. A copy of the AEFI report, with identifiers removed but including the subject’s assigned study number, must also be faxed at the same time to the Public Health Agency (fax 613-954-9874). Notification regarding SAEs as defined above must be reported within 24 hours of knowledge of their occurrence. If the investigator concludes that there is a proven cause for the event, other than vaccine, it need not be reported. Where there is any doubt, the event should be reported as an AEFI. Since many serious events require investigation beyond the 24 hour reporting window, before a proven etiology for the event is found, it is expected that most such events will be reported.

Serious Adverse Event (SAE) Follow-up Reporting by the Investigator and Causality Assessment

All SAEs that occur during the 21 day study follow-up period will be eligible for causality review by the national expert Advisory Committee on Causality Assessment (ACCA). Depending on the nature of the SAE, specific documents relating to the nature and results of investigations, hospital discharge summaries, expert consultant opinion and other related documents will be requested in order to facilitate the causality assessment process. The study site investigator(s) will be asked to assist in securing these documents. All personal identifying information is to be removed from such documents before being submitted for ACCA review which is only done with assurances of individual subject anonymity.

Reporting of AEFIs and SAEs Occurring After the Study Ends (ie >21 days after immunization)

Any SAE occurring after subject trial termination but possibly related to influenza vaccine should be reported according to local and national reporting standards.

Recruitment numbers and strategy

It is expected that each participating site will enroll a total of 120 subjects, all meeting one or the other age criteria but not both. All subjects would normally be due to receive the annual influenza vaccine regardless of whether or not they participate in the study. In order to have broad Canadian regional representation at least 3 different province/territories will be chosen to participate. It is anticipated that the likely recruitment sites will be: Public Health immunization clinics, Hospital staff immunization clinics, Nursing Home / Personal Care Home staff and resident immunization clinics, Public Health Offices, the Canadian military, First Nations and Inuit Health Branch immunization clinics.

Specific recruitment procedures will be up to the participating study sites, to be in compliance with standard practice related to the annual immunization campaign. It is assumed that the sites normally provide vaccines to the study eligible population and thus have freedom to contact potential participants without violating personal privacy or confidentiality of health information.

Participant Information and Consent

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Prior to enrolment, eligible subjects must have all aspects of the trial explained to them, have the opportunity to ask and have answered any questions and provide a fully informed consent including a signed and witnessed consent form that has been approved by both the Health Canada and local IRBs. Provision of influenza vaccine should be done in accordance with the local standard of practice (including immunization of women who are or may be pregnant), since participants will be receiving vaccine that has full authorization for marketing in Canada. The additional procedures dictated by the study involve keeping a personal diary for 21 days after immunization to record any possible adverse events and consenting to 3 follow-up interviews (by phone or clinic visit) by study site personnel to capture the experience as of Day 3, 7 and 21 post immunization. Original signed informed consent forms should be kept by each study site and a copy given to the subject, or for child participants, to their legal guardian(s).

**Inclusion Criteria**
- 18 years of age or older on the day of enrollment
- informed consent signed
- able to attend all scheduled visits and to comply with all trial procedures

**Exclusion Criteria**
- systemic hypersensitivity to egg proteins, chick proteins or to any of the vaccine components
- history of a life threatening reaction to influenza vaccine or any vaccine containing the same substances
- thrombocytopenia or any bleeding disorder that contraindicates IM injection
- received any vaccine within the prior four weeks
- received influenza vaccine within the prior 6 months
- scheduled or planning to receive any vaccination during the 21 day interval following the date of influenza immunization
- receipt of any blood or blood-derived products within the past 3 months
- any condition that compromises immune response
  - congenital or acquired immunodeficiency
  - chemotherapy, radiation therapy or any other immunosuppressive therapy within the prior 6 months
  - long term systemic corticosteroid therapy
- chronic illness at a stage that could interfere with trial conduct or completion
- any other condition including abuse of alcohol, drug addiction of imposed confinement that may interfere with ability to comply with trial procedures

**Vaccine Administration, Storage and Handling**
This will be done following local standard practice for conducting the annual influenza vaccine campaign. Any deviations from this practice, if affecting specific study subjects, should be recorded in the study site source document(s) for affected subject(s) as appropriate. Any deviations from this practice that affect a group of subjects should be documented in detail, by the site investigator who would also notify the Public Health Agency of any such occurrence.

**Concomitant Therapy**
All prescription and over the counter medications taken by subjects at the time of enrolment should be recorded in the Daily Medication Log on the Subject Enrolment and Day 0
Observations Form (Appendix 2). Any new medications started after immunization up to and including the time of study completion (Day 21) should be recorded (trade name, prescription or over the counter medication, treatment or prophylaxis purpose, start and stop dates, dosage, route and indication) on the Subject New Medication Log (see appendix 5). The New Medication Log should also be used to capture any changes in the frequency or dosage of medicines recorded on the Daily Medication Log at enrollment that occur for 21 days following immunization.

Clinical Supplies

Paper case report forms, subject diaries and report forms, plastic templates for measuring injection site reaction size and thermometers will be provided by the Public Health Agency of Canada.

Vaccine for Enrolled Subjects
For maximum utility, safety data collected during this trial must be available at least in summary form (total recruited, proportion with any/severe injection site reactions; proportion with any/severe systemic reactions within 3 and 7 days of immunization) at the same time or very shortly after the initiation of the annual campaign in most parts of Canada (see Appendix 1). Vaccine is usually released for marketing by mid September but most programs do not get started until the first or second week of October. Aside from needing the safety data to be available as soon as possible, it was clear from the 2006 pilot that doing the study concurrently with the annual influenza campaign was extremely difficult. Thus for 2007 and subsequent seasons, the goal will be to choose participating study sites that can initiate the study within two weeks of the release of the annual vaccine and complete enrollment within a week.

Given these timelines it is essential that each participating site have their allotment of vaccine to be used in the study as soon as possible after marketing authorization is granted by the regulator. Arrangements for ensuring shipment of adequate doses of the annual vaccine will be made with each Provincial/Territorial jurisdiction as appropriate to the location of each study site. The usual route of shipping as used in the given jurisdiction will be followed wherever possible. The difference will be that the vaccine doses to be used for study volunteers must be packaged in a way that clearly identifies them and early delivery must be ensured. The manufacturer and range of lot numbers will be the same as those designated for use in the annual campaign at each study site. This study is not powered to compare vaccines by lot number or manufacturing source. However, one of the considerations for selection of participating sites will be to try to ensure that the two vaccines which form the bulk of doses administered in Canada each year are equitably distributed across the study population.

Assessments Methods and Endpoints
Safety Endpoints and Assessments Methods

Definition of safety terms:

Adverse Event Following Immunization (AEFI): An AEFI is defined as any untoward medical occurrence following immunization. By definition, an AEFI is a temporal association and does not necessarily indicate a causal relationship between immunization and the following event. The
AEFI could be any unfavorable or unintended sign, symptom or disease, including worsening of pre-existing disease, following immunization. Pre-existing conditions, or surgery undertaken following immunization to treat pre-existing conditions, are not considered AEFI and should not be reported as such.

Adverse Reaction
Some events following immunization are expected in a proportion of subjects and are considered causally related to the vaccine as a rule. These would include injection site reactions.

Solicited reaction
A solicited reaction is a term prelisted in the case report form and patient diary (Appendix 3). Assessment for these reactions is a primary objective of this study and considered mandatory. A solicited reaction is defined by a combination of:

- a symptom or sign and
- onset-post immunization

For this trial solicited reactions include symptoms and signs related to the injection site (pain, redness, swelling, induration and bruising) and more general events (fever, headache, feeling unwell, muscle aches/pains, chills/shivering).

Unsolicited adverse events or reactions
An unsolicited adverse event is an observed adverse event that follows immunization but does not fulfill the conditions prelisted in the patient diary (Appendix 3) in terms of symptom/sign and/or timing of onset post-vaccination. For example the patient diary card collects information about headache occurring from day 0 to day 7 following immunization. In this context headache is a solicited adverse event. However, if headache should first appear 9 days after immunization it should be reported as an unsolicited adverse event (Appendix 3). If diarrhea or vomiting were to occur from day 0 through 21 after immunization, each would be considered an unsolicited adverse event because neither is listed on the patient diary card.

Serious Adverse Event (SAE)
The criteria for considering an AEFI “Serious” are based on those described by the World Health Organization and include any AEFI that:

- results in death
- is life-threatening (such as anaphylaxis)
- requires inpatient hospitalization or prolongation of an existing hospitalization
- results in persistent or significant disability / incapacity

Normally in safety studies of products that have not yet been authorized for marketing every single SAE that follows immunization is reported regardless of whether or not there is another ready explanation. This might include a hospital admission for a traumatic injury that occurs during the post immunization observation interval, up to 21 days after injection. For this postmarketing-surveillance study, we are interested in collecting details on all serious AEFI that do not have a ready explanation. However, those that can clearly be explained as due to etiologies other than vaccine, should not be reported. An example would be the occurrence of meningitis following immunization for which a clear etiology is proven (eg N. meningitidis, Herpes simplex.
virus, Coxsackie virus) These decisions should be made by the study site principal investigator. If there is any doubt, however, the event should be reported as an AEFI.

**AEFI reporting in Canada**
Criteria for reporting AEFI in Canada are as follows:
- the event is temporally associated with immunization  **AND**
- the event has no other proven explanation  **AND**
- the event meets one or more of the following
  - serious nature (fatal, life-threatening, requiring hospitalization, resulting in permanent disability, causing a congenital anomaly/birth defect)
  - required urgent medical attention
  - was an unusual or unexpected event

All events that meet these criteria for the 21 days following influenza immunization must be reported using the locally approved version of the national AEFI report form.

Events that don’t meet these criteria, but that are solicited or unsolicited events as defined above will be reported on designated study forms.

**Endpoints**
Safety will be evaluated within 21 days following injection of one of the distributed annual influenza vaccines:
- the occurrence, duration, severity and relationship to immunization of any injection site reactions or systemic adverse events occurring within 30 minutes of immunization
- the occurrence, time to onset, duration and severity of solicited events during the first 3 days following immunization
- the occurrence, time to onset, duration and severity of solicited events for up to 7 days following immunization
- the occurrence, nature, time to onset, duration, severity and relationship to vaccination of unsolicited adverse events up to 21 days following immunization
- the occurrence, nature, time to onset, duration, severity, outcome and causality assessment of any SAE occurring within 21 days of immunization.

**Data Collection and Management**

**Data Collection, Case Report Form Completion (CRF)**
Triplicate NCR paper case report forms will also be provided to the sites and are to be filled in for all subjects. One copy is designated for return to the Vaccine Safety Section of the Public Health Agency of Canada where the data will be entered into an electronic data base for purpose of analysis. Sites are to courier the Public Health Agency copy of each completed section of the CRF for each study time point (enrolment day 0, day 3, day 7 and day 21) on a weekly basis to enable timeliness of data entry.

**Subject Privacy and Confidentiality**
Patient identifying information (name, address including postal code, telephone) will be collected by the study personnel and kept confidentially at each study site. Paper CRFs will use triplicate
NCR paper and be designed such that any identifying information recorded on a form will be blocked out in the copy to be sent to the Public Health Agency once the study is complete. No identifying information will be entered into the web-based CRF. The only personal information to be collected will be gender, date of birth and 3 digit postal code. Each subject will be assigned a unique study participant number that will be recorded on all electronic CRF’s as well as the subject diary card. No identifying information will ever be forwarded to or shared with the Public Health Agency of Canada. In the event that there is a serious adverse event or other event that meets the criteria for national AEFI reporting, personal identification data may be shared with the province/territory that administers the annual influenza program, in accordance with standard practice.

Statistical Methods

Interim summary reports will be simple in nature, providing a running total of subjects enrolled as well as the proportion with any injection site or systemic reactions following immunization on day 0, by day 3 and/or by day 7 as well as the proportion meeting the definition for severe local or systemic reactions occurring with the same time frames.

The final study analysis will address the number and percentage of subjects experiencing injection site or systemic adverse reactions or events until 21 days after injection (observed reactions within 30 minutes of immunization, solicited reactions from 0 to 7 days and unsolicited adverse events / reactions until 21 days). The frequency, severity, time to onset and duration of each solicited and unsolicited adverse event will be determined and types of action taken described. Additionally the proportion of subjects with injection site reactions of >5cm observed for more than 3 days as well as those with measured temperature ≥38.0°C on 2 or more consecutive days will be determined. The temperature cut off for fever is chosen to be that defined by the Brighton Collaboration.6

All SAEs that meet national reporting guidelines will be described in terms of frequency, time to onset, duration, severity, action taken, outcome and causality assessment.

For the 95% Confidence Interval computation, the Clopper-Pearson method for determination of exact binomial distribution for Confidence Intervals of proportions will be used.7

Populations to be Analyzed
Analyses will be done on the study population as a whole, as well as for the three age-related subgroups.

Determination of Sample Size and Power Calculation
This is an observational study with no specific testable hypotheses. The main short term goal of the study is to ensure that the annual influenza vaccine is behaving as expected in terms of “very common” (≥ 10% of doses administered) and “common” (≥ 1% up to <10% of doses administered) reactogenicity events including injection site reactions and fever. The “expected” reactogenicity is gained from pre-licensure and post-marketing published literature. The annually distributed vaccine changes from year to year depending on the predicted circulating strains of influenza virus for the subsequent annual epidemic. In Canada, confirmatory clinical trials involving 100 to 120 subjects are usually required for marketing authorization. These data are
provided to the Biologics Genetics Therapeutics Directorate (vaccine regulators in Canada) who reviews them prior to issuing an authorization for marketing. While the manufacturer may be required to change the product monograph based on these data, the data are not made public or shared with immunization providers. In contrast, the data collected as part of this post-marketing study will be made available to provincial/territorial health authorities, the regulator, vaccine providers in general and the public. The sample size was chosen to enable detection of events that occur with a frequency of 1% or higher.

Although at least 3 manufacturers distribute influenza vaccine in Canada each year, the strain makeup of the vaccines is the same. There is no intent to compare one manufacturer’s product to another in terms of reactogenicity, nor is the study specifically powered to assess lot to lot variation for a given manufacturer’s product. However, should a safety signal emerge during the postmarketing surveillance, such as occurred in 2000 with the oculo respiratory syndrome, analyses will be done to see if a specific product or specific lot is implicated.

**Reporting of Results**

**Interim Reports**
A weekly summary report of study progress and outcomes will be written and shared with the vaccine regulator (BGTD) directly and members of the Federal/Provincial/Territorial Vaccine Vigilance Working Group by way of a secure website hosted by the Canadian Network for Public Health Information (CNPHI), who in turn can share the data with the appropriate jurisdictional health authorities. Any disturbing trends in the safety data will be reviewed by IRID’s vaccine safety team in conjunction with the regulators (BGTD) and communicated on an urgent basis to appropriate FPT stakeholders. If warranted selected SAEs will be referred to the independent Advisory Committee on Causality Assessment for review. A risk-management approach will be undertaken to any safety issues of concern that will include appropriate communication with the public.

**Final Report**
Once all data have been received and analyzed for solicited, unsolicited and SAEs occurring during the 0 through 21 day follow for all study subjects, a final report will be written and shared with all participants in the trial including the vaccine regulators, and vaccine manufacturers. It is anticipated that the results will be published in a peer-reviewed publication as well as posted on the public health agency website.

**Financial Contract**
Standard “Memoranda of Agreement for Services” will be drawn up according to Health Canada guidelines with each of the chosen provincial, territorial, or municipal levels of government participating in the enhanced vaccine safety surveillance. The total amount of each contract remains to be negotiated.

**Stipends for Participation**
The study budget will be based on estimated costs to conduct the study in a variety of regions in Canada. The majority of cost is related to human resources needed to conduct the study protocol as written and regional variation in salary will be respected. Individual study sites will be
expected to provide the study deliverables for the stated budget. Individual sites may choose, in accordance with local standards set by the IRB and usual practice, as to whether or not they wish to provide a stipend to individuals for participating in the study.

References


2. European Medical Agency (EMEA). Note for guidance on harmonization of requirements for influenza vaccines of the. (CPMP/BWP/214/96)


