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.[1] 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. [1] 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). [2]

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.[3] 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[4] and 5% to 34% in those with a prior occurrence of ORS.[5] 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 2006 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 the 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 age-related safety of the inactivated, split-virion influenza vaccines used during the annual influenza campaign.

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 local or systemic adverse events occurring within 30 minutes after injection.

2. Occurrence, time to onset, number of days of occurrence and severity of solicited injection site reactions and systemic reactions, as listed on the subject diary card and occurring up to seven days after vaccination.
3. Frequency of occurrence of each of the following during the 3 days after immunization:
    a. injection site induration measuring >5cm and observed for more than 3 days
    b. injection site ecchymosis (bruising)
    c. fever ≥38.0C lasting 24 hours or more (Brighton Collaboration Definition [6])
    d. malaise
    e. rigors
4. Occurrence, nature, time to onset, duration, severity and relationship to immunization of unsolicited, spontaneously reported adverse events up to 21 days after immunization.

Additionally each participating study site will be asked to report any serious adverse event that they are aware of, occurring up to eight weeks after immunization, if there is no other reasonable explanation.

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 although individual centres may focus on only one of the designated age groups for study. 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 in time to recruit subjects during the 2006 annual influenza immunization campaign
- ability to conduct similar studies for the 2007 annual influenza immunization campaigns
- for 2006, ability to recruit sufficient subjects before the end of the annual influenza campaign
- for 2007, ability to recruit all subjects during the first 2 weeks of the annual campaign (ability to do this for 2006 as well, while not required, will be a strong point in favor of being chosen to participate)
- ability to conduct the protocol as written with the designated funds to be provided based on anticipated recruitment.

Independent Ethics Committee

The protocol is being submitted to Health Canada's IRB for approval by the Public Health Agency. In addition, each participant will be required to obtain local IRB approval before initiating the study. If any changes to the consent form as approved by Health Canada's IRB are considered necessary for local IRB approval, the revised consent forms will be submitted to Health Canada's IRB for review and approval before initiating the study locally. Any changes in the study protocol, data collection instruments or consent forms that are made following the 2006 study year and prior to the initiation of the 2007 study year will be submitted to the Health Canada IRB as well as all participating site local IRB's.

Detailed Protocol

Design:

- Observational cohort study of age-specific individuals immunized with influenza vaccine as distributed for use in the annual campaign and followed actively for safety outcomes during the 21 (± 3) days post-immunization

Study populations:

- 600 healthy adults aged 20 to ≤ 60 years (two to three recruiting sites)
- 150 adults aged >60 years (one to two recruiting sites)
- 150 Children aged 6 to <24 months (one to two recruiting sites)

Study Plan

Overview

- Study subjects assessed directly on the day of immunization (Day 0) and the subject enrolment form completed (appendix 1)
- Solicited local and systemic events occurring within 7 days of immunization to be recorded by study participants on the subject Diary Card.(appendix 2)
- Unsolicited adverse events occurring within 21 days of immunization to be recorded by study participants on the subject Unsolicited Adverse Event Report Card. (appendix 3)
- Phone follow-up at 4, 8 and 21(± 3) days after immunization to subject entries for both solicited and unsolicited adverse events.
- All data entry by participating study sites to be entered directly into an electronic database and submitted on a weekly basis to the Public Health Agency of Canada.
- All adverse events 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 (Appendix 4)
- All serious adverse events (fatal, life threatening, requiring hospital admission or prolonging an existing hospital admission, causing residual damage, birth defect or congenital anomaly) 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 1) 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).

Subjects will be kept under observation for 30 minutes after being immunized to ensure their safety. During this interval subjects will be shown how to complete all subject report forms (Appedices 2, 3 and 5) and taught the correct method for taking an oral temperature daily using a digital thermometer and for using the ruler to measure the size of any injection side redness, swelling, induration or bruising. At the end of the 30 minutes the injection site will be examined and any local reactions or systemic adverse events recorded by study personnel on the Enrolment and Day 0 Observations Form (Appendix 1). Any adverse event occurring within this time period that meets the national AEFI reporting criteria will also be recorded on the Canadian AEFI report form.

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 2. Oral temperatures will be routinely taken at the same time each day for 7 days following immunization and recorded in the diary card. 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, malaise, myalgia or rigors.
- daily measurement of the maximum diameter of any redness, swelling, induration or bruising at the injection site

If any solicited AEs are not resolved by Day 7, subjects will record the date of the last day the AE was present.

Adverse Events from D0 to D21 after Immunization

A separate report card for unsolicited adverse events (Appendix 3) will be provided and subjects taught how to complete it during the 30minute post-immunization observation period. This card will be used to record all unsolicited events including those that meet national reporting criteria. Subjects will record a description of each AE along with a start and stop date, an assessment of severity in terms of impact on daily activities (mild: doesn't interfere with daily activities; moderate: interferes with daily activities; severe: unable to do daily activities) and whatever actions were taken to deal with the adverse event (healthcare utilization, over the counter medication, prescription medicine etc).

Telephone follow up by Study Centre:
Subjects will be phoned on study days 4, 8 and 22 to collect information on solicited events as recorded in the diary card as well as any recorded unsolicited adverse events at the time of the call. All data will be entered directly into an electronic case report from (eCRF) at the time of the call. Action taken for any adverse event will be recorded as text in the eCRF, and also coded as one of the following: 0=No action; 1=over the counter medication; 2= health care contact (defined as physician/nurse telephone contact; physician/nurse evaluation; emergency room visit); 3=health care contact and prescription of new medication; 4= hospitalization. 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.

If any unsolicited adverse event meets the national AEFI reporting criteria a national report form will be completed, using the electronic software provided. The report will be submitted not only to the Public Health Agency as part of the study deliverables, but also to the subject's provincial/territorial health jurisdiction.

Diary Card Collection
The study site will ensure that all subject diary cards and report forms are collected. Originals will be stored at the study site; Copies of the cards, with any personal identifiers such as name removed, will be forwarded to the Public Health Agency of Canada.

Serious Adverse Event (SAE) Reporting Procedure
All SAEs, that meet national reporting guidelines, including the specification that there be no other proven explanation, must be reported to the Public Health Agency as well as the provincial/territorial jurisdiction within 24 hours of knowledge of their occurrence. If the investigator concludes that there is a proven cause for the event, other than vaccine, they 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.

The supplied eCRF software will enable the secure transmission of an AEFI report by email directly to the Public Health Agency as well as to the appropriate regional jurisdiction. Fax numbers for both the Vaccine Safety Section within the Public Health Agency as well as the appropriate provincial/territorial health unit will be provided so that printed reports can be submitted in the event of internet disruption.

If the AEFI is of a non-serious nature the AEFI report will be forwarded electronically at the same time as the rest of the study data. If the AEFI is an SAE the AEFI report will be submitted to both PHAC and the appropriate provincial/territorial jurisdiction within 24 hours, using the electronic software provided.

Serious Adverse Event (SAE) Follow-up Reporting by the Investigator and Causality Assessment
All SAEs that occur during the trial 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 Serious Adverse Events (SAE) Occurring after Subject Trial Termination
Any SAE occurring after subject trial termination but possibly related to influenza vaccine must also be reported by the Investigator as soon as he/she is alerted of it. In such a case, the procedure to be followed to report the SAE provincially/territorially as well as nationally is identical to that described above.

Recruitment numbers and strategy
From 4 to 7 study sites will each enroll 75 to 200 subjects, each of whom would normally be due to receive the annual influenza vaccine. Where possible, depending on how many potential participating sites meet the study criteria, at least 3 different province/territories will be chosen to participate. It is anticipated that the likely recruitment sites will be:

- for healthy adults aged 18 and older: Public Health immunization clinics, Hospital staff immunization clinics, Nursing Home / Personal Care Home staff and resident immunization clinics, Public Health Offices, the Canadian military
- for children aged 6 to <24 months old: public health clinics serving children, pediatrician offices, clinical vaccine investigators who regularly enroll children in settings where annual influenza immunization of such children is consistent with the provincial/territorial routine immunization schedule

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
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, consenting to 3 phone follow-ups by study site personnel on Days 4, 8 and 22 and returning the subject diary and report cards to the study site at the end of the study. 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
- meets one of the two age criteria on day of enrolment
    - 18 years of age or older
    - at least 6 months old but not yet reached 2nd birthday
- 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 medications taken by subjects at the time of enrolment and throughout the study up to 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 Subject Concomitant Medication Log (see appendix 3). These data should be maintained at the study site. They will only be shared with the study sponsor (PHAC) in the event of occurrence of a severe adverse event that requires review for causality assessment. In this case they will be submitted with the Canadian AEFI report. This does not include medications taken to treat an AEFI since these should be captured on the patient diary and, in turn, the electronic case report form.

Clinical Supplies

Protocols, eCRF and associated software, Subject diaries and report forms, rulers and thermometers will be provided by the Public Health Agency of Canada.

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 AEFIs 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. 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, malaise, myalgia and rigors).

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 2) 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
- causes a congenital anomaly/birth defect
- is an important medical event. This is somewhat arbitrary and based on medical judgment as to whether or not the event, while not immediately life-threatening or requiring hospitalization, nevertheless may jeopardize a patient or require intervention to prevent any of the other outcomes listed above.

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
    - was expected but is being observed to occur with greater than usual frequency

All events that meet these criteria for the 21 days following influenza immunization must be reported using the revised Canadian AEFI report form (Appendix) which will be included in the eCRG provided to each participating site.

In addition, several events have been designated to be of specific public health interest as related to their occurrence following influenza vaccine, even if not very severe. For this study these include the following, all of which are listed on the revised Canadian AEFI report form and should be reported if they occur within 21 days of immunization:

- Bell's Palsy
- Oculorespiratory syndrome

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

Finally, each study site is encouraged to report, should they be made aware of any occurrence in study subjects of Guillain Barre Syndrome that occurs >3 weeks but <8 weeks after immunization as well as any other event that meets the above criteria but occurs from 22 to 30 days after immunization. The revised Canadian AEFI report form will be used for this purpose.

Reporting to Local Jurisdictions
In so far as any AEFI occurring in study subjects during the course of the trial meet the national reporting criteria as defined above, an AEFI report form must be submitted to local provincial / territorial health authorities at the same time as submitting to the Public Health Agency of Canada. Reporting will be enabled through the use of the eCRF and associated software provided as part of this study since it facilitates generation of a report directly to the local health jurisdiction electronically or via a printed paper form. For local reporting, patient identifiers are needed to enable appropriate investigation, follow-up and public health action. The electronic software provided is designed to permit the entry of such identifiers for purposes of local reporting while at the same time censoring such information from any study data transmitted to the Public Health Agency of Canada.

Endpoints
Safety will be evaluated within 21 days following injection of one of the 2006 distributed influenza vaccines, in each of the age-specific study groups (healthy 18to < 61 year olds; healthy individuals aged 61 years and older; healthy children aged 6mos to <24 mos) for:

- 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 of any of the following within three days after immunization:
    - injection site induration exceeding 5 cm that is observed for > 3 days
    - injection site ecchymosis (bruising)
    - fever (oral temperature $\geq 38.0^{o}C$) that occurs during two or more consecutive 24 hour periods
    - malaise
    - rigors (shivering)
- the occurrence, time to onset, number of days of occurrence, 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 AEFI meeting national reporting criteria that are reported at anytime following immunization.

Data Collection and Management

Data Collection, CRF Completion

A limited-use ACCESS database (eCRF) containing all study related report forms as well as an updated version of the national AEFI report form will be provided to each centre participating in the post-marketing study. Training in the use of the electronic database will be provided prior to its use in the post-marketing study. Technological support will be available throughout the trial should there be any problems with data entry or transfer. Hard copies (printouts) of all completed data entry forms must be made at the time of data entry and stored at the study site in duplicate to prevent accidental loss of data. Additionally back-up processes for electronic data will be undertaken on a daily basis to guard against data loss.

Electronic Data Transmission to Public Health Agency

Throughout the study period data will be transmitted to the Public Health Agency of Canada via secure email processes on a weekly basis. Individual subject data may be transmitted on 4 different occasions depending on the day of the week they are enrolled, including the enrollment/30minute safety observations, day 4, day 8 and day 22 follow-up data. In addition, SAE reports are to be submitted within 24 hours of initial awareness and data capture to both the public health agency and the appropriate provincial/territorial jurisdiction.

Subject Privacy and Confidentiality

Patient identifying information (name, address including postal code, telephone), and in the case of child participants, name and contact information of their legal guardian(s) will be collected by the study personnel and kept confidentially at each study site. The electronic database provided to all study sites will enable storing this data electronically in a secure manner. 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

The 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 induration >5cm observed for more than 3 days as well as those with measured temperature ≥38.0^{o}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 (Appendix 4) 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. Additional studies are being done, as part of a separate protocol but with the identical design for safety, in 120 adults aged 18 to <61 years. The safety results for all similarly aged subjects enrolled in both studies will be pooled and analysed for safety endpoints using the methods described above. Thus the total subject groups will be up to 720 adults aged 18 to <61 years, 150 adults aged >60 and 150 children aged 6 to <24 months.

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 oculorespiratory syndrome, analyses will be done to see if a specific product or specific lot is implicated.

Reporting of Results

Interim Reports
All safety data will be submitted weekly to the Public Health Agency for this protocol as well as for the other protocol involving up to 120 healthy adults aged 18 to <61 years of age. These data will be analyzed on a weekly basis to build a cumulative profile of reactogenicity and AEFI frequency over time at each of the set study endpoints (30 minutes, 3 days, 7 days, 21 days and ongoing for any SAEs) following immunization. Results will be shared on a weekly basis with the vaccine regulator (BGTD) directly and members of the Federal/Provincial/Territorial Adverse Event Reporting Standards Task 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 the regulators, the AERSTG group via teleconference and the independent Advisory Committee on Causality Assessment. 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. It is anticipated that the sites participating in the study for 2006/2007 will conduct similar studies for a minimum of 2 additional years although there may be some minor changes in the protocol. The total amount of each contract remains to be negotiated.

Stipends for Participation
The study budget will be a global one based on estimated costs to conduct the study in a variety of regions in Canada. 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

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