Protocol

Active Surveillance of Adverse Events Following Immunization Among Healthcare Workers Immunized With the Influenza Vaccine

Principal investigator:
Dr Gaston De Serres
Centre Hospitalier Universitaire de Québec
2400 D’Estimauville
Quebec City, Quebec, Canada
G1E 7G9

Co-investigators:

Dr Louis Valiquette
Centre Hospitalier Universitaire de Sherbrooke,
3001 12e Avenue Nord, Sherbrooke
J1H 5N4

Dr Julie Bettinger
BC Children's and Women's Hospital
University of British Columbia
950 West 28th Avenue, Room A-5
Vancouver, BC
V5Z4H4

Dr Grant Stiver
Vancouver General Hospital,
Division of Infectious Diseases, 2733
Heather Street, D 452
Vancouver, BC, Canada
V5Z 3J5

Dr Allison McGeer
Mount Sinai Hospital
Joseph and Wolf Lebovic Health Complex
600 University Avenue
Toronto, ON
M5G 1X5

Dr Ann McCarthy
Ottawa Hospital General Campus
501 Smyth Road,
Ottawa, Ontario
K1H 8L6

Dr Shelly McNeil
Queen Elizabeth II Health Sciences Centre and Canadian Center for Vaccinology
Halifax
5850/5980 University Avenue, Box 9700
Halifax, NS
B3K 6R8
# Table of contents

1. INTRODUCTION ........................................................................................................ p.3
2. STUDY OBJECTIVE.................................................................................................... p.4
3. METHODS ................................................................................................................ p.4
   3.1 Recruitment ........................................................................................................ p.4
   3.2 Study procedures ................................................................................................. p.5
   3.3 Online data collection tool ................................................................................ p.5
   3.4 Controls .............................................................................................................. p.6
   3.5 Analyses .............................................................................................................. p.6
4. ETHICS .................................................................................................................... p.6
5. EXPECTED RESULTS .............................................................................................. p.7
6. RESEARCH TEAM .................................................................................................. p.7
7. BUDGET .................................................................................................................. p.7
8. APPENDIX 1 ......................................................................................................... p.8
9. APPENDIX 2 ......................................................................................................... p.9
10. APPENDIX 3 ......................................................................................................... p.21
11. APPENDIX 4 ......................................................................................................... p.25
12. APPENDIX 5 ......................................................................................................... p.26
13. APPENDIX 6 ......................................................................................................... p.29
14. REFERENCES ....................................................................................................... p.32
1. INTRODUCTION

Influenza vaccines are continuously modified to adjust to the virus antigenic shifts or drifts, and its safety profile may vary. While generally considered safe, unexpected adverse events have been reported with influenza vaccines. In 1976, the swine influenza vaccines have been associated with the Guillain-Barré syndrome. In 2001, an unknown adverse event dubbed the oculorespiratory syndrome (ORS) affected a large number of people administered the seasonal influenza vaccine in Canada. The ORS is an adverse event resembling allergy, with an onset within 24 hours of vaccination and causing several signs/symptoms: bilateral conjunctivitis, facial/lip/tongue oedema, sore throat, difficulty swallowing, cough, hoarseness, dyspnea, chest tightness. Since its first detection in 2001, ORS has been reported every year with the annual influenza vaccination. In 2009, the pandemic vaccine has been associated with an increase of anaphylaxis and allergic-like reactions in Canada. It was also associated with paresthesias occurring in the first 24 hours after vaccination. These paresthesias affected several anatomical areas and do not correspond to any specific nerve, spinal root or cerebral structure territory. Sometimes, they are accompanied with muscular weakness and visual or speech problems. They can persist for months and do not correspond to any classical neurological disease. In 2010, an Australian influenza vaccine has been associated with convulsions in children.

The size of the influenza seasonal mass immunization campaign and the speed with which it is administered put special responsibility on public health and leave monitoring of unexpected adverse events following immunization on the forefront of public health activities. Before annual licensure, manufacturers have to conduct trials in a very limited number (<200) of healthy adults and elderly people. This number is insufficient to detect adverse events occurring even at a rate of 1-2% of vaccinees. Rare side effects could only be detected when large number of people are given the vaccine and will be picked through passive surveillance of adverse events (AE) conducted on the whole population. The sensitivity of this passive surveillance system is not high and its timeliness is not necessarily optimal given that most doses of vaccines are administered in the first 4-6 weeks of the annual campaign.

This surveillance, occurring early in the campaign, is meant to quickly gather and analyze safety data on thousands of vaccinated individuals to inform public health authorities before the core weeks of the annual campaign, should a problem be detected. Health care workers (HCW) are targeted for vaccination to both protect them against influenza and against transmitting the infection to their often already debilitated and frail patients. It is important for HCW to be vaccinated early in order to be immune well before the virus starts circulating in the population, which may happen as soon as early November. HCW are also highly motivated in ensuring that vaccines are safe, they are well aware of adverse events and are good at reporting them.

In 2009, starting with the new pandemic Influenza vaccine, we piloted a web-based active surveillance of a large number of health care workers vaccinated with the new adjuvanted monovalent pH1N1 influenza vaccine (Arepanrix® GSK, Canada). 6242 HCW were recruited at three different sites. A total of 468 adverse events (local reactions, fever, systemic reactions, gastrointestinal and respiratory problems) were reported. 80% of the HCW recruited completed at least one of the three surveys and 52% responded to all questionnaires. During this surveillance,
we found that local reactions caused work absenteeism or medical consultation, that ~1/2000 vaccinees experienced an allergic symptom and that ~1/1000 had paresthesias.

In 2010, we recruited 7467 HCW from 6 different sites. Results have shown that the seasonal vaccine was less reactogenic than the pandemic vaccine. The completeness of surveys was higher compared to the previous year, since 85% of all participants responded to at least one of the 3 surveys and 61% completed all of them.

Not every health problem occurring after a vaccine is caused by the vaccine. At any time of the year, people become sick with different diseases at a frequency corresponding to the “background rate”. After a vaccine, some health problems happen as part of the background rate and only the excess above that rate is attributable to the vaccine. To calculate the risks attributable to the vaccine, the surveillance needs to estimate the background rate in individuals that have not been recently vaccinated (control participants).

For the 2011-2012 season, the changes to our surveillance will include the addition of new sites and the recruitment of more than 10000 HCW. A control group will be added to allow an estimation of the background rate of diseases in order to calculate the risks attributable to the vaccine. In addition to the main outcome (adverse events causing medical visit or work absenteeism), the surveillance will collect data on milder outcomes (local reactions, oculo-respiratory syndrome (ORS) and paresthesia) that are also relevant for the monitoring of the safety of the vaccine.

2. STUDY OBJECTIVES
The main objective of this project is to estimate, in HCW vaccinated against influenza, the frequency of adverse events following immunization (AEFI) of sufficient severity to cause work absenteeism or medical consultation.

The secondary objective is to estimate the incidence of local reactions, oculo-respiratory syndrome (ORS), and paresthesia after vaccination

3. METHODS
The web-based active surveillance will include 6 to 10 Canadian hospitals (Quebec City, 2 in Vancouver, Toronto, Halifax, Ottawa, Sherbrooke and a possibility of 3 others sites).

3.1 Recruitment
Recruitment of HCW receiving the influenza vaccine in 2011-2012 will be done at the time of vaccination. Before being vaccinated, HCW have to complete a short questionnaire to ensure that they have no contraindications and sign a consent for vaccination. We will attach to this surveillance project’s information and consent form, describing the web-based active surveillance and asking if they would agree to participate in the active surveillance, to the consent for vaccination. Only those with an active email address will be eligible to participate. Those who are interested will sign this short consent form (Appendix 1) and provide their email address and their personal and professional phone numbers.
3.2 Study procedures
After enrolment, email addresses will be entered in a database. At day 3 following immunization, an email will be sent to confirm their participation in this surveillance project. This email will also allow the study coordinators to see if the email address is valid or not. If an email address contains a mistake, the participant will be contacted to confirm their email address.

Participants will be sent an email at day 8 following immunization inviting them to respond to a short survey about demographic data (age, sex and occupation), past influenza immunization history, and to ask about the occurrence of any adverse event (AE) for the first 7 days post-vaccination.

At day 29, participants will be sent another email inviting them to respond to a short survey on the occurrence of AE for the period of 8 to 28 days post-vaccination. If a participant had not answered the day 8 survey, the questions in the survey at day 29 will cover the entire 28 day period after vaccination and will collect demographic data and past immunization history as outlined above.

The surveys will be accessible by clicking on a link embedded in the emails. The link will provide a secure access to the survey website using secure data transfer protocols. For each period, participants will be asked questions regarding the occurrence of a list of signs and/or symptoms following immunization (Appendix 2).

For each survey, if the participant fails to answer within 72 hours, a reminder email will be sent. Participants reporting adverse events severe enough to cause work absenteeism and/or medical consultation will be contacted within 48 hours (or more if the nurse is unable to reach the participant) by a nurse specifically trained in obtaining a detailed history of possible adverse events following immunization (as detailed in Appendix 3). Patients reporting numbness occurring in the first 24 hours after vaccination will also be called to obtain further details.

Once validated, the data will be entered promptly by the research nurse or a member of the research team in a restricted access web-based database, which will allow a real-time data analysis. In this database, participants will only be identified by a unique number.

3.3 Online data collection tool
All sites will use the SimpleSurvey software. SimpleSurvey provides an online survey tools which allow tracking of response rates and results can be viewed in real time. This software is developed, designed, hosted, and supported entirely in Canada by OutSideSoft Solutions inc. (Saint-Jean-sur-Richelieu, Quebec). The database will be accessible through a secure web application with personal passwords for all sites, providing a secure environment (encryption, firewalls, frequent backups and recovery plan). Personal information will be kept on the local sever and not on this Software. Only people in local research team will have access to personal data (name, phone number, etc.). Finally, data could be downloaded to the local hardware in a variety of formats to allow for further and more complicated statistical analyses and modeling. Sixty (60) days after the end of surveillance, databases will be deleted from the SimpleSurvey server.
3.4 Controls
To estimate the risks attributable to the vaccine, we will compare the frequency of AEs occurring after vaccination to the background incidence of AEs in controls (people not recently vaccinated). This background incidence will be estimated in HCW over a seven day period occurring one or two weeks before the vaccination campaign starts at their hospital.

Controls for 2011
To recruit controls, we will, in September or October 2011, contact by email the HCW who participated to the active surveillance studies in either 2009 or 2010. The email (Appendix 4) will first present a summary of the results of these studies during the previous two years (Appendix 6). It will then invite HCW to be part of our control group and to provide data about work absenteeism or medical consultation for onset of new diseases for a seven day period before the 2011 vaccination campaign. HCW who will agree to participate will access the survey by clicking on a hyperlink. With this electronic survey we will collect data about the occurrence of clinical problems that occurred in the last 7 days (Appendix 5). The incidence of these clinical problems will be used to compare the frequency of AE after vaccination.

Controls for 2012
The consent form in 2011 will request HCW participating to the surveillance this year (2011) to agree to receive an email with a survey about two weeks before the 2012-2013 vaccination campaign. That survey will collect data about the occurrence of clinical problems that occurred in the last 7 days (Appendix 5).

3.5 Analyses
Adverse events reported through the active surveillance systems will be classified using standardized case definitions from the Brighton Collaboration\(^5\text{-}\text{18}\), when available. The risk of absenteeism and medical consultation due to new or exacerbated medical condition attributable to the vaccine will be estimated by subtracting the incidence of AEs in the control period to those observed after immunization with the seasonal influenza vaccine.

4. ETHICS
All healthcare workers vaccinated in the participating institutions will be invited to participate to this active surveillance. Those who agree will have to sign a short consent form. The data collected will be kept confidential. All data collected by the nurse during the interviews will be recorded on paper, and kept in a locked file of the local site. Validated data will be entered on a second database using a generated unique identifier (ID) and access will be limited to the trained nurse and site research staff.

5 EXPECTED RESULTS
Influenza is the largest of all immunization programs in Canada. While reassuring, prelicensure clinical trials are too small to detect even rather frequent adverse reactions to vaccines. The current surveillance will add to the passive surveillance system by providing results about a significant number of people vaccinated early in the annual campaign. It will also reinforce the capacity of occupational health offices or other departments in charge of vaccinating HCW to monitor the
safety of the vaccines in their employees. This third year of the study should allow us to expand this surveillance which, we hope, will become a routine and an intrinsic component of vaccine safety monitoring.

6 RESEARCH TEAM
Dr Gaston De Serres, Centre Hospitalier Universitaire de Québec, Quebec City
Dr Louis Valiquette, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke
Dr Julie Bettinger, Vaccine Evaluation Center, BC Children’s and Women’s Hospital, Vancouver
Dr Grant Stiver, Vancouver General Hospital, Vancouver
Dr Allison McGeer, Mount Sinai Hospital, Toronto
Dr Ann McCarthy, Ottawa General Hospital, Ottawa
Dr Shelly McNeil, Queen Elizabeth II Health Sciences Centre and IWK Health Centre

7 BUDGET
Each participating site will receive the following budget

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Appendix 1
(Consent Form – see attached)
Appendix 2

Day 3 email message

This email is to confirm your participation to the ACTIVE MONITORING OF INFLUENZA VACCINE SAFETY IN HEALTH CARE WORKERS. In a few days, you will receive the first survey to complete.

If you have questions, you can contact Kristy at 416-586-4800 ext. 2767.

Thanks for your participation.
Day 8 survey

1. Please indicate your gender.
   □ Female
   □ Male

2. What is your age? __________ years

3. What is your occupation at the hospital? Select from the drop down menu
   □ Physician
   □ Nurse/assistant nurse
   □ Patient care assistant (PCA)
   □ Medical Technician (Laboratory, medical imagery, etc…)
   □ Others health professionals or technicians (Pharmacist / Psychologist/ occupational, physical or respiratory therapist/ dietician/social worker, etc…)
   □ Housekeeping, logistics and food service
   □ Administrative/ secretary/ office work
   □ Other

4. Have you been vaccinated against pandemic A/H1N1 influenza in 2009?
   □ No
   □ Yes

5. In the last 3 years, how many times have you been vaccinated against seasonal influenza?
   □ 0    □ 1    □ 2    □ 3

Adverse events after vaccination
In the first 24 hours following the vaccination, have you experienced the onset of:

6. Redness of both eyes (bilateral conjunctivitis), or swelling of your face/eyelids/lips or tongue, or a hoarse voice, or chest tightness/discomfort?
   No
   Yes

7. Numbness, tingling, pins and needles, decreased sensation or burning sensation anywhere in your body that lasted more than 24 hours?
   No
   Yes

In the first week (7 days) following the vaccination, have you experienced the onset of:

8. A local injection site reaction severe enough to limit you in your normal daily activities?
   No
   Yes

9. Any other symptom severe enough to limit your normal daily activities?
   No
   Yes
If the participant answered « No » to questions 6 to 9, the questionnaire ends and this message will appear: Thanks for your help with this surveillance project. You will receive the second survey in about 3 weeks.

If the participant answered « yes » to some of the previous questions, other windows with questions related to the declared symptoms will appear.

6a. If « yes » is given to question 6, the following questions will appear.

You mentioned having experienced redness of both eyes (bilateral conjunctivitis), or swelling of your face/eyelids/lips or tongue, or a hoarse voice, or chest tightness/discomfort. Please check all symptoms you experienced with onset within 24 hours of your vaccination.

Ocular problems
- Redness of both eyes
- Painful eyes
- Itchy eyes
- Tearing or eye discharge
- Swelling of the eyelid

Respiratory problems
- Sore throat
- Swelling of the throat
- Cough
- Chest tightness/discomfort
- Wheezing
- Swelling of the tongue
- Difficulty swallowing
- Hoarseness
- Difficulty breathing

Skin problems
- Swelling of a part of your face/lips/tongue (excluding the eyelid)
- Rash (redness of your skin) with itching
- Rash (redness of your skin) without itching

Other problems
- Fever (Temperature measured and above 38.5C)
- Feverishness/Chills

6b. How would you describe the severity of these symptoms overall?
- Easily tolerated
- Uncomfortable, but didn’t require missing work or consulting a health care provider
- Severe enough to miss work or to have to miss work, if work was scheduled during this period
- Severe enough to require consulting a physician or a nurse
- Severe enough to miss work and to require a medical consultation

6c. How long after the vaccination did these symptoms first appear?

________ minutes   or   ________ hours
6d. How long did these symptoms last?

_____ minutes or _____ hours or _____ days or They are still present

6e. Do you think that these symptoms are related to the vaccine?

No
Yes
Don’t know

7a. If « yes » is given to question 7, these questions will appear.

Please check all areas where you felt unusual sensations (numbness, tingling, prickling, decreased sensation or burning sensation)

- Upper limbs vaccinated side
- Upper limbs unvaccinated side
- Lower limbs vaccinated side
- Lower limbs unvaccinated side
- Trunk or back
- Face
- Scalp or ears
- Neck

7b. How would you describe the severity of these symptoms?

- Easily tolerated
- Uncomfortable, but didn't require missing work or consulting a health care provider
- Severe enough to miss work or to have to miss work, if work was scheduled during this period
- Severe enough to require consulting a physician or a nurse
- Severe enough to miss work and to require a medical consultation

7c. How long after the vaccination did these symptoms first appear?

_______ minutes or _______ hours

7d. How long did these symptoms last?

_______ days or _______ hours or They are still present

7e. Do you think that these symptoms are related to the vaccine?

No
Yes
Don’t know

8a. If « yes » is given to question 8 this questions will appear.

You mentioned having experienced a local reaction severe enough to limit your regular activities in the 7 days period following the vaccination. How would you describe that local reaction? Please check all symptoms that occurred in the 7 days following the vaccination.

- Redness at the site of the injection
- Pain at the site of the injection
Swelling at the site of the injection
   Specify (select from the drop down menu)
   Small (smaller than an Oreo cookie)
   medium (bigger than an Oreo cookie but don’t involved the arm up to the joints)
   Large (involved the arm up to the joints)
   Very Large (went beyond the joints)

8b. How would you describe the severity of these symptoms?
   Easily tolerated
   Uncomfortable, but didn't require missing work or consulting a health care provider
   Severe enough to miss work or to have to miss work, if work was scheduled during this period
   Severe enough to require consulting a physician or a nurse
   Severe enough to miss work and to require a medical consultation

8c. How long after the vaccination did these symptoms first appear?
   _______ days

8d. How long did these symptoms last?
   _______ days       They are still present

9a. If « yes » is given to question 9, this questions will appear.
   You mentioned having symptoms that were severe enough to limit you in your daily activities. Please check all symptoms occurred in the 7 days following the vaccination.
   Fever, feverishness, chills
   Feeling unwell/fatigue/generalized muscular and/or joint pain
   Respiratory infection (cold, flu, pharyngitis, tonsillitis, sinusitis, bronchitis, pneumonia)
   Gastrointestinal problem (nausea and/or vomiting and/or diarrhea)
   Allergic reaction and/or allergic like reaction (e.g. rash/urticaria)
   Other, please specify: ___________________________ ___________________________

9b. How would you describe the severity of these symptoms?
   Easily tolerated
   Uncomfortable, but didn't require missing work or consulting a health care provider
   Severe enough to miss work or to have to miss work, if work was scheduled during this period
   Severe enough to require consulting a physician or a nurse
   Severe enough to miss work and to require a medical consultation

9c. How long did these symptoms last?
   _____ minutes or _____ hours  or  _____ days  or  They are still present

9e. Do you think that these symptoms are related to the vaccine?
   No
   Yes
   Don’t know
At the end this message will appear:

Thanks for your help with this surveillance project. You will receive the second survey in about 3 weeks.

If you have answered that you have missed work and/or required a medical consultation and/or have experienced numbness in your body, a research nurse will contact you within 48 hours to collect more information about your health problem. (We will use the phone number given in the consent form.)
Day 29
Survey A. Participants who have responded to the day 8 survey

You have already responded to the survey about the presence or absence of symptoms in the first 7 days after your influenza vaccination.

1. For the period between 8 and 28 days following vaccination, have you experienced the worsening of an existing medical condition or the occurrence of any new symptom severe enough to limit your normal daily activities?
   
   No
   Yes
   
   If the participant answered « no », the survey goes to the end message
   If the participant answered « yes » the following questions will appear:

1a. You declared having symptoms that were severe enough to limit you in doing your activities. Please check all symptoms occurred between 8 and 28 days following the vaccination.
   Fever, feverishness, chills
   Feeling unwell/fatigue/generalized muscular and/or joint pain
   Respiratory infection (cold, flu, pharyngitis, tonsillitis, sinusitis, bronchitis, pneumonia)
   Gastrointestinal problem (nausea and/or vomiting and/or diarrhea)
   Allergic reaction and/or allergic like reaction (rash/urticaria)
   Other, please specify:

1b. How would you describe the severity of these symptoms?
   Easily tolerated
   Uncomfortable, but didn't require missing work or consulting a health care provider
   Severe enough to miss work or to have to miss work, if work was scheduled during this period
   Severe enough to require consulting a physician or a nurse
   Severe enough to miss work and to require a medical consultation

1c. How many days after the vaccination did these symptoms appear?
   ________ days

1d. How long did these symptoms last?
   _____ hours or ______ days    They are still present

1e. Do you think that these symptoms are related to the vaccine?
   No
   Yes
   Don’t know

At the end this message will appear: **Thanks for your help with this surveillance project. You will receive the third survey in about two weeks before the 2012-2013 vaccination campaign. If you have answered that you have missed work and/or required a medical consultation and or have experienced numbness in you body a research nurse will contact you within 48 hours to collect more information about your health problem. (We will use the phone number given in the consent form.)**
Day 29
Survey B. Participants who did not respond to the day 8 survey

1. Please indicate your gender.
   □ Female
   □ Male

2. How old are you? ________ years

3. What is your occupation at the hospital? Select from the dropdown menu
   □ Physician
   □ Nurse/assistant nurse
   □ Patient care assistant (PCA)
   □ Medical Technician (Laboratory, medical imagery, etc…)
   □ Other health professional or technician (Pharmacist, Psychologist, occupational, physical or respiratory therapist, dietician, social worker, etc.)
   □ Housekeeping, logistics and food service
   □ Administrative, secretary, office work
   □ Other, specify:___________

4. Have you been vaccinated against pandemic A/H1N1 influenza in 2009?
   No
   □ Yes

5. In the last 3 years, how many times have you been vaccinated against seasonal influenza?
   □ 0
   □ 1
   □ 2
   □ 3

Adverse events after vaccination
In the first 24 hours following the vaccination, have you experienced the onset of:

6. Redness of both eyes (bilateral conjunctivitis), or swelling of your face/eyelids/lips or tongue, or a hoarse voice, or chest tightness/discomfort?
   No
   Yes

7. Numbness, tingling, pins and needles, decreased sensation or burning sensation anywhere in your body that lasted more than 24 hours?
   No
   Yes

8. In the 7 days following the vaccination (including the first 24 hours), have you experienced a local injection site reaction severe enough to limit you in your normal daily activities?
   No
   Yes

9. In the 28 days (including the first 24 hours) have you experience any other symptom severe enough to limit your normal daily activities?
   No
   Yes
If the participant answered « No » to questions 6 to 9, the survey will go to the end message.

If the participant answered « yes » to some of the previous questions, other windows with questions related to the declared symptoms will appear.

6a. If « yes » is given to question 6, the following questions will appear.

You mentioned having experienced redness of both eyes (bilateral conjunctivitis), or swelling of your face/eyelids/lips or tongue, or a hoarse voice, or chest tightness/discomfort. Please check all symptoms you experienced with onset within 24 hours of your vaccination.

Ocular problems
- Redness of both eyes
- Painful eyes
- Itchy eyes
- Tearing or eye discharge
- Swelling of the eyelid

Respiratory problems
- Sore throat
- Swelling of the throat
- Cough
- Chest tightness/discomfort
- Difficulty swallowing
- Hoarseness
- Difficulty breathing
- Wheezing

Skin problems
- Swelling of a part of your face/lips/tongue (excluding the eyelid)
- Rash (redness of your skin) with itching
- Rash (redness of your skin) without itching

Other problems
- Fever (measured)
- Feverishness/Chills

6b. How would you describe the severity of these symptoms?
- Easily tolerated
- Uncomfortable, but didn't require missing work or consulting a health care provider
- Severe enough to miss work or to have to miss work, if work was scheduled during this period
- Severe enough to require consulting a physician or a nurse
- Severe enough to miss work and to require a medical consultation

6c. How long after the vaccination did these symptoms first appear?
_____ minutes or _____ hours

6d. How long did these symptoms last?
_____ minutes or _____ hours or _____ days  They are still present

6e. Do you think that these symptoms are related to the vaccine?
- No
- Yes
- Don’t know
7a. If «yes» is given to question 7, these questions will appear.

Please check all areas where you felt unusual sensations (numbness, tingling, prickling, decreased sensation or burning sensation)

- Upper limbs vaccinated side
- Upper limbs unvaccinated side
- Lower limbs vaccinated side
- Lower limbs unvaccinated side
- Trunk or back
- Face
- Scalp or ears
- Neck

7b. How would you describe the severity of these symptoms?
- Easily tolerated
- Uncomfortable, but didn't require missing work or consulting a health care provider
- Severe enough to miss work or to have to miss work, if work was scheduled during this period
- Severe enough to require consulting a physician or a nurse for this problem
- Severe enough to miss work and require a medical consultation for this problem

7c. How long after the vaccination did these symptoms first appear?

________ minutes or ________ hours

7d. How long did these symptoms last?

________ minutes or ________ hours ________ days or They are still present

7e. Do you think these symptoms are related to the vaccine?
- No
- Yes
- Don't know

8a. If «yes» is given to question 8 (local reaction) these questions will appear.

You declared having experienced a local reaction severe enough to limit you in your regular activities in the 7 day period following the vaccination. How would you describe this local reaction? Please check all symptoms that occurred in the 7 days following the vaccination.

- Redness at the site of the injection
- Pain at the site of the injection
- Swelling at the site of the injection
- Specify (select from the drop down menu)
  - Small (smaller than an Oreo cookie)
  - medium (bigger than an oreo cookie but don’t involved the arm up to the joints)
  - Large (involved the arm up to the joints)
  - Very Large (went beyond the joints)

8b. How would you describe the severity of these symptoms?
- Easily tolerated
- Uncomfortable, but didn't require missing work or consulting a health care provider
- Severe enough to miss work or to have to miss work, if work was scheduled during this period
- Severe enough to require consulting a physician or a nurse
- Severe enough to miss work and to require a medical consultation
8c. How long after the vaccination did these symptoms first appear?

_________days

8d. How long did these symptoms last?

_________days They are still present

9a. If «yes» is given to question 9, these questions will appear.

You declared having symptoms that were severe enough to limit you in your daily activities. Please check all symptoms occurred in the 28 days following the vaccination.

- Fever, feverishness, chills
- Feeling unwell/fatigue/generalized muscular and/or joint pain
- Respiratory infection (cold, flu, pharyngitis, tonsillitis, sinusitis, bronchitis, pneumonia)
- Gastrointestinal problem (nausea and/or vomiting and/or diarrhea)
- Allergic reaction and/or allergic like reaction (rash/urticaria)
- Other, please specify: __________________________ __________________________

9b. How would you describe the severity of these symptoms?

- Easily tolerated
- Uncomfortable, but didn't require missing work or consulting a health care provider
- Severe enough to miss work or to have to miss work, if work was scheduled during this period
- Severe enough to require consulting a physician or a nurse
- Severe enough to miss work and require a medical consultation

9c. How long after the vaccination did these symptoms first appear?

_________ minutes or ________ hours or ________ days

9d. How long did these symptoms last?

_________ minutes or ________ hours or ________ days They are still present

9e. Do you think that these symptoms are related to the vaccine?

- No
- Yes
- Don’t know

At the end this message will appear: Thanks for your help with this surveillance project. You will receive the third survey in about two weeks before the 2012-2013 vaccination campaign. If you have answered that you have missed work and/or required a medical consultation and or have experienced numbness in you body a research nurse will contact you within 48 hours to collect more information about your health problem. (We will use the phone number given in the consent form.)
# Appendix 3
## POST-VACCINATION ADVERSE EVENTS REPORT

### Demographic data

<table>
<thead>
<tr>
<th>Identification #: [_____________]</th>
</tr>
</thead>
</table>

| 1. Initial (first)                  | [_____________] |
| 2. Initial (last)                  | [_____________] |
| 3. Date of birth (MMM/YY)          | [_____/_____/_____] |
| 4. Sex                             | □ Male □ Female |

### Vaccination history

| 6. Vaccination date (DD/MMM/YY)    | [_____/_____/_____] |
| 7. Vaccination site                | □ Left arm □ Other, specify: |
|                                   | □ Right arm [_____________] |
|                                   | □ Don’t know |
| 8. Have you been vaccinated against the seasonal flu in the past? | □ Yes □ No |
| 8.1. If yes, have you already had adverse events following a vaccination? | □ Yes □ No |
| 8.2. Please describe this adverse event: |
|                                         |
|                                         |
|                                         |

| 9. Have you been vaccinated against Influenza A (H1N1) in 2009? | □ Yes □ No |
| 9.1. If yes, have you already had adverse events following a vaccination? | □ Yes □ No |
| 9.2. Please describe this adverse event: |
|                                         |
|                                         |
|                                         |

### Reason(s) for report

| 10. □ Absence from work (or had to miss work, if work was scheduled during this period) Number of days: [_____] |
| □ Medical consultation |
| □ Numbness decreased sensation or burning sensation anywhere in your body |

<p>| 11. If there are several reasons for the report, are they for the same event? | □ Yes □ No |
| 12. Worsening of a previous medical condition? | □ Yes □ No |</p>
<table>
<thead>
<tr>
<th>Description of the event (symptoms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13. Date of symptoms appeared (DD/MMM/YY)</td>
</tr>
<tr>
<td>14. Amount of time between vaccination and first appearance of symptoms</td>
</tr>
<tr>
<td>15. Please describe the event:</td>
</tr>
<tr>
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<td></td>
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<tr>
<td></td>
</tr>
</tbody>
</table>
### Medical consultation

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Don’t know</th>
</tr>
</thead>
<tbody>
<tr>
<td>16. Medical consultation?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17. Type of medical consultation?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18. Diagnosis?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.1 If yes, specify diagnosis:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.2 Treatment received?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.2.1 If yes, specify:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19. Hospitalization?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19.1 If yes, Admission date (YY/MMM/DD):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19.1 If yes, Discharge date (YY/MMM/DD):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19.2 Admitted to intensive care unit?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19.2.1 Length of stay:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20. Total length of the episode?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21. Symptoms still present?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22. Outcome:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Hospitalization due to health problem

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Don’t know</th>
</tr>
</thead>
<tbody>
<tr>
<td>19. Hospitalization?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19.1 If yes, Admission date (YY/MMM/DD):</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>19.1 If yes, Discharge date (YY/MMM/DD):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19.2 Admitted to intensive care unit?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19.2.1 Length of stay:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Progression of clinical features at time of phone interview

<table>
<thead>
<tr>
<th>Question</th>
<th>[_____]</th>
<th>Days</th>
<th>Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>20. Total length of the episode?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21. Symptoms still present?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Severity of case

<table>
<thead>
<tr>
<th>Severity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slight</td>
<td>Easily tolerated</td>
</tr>
<tr>
<td>Moderate</td>
<td>Bad enough to limit you in your regular activities</td>
</tr>
<tr>
<td>Severe</td>
<td>Bad enough to prevent you from going about your regular activities</td>
</tr>
</tbody>
</table>

### Follow-up call authorization

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>If needed, can a nurse call you to do a follow-up?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis (to be completed by nurse after the phone interview)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Local reactions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Pain, heat, redness, drowsiness, induration, etc.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Systemic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Fever and/or poor general condition (myalgia, fatigue, headache, etc.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Insomnia/sleep disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Allergies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Severe allergic reaction (anaphylaxis/bronchospasm/difficulty breathing)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Moderate allergic reaction (itchiness/rash/swelling)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardio-respiratory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Acute respiratory infection (otitis, cold, flu, sore throat, tonsillitis, laryngitis, sinusitis, etc.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Respiratory infection (pneumonia, bronchitis, etc.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Asthma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Cardiac problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gastro-intestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Gastroenteritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Other digestive problems (diverticulitis, Crohn’s disease, intestinal subocclusion, etc.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Traumatic musculoskeletal problem (sprain, fracture, etc.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Non-traumatic musculoskeletal problem (arthritis, myalgia, etc.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neurological</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Paresthesia/numbness/tingling</td>
<td></td>
<td></td>
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<tr>
<td>□ Gynecological problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Cancer of pre-cancerous cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Zona</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Hyper/hypotension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Psychological problems (depression, anxiety, etc.)</td>
<td></td>
<td></td>
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<tr>
<td>□ Urinary infection</td>
<td></td>
<td></td>
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<tr>
<td>□ Food poisoning</td>
<td></td>
<td></td>
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<tr>
<td>□ Surgery</td>
<td></td>
<td></td>
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<tr>
<td>□ Eye/ear problem</td>
<td></td>
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<tr>
<td>□ Skin problem (that is not an allergic reaction)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Other, specify: [________________________________________]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Completed by**

<table>
<thead>
<tr>
<th>Last Name, First Name:</th>
<th>[__________________________]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phone number:</td>
<td>[<strong><strong>] [</strong></strong>]-[<strong><strong>][ext:</strong></strong>]</td>
</tr>
<tr>
<td>Profession:</td>
<td>□ Nurse □ Doctor □ Other, specify: [__________________________]</td>
</tr>
</tbody>
</table>

**Interview date**

(YY/MMM/DD): [________/________/________]

**Signature**
Appendix 4

Email presenting the results of the surveillance in the previous two years and requesting participation as controls for 2011

(to be sent in August or September 2011)

Over the past two years, the surveillance of influenza vaccine adverse events in which you participated with thousands of other health workers across Canada, allowed us to gather essential data on the safety of vaccines against influenza. Thanks for your participation. Please find below a summary of the results of these past two years.

(Document of the result will be insert here see Appendix 5)

During these two years, the surveillance has only been collecting data about the frequency of health problems occurring after the vaccine. However, this does not represent the risk of adverse event attributable to the vaccine. At any time of the year, people become sick with different diseases at a frequency that we call the “background rate”. After a vaccine, some health problems happen as part of the background rate and only the excess above that rate is attributable to the vaccine. The background rate has to be estimated in individuals that have not been recently vaccinated (control participants). We solicit your participation to help us estimate this background rate. If you agree to participate as a control, you will receive a short electronic questionnaire collecting information about new health problems which have resulted in missed work days and/or physician consultation during a 7 day period shortly before the beginning of the 2011 influenza vaccination period. If such a problem is reported, you will be contacted by the research team to enquire about signs and symptoms of the health problem. Your participation as a control does not preclude your vaccination in 2011. In fact we encourage you to be vaccinated in 2011 and to also participate to the surveillance after vaccination

Your decision to take part in this active surveillance project is entirely voluntary (your choice). There is no direct benefit from participating in this surveillance, but the information that will be collected might contribute to a better understanding of the influenza vaccine's safety.

The research staff will keep all your information confidential, unless release is required by law. Only study staff at this site will have access to your study record which contains information that directly identifies you. To maintain confidentiality, a code number will be assigned to the study information. Your anonymized, but coded, record may be reviewed by representatives from the Mount Sinai Hospital Research Ethics Board, the regulatory authorities in Canada such as Health Canada or the Canadian Institutes of Health Research for audit purpose. Any study information leaving this site will not include information that directly identifies you. Anonymized data that contain no information that could identify you personally may be used publicly, such as for research and teaching purposes.

If you choose to participate in this surveillance project, you can also stop at any time. Should you have any questions regarding your rights as a study participant, you can contact Ronald Heslegrave, PhD, Chair of the Mount Sinai Hospital Research Ethics Board (REB) or the Research Ethics office at (416) 586-4875. If you have any questions regarding this project, you can call Dr. Brenda Coleman at 416-586-4538 or Dr Allison McGeer, at 416-586-3118.

If you agree to participate, click the link below to access to the survey:

<<Insert the link here>>

Thank you for your participation.
Appendix 5
Survey for controls

1. Please indicate your gender.
   ☐ Female
   ☐ Male

2. How old are you? __________ years

3. What is your occupation at the hospital? Select from the dropdown menu
   ☐ Physician
   ☐ Nurse/assistant nurse
   ☐ Patient care assistant (PCA)
   ☐ Medical Technician (Laboratory, medical imagery, etc…)
   ☐ Other health professional or technician (pharmacist, psychologist, occupational, physical or respiratory therapist, dietician, social worker, etc.)
   ☐ Housekeeping, logistics and food service
   ☐ Administrative, secretary, office work
   ☐ Other, specify: __________

4. Have you been vaccinated against pandemic A/H1N1 influenza in 2009?
   ☐ No
   ☐ Yes

5. In the last 3 years, how many times have you been vaccinated against seasonal influenza ?
   ☐ 0
   ☐ 1
   ☐ 2
   ☐ 3

In the last week (past 7 days) have you experienced the onset of:

6. Redness of both eyes (bilateral conjunctivitis), or swelling of your face/eyelids/lips or tongue, or a hoarse voice, or chest tightness/discomfort?
   No
   Yes

7. Numbness, tingling, pins and needles, decreased sensation or burning sensation anywhere in your body that lasted more than 24 hours?
   No
   Yes

8. Any other symptom severe enough to limit you in your normal daily activities?
   No
   Yes

If the participant answered « no » to questions 6 to 8, the questionnaire ends and this message will appear: Thanks for your help with this surveillance project.

If the participant answered « yes » to one questions, other windows (with questions related to the question answered yes ) will appear:
6a. If «yes» is given to question 6, the following questions will appear.

You mentioned having experienced redness of both eyes (bilateral conjunctivitis), or swelling of your face/eyelids/lips or tongue, or a hoarse voice, or chest tightness/discomfort. Please check all symptoms you experienced.

**Ocular problems**
- Redness of both eyes
- Tearing or eye discharge
- Painful eyes
- Swelling of the eyelid
- Itchy eyes

**Respiratory problems**
- Sore throat
- Swelling of the tongue
- Swelling of the throat
- Difficulty swallowing
- Cough
- Hoarseness
- Chest tightness/discomfort
- Difficulty breathing
- Wheezing

**Skin problems**
- Swelling of a part of your face/lips/tongue (excluding the eyelid)
- Rash (redness of your skin) with itching
- Rash (redness of your skin) without itching

**Other problems**
- Fever (measured)
- Feverishness/Chills

6b. How would you describe the severity of these symptoms?
- Easily tolerated
- Uncomfortable, but didn’t require missing work or consulting a health care provider
- Severe enough to miss work or to have to miss work, if work was scheduled during this period
- Severe enough to require consulting a physician or a nurse
- Severe enough to miss work and to require a medical consultation

6c. Which day of the week did this problem appear? Select from the drop down menu
- Monday
- Tuesday
- Wednesday
- Thursday
- Friday
- Saturday
- Sunday

6d. How long did these symptoms last?
7a. If « yes » is given to question 7, these questions will appear.

Please check all areas where you felt unusual sensations (numbness, tingling, prickling, decreased sensation or burning sensation) in the last week

- Upper limbs
- Lower limbs
- Trunk or back
- Face
- Scalp or ears
- Neck

7b. How would you describe the severity of these symptoms?
   - Easily tolerated
   - Uncomfortable, but didn't require missing work or consulting a health care provider
   - Severe enough to miss work or to have to miss work, if work was scheduled during this period
   - Severe enough to require consulting a physician or a nurse
   - Severe enough to miss work and to require a medical consultation

7c. Which day of the week did this problem appear? Select from the drop down menu
   - Monday
   - Tuesday
   - Wednesday
   - Thursday
   - Friday
   - Saturday
   - Sunday

7d. How long did these symptoms last?

   _______ hours or _______ days or They are still present

8a. If « yes » is given to question 8, these questions will appear.

You declared having symptoms that were severe enough to limit you in your daily activities. Please check all symptoms occurred in the last 7 days.

   Fever, feverishness, chills
   Feeling unwell/fatigue/generalized muscular and/or joint pain
   Respiratory infection (cold, flu, pharyngitis, tonsillitis, sinusitis, bronchitis, pneumonia)
   Gastrointestinal problem (nausea and/or vomiting and/or diarrhea)
   Allergic reaction and/or allergic like reaction (rash/urticaria)
   Other, please specify: __________________________________________________________

8b. How would you describe the severity of these symptoms?
   - Easily tolerated
   - Uncomfortable, but didn't require missing work or consulting a health care provider
   - Severe enough to miss work or to have to miss work, if work was scheduled during this period
   - Severe enough to require consulting a physician or a nurse
   - Severe enough to miss work and to require a medical consultation
8c. How long did these symptoms last?

_____ minutes or _____ hours or _____ days or They are still present

Thanks for your help with this surveillance project. If you have answered that you have missed work and/or required a medical consultation and/or have experienced numbness in your body in the last seven days, a research nurse will contact you within 48 hours to collect more information about your health problem. (We will use the phone number given in the consent form.)
Appendix 6
Active Electronic Surveillance of a Large Number of Healthcare Workers Following the Administration of Influenza Vaccines in 2009 and 2010

INTRODUCTION

Influenza vaccine is modified annually to match the circulating virus. While the safety profile of the influenza vaccine is generally good, unexpected adverse events may occur. Health care workers (HCW) are vaccinated annually to ensure their personal protection and indirectly protect their patients from acquiring influenza. Given their commitment, the monitoring of the safety of the influenza vaccine in HCW is important.

Over the past two years, several thousands of HCW participated to a web-based active surveillance after being administered the pandemic vaccine (in 2009) or the seasonal vaccine (in 2010). In 2009, the surveillance included 3 hospitals whereas, in 2010, 7 sites did. This summarizes the results of this surveillance during the two years.

METHODS

During the pandemic vaccination campaigns in 2009 and the seasonal vaccination period in fall 2010, all HCW receiving the influenza vaccine and working in one of the participating sites were invited to be part of the study. After signing a short inform consent form, HCW had to provide their email address and to complete short electronic surveys. The main outcomes were the occurrence of any new health problem or the exacerbation of an existing condition that were severe enough to cause work absenteeism (WA) or to require medical consultation (MC). These outcomes were assessed for the first week (day 8 survey) or for four weeks (day 29 survey) after vaccination. In 2009, a third survey monitored the presence of serious adverse events (SAE) occurring 1 to 6 months after the pandemic vaccine.

RESULTS

In 2009, among the 6242 participants, about two-thirds responded to the surveys compared to three quarters of the 7467 participants in 2010 (see Table below). In 2009, 440 (7%) reported one of the following main outcomes: 55% reported work absenteeism, 20% required a medical consultation, and 26% had both absenteeism and medical consultation. Approximately 1 vaccine out of 200 presented with local reactions to the pandemic vaccine significant enough to cause work absenteeism and medical consultation. Systemic symptoms (eg. fever, fatigue, malaise) were also frequent. Four HCW reported allergic-like reactions with onset within 24 hours after vaccination: one had anaphylaxis and was sent to the emergency room, one had mouth/throat swelling and two had urticaria. Five (~1/1250) reported numbness and/or prickling sensations within 7 days after vaccination.

At 6 months, among the 3064 (63%) who responded, 35 had a SAE (hospitalization, life-threatening event, invalidity or stillborn/congenital anomalies in a child) that occurred between 1 and 6 month post vaccination. Apart from a few infections, all diagnoses were different suggesting no cluster of SAE associated with the vaccine.

CONCLUSION

As no unexpected AE was reported, this active surveillance seems to confirm the safety of the influenza vaccine. The pandemic vaccine was associated with more adverse events than the 2010-2011 seasonal vaccine. Active surveillance of adverse events in HCW should be part of the annual evaluation of the safety of the influenza vaccine.

At any time of the year, people become sick with different diseases at a frequency called the “background rate”. After a vaccine, some health problems happen as part of the background rate and only the excess above that rate is attributable to the vaccine. The most important improvement needed for the current surveillance is the addition of a control group to estimate that background rate and then derive the risks really attributable to the vaccine.
References