INVESTIGATING THE ASSOCIATION OF RECEIPT OF SEASONAL INFLUENZA VACCINE WITH OCCURRENCE OF ANESTHESIA/PARESTHESIA, HEADACHES AND GENERALIZED CONVULSIVE SEIZURES FOR ALL AGES, CANADA 2012/13-2016/17

by

May Ahmed

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The following individuals certify that they have read, and recommend to the Faculty of Graduate and Postdoctoral Studies for acceptance, a thesis entitled:

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Examining Committee:

Dr. Julie Bettinger

Supervisor

Dr. Monika Naus

Supervisory Committee Member

Dr. Joel Singer

Supervisory Committee Member

Dr. Jane Buxton

Additional Examiner

Abstract

Introduction/background: Concern about adverse events following immunization (AEFI) is frequently cited by both those who receive vaccines and those who decline to receive vaccines. Neurological adverse events are especially concerning. Our aim is to detect associations for occurrence of anesthesia/paresthesia (numbness, tingling, pins and needles, decreased sensation, or burning sensations anywhere in the body), severe headaches, and generalized convulsive seizures (GCS) in the presence and absence of seasonal influenza vaccination.

Methods: Data were analyzed from the Canadian National Vaccine Safety Network that annually collects safety data during the seasonal influenza vaccination campaign. Events were self-reported and prevented daily activity, led to absenteeism, or required medical attention. Controls were previous year vaccinees; events in controls were collected prior to the start of influenza vaccination each year. Total sample size for investigating anesthesia/paresthesia was 107,565 from 2012-2016, and 97,420 for investigating severe headaches and GCS from 2013-2016. Multivariable logistic regression was used to determine the association between seasonal influenza vaccination and occurrence of anesthesia/paresthesia or severe headaches adjusted for gender, age group, reporting center, and year. Fisher's exact test was used to measure risk of occurrence of GCS.

Results: 104 (0.10%) participants reported anesthesia/paresthesia; 63 (0.09%) versus 41 (0.11%) in vaccinees and controls, respectively. Severe headaches were reported by 1,361 (1.40%) participants; 907 (1.48%) versus 454 (1.26%) in vaccinees and controls, respectively. Adjusted OR of anesthesia/paresthesia among those with seasonal influenza vaccination was 0.89 (95% CI = 0.60, 1.32), and of severe headaches was 1.21 (95% CI = 1.08, 1.36). No specific vaccine product was associated with this increased risk. Three participants were identified with GCS; difference in proportions between groups was not statistically significant ($p = 0.301$).

Conclusions: Results are reassuring on the safety of seasonal influenza vaccines. Anesthesia/paresthesia was rare (≥ 0.01 and < 0.1%), while severe headaches were common (≥ 1% and < 10%), and GCS was a very rare (< 0.01%) AEFI. No associations were found for anesthesia/paresthesia and GCS. There was a higher risk of severe headaches that merits counseling at the time of vaccination. Ongoing monitoring is crucial to maintaining confidence in seasonal influenza vaccination safety.

Lay Summary

This research looked at three potential side effects from the flu shot using five years of data from five provinces across Canada. We did not find numbness, tingling, pins and needles, decreased sensation, or burning sensations linked to the flu shot, but we did find differences in how it was described compared to people who did not get the flu shot and had the same complaint. We found a higher possibility of getting severe headaches if a person took the flu shot than if someone did not, which is expected from knowing how the vaccine works. Finally, we did not see a relationship between the flu shot and seizures. Overall, the safety of the flu shot is reassuring, but it is still important to keep monitoring these side effects and continuously share results.

Preface

This thesis was completed based on data from the Canadian National Vaccine Safety (CANVAS) Network. Under the guidance of my supervisor, Dr. Julie Bettinger, and my committee members, Dr. Monika Naus and Dr. Joel Singer, I was responsible for planning this project, conducting the literature review, contributing to the methodologies, carrying out all statistical analyses, and interpreting findings.

Other investigators and participating sites involved in the CANVAS Network:

- Louis Valiquette, Centre Hospitalier Universitaire de Sherbrooke
- Otto Vanderkooi, Alberta Children's Hospital, University of Calgary
- Brenda Coleman, Mount Sinai Hospital
- Gaston De Serres, Centre Hospitalier Universitaire de Québec
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- Anne McCarthy, Ottawa Hospital General Campus

The study had REB approval from Children's & Women's Health Centre of British Columbia (REB # H10-02274) and at each participating site.

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List of Abbreviations

AE	Adverse event
AEFI	Adverse event following immunization
CAEFISS	Canadian Adverse Events Following Immunization Surveillance Systems
CANVAS	Canadian National Vaccine Safety
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COSTART	Coding Symbols for a Thesaurus of Adverse Reaction Terms
DTaP	Diphtheria, tetanus, and acellular pertussis
FASTMum	Follow-up and Active Surveillance of Trivalent influenza vaccine in Mums
FDA	Food and Drug Administration
FS	Febrile seizures
GBS	Guillain-Barré syndrome
GCS	Generalized convulsive seizures
GMP	Good Manufacturing Practice
HARTS	Hoechst Adverse Reaction Terminology System
HC	Health Canada
HCW	Healthcare worker
ICD-9	International Classification of Diseases Ninth Revision
ICD9-CM	Clinical Modification of ICD-9
ID	Intradermal
IIS	Immunization information system
IIV	Inactivated influenza vaccine
IM	Intramuscular
Imm/ARI	Immunization and Adverse Reaction to Immunization
IMPACT	Canadian Immunization Monitoring Program ACTive
IN	Intranasal
IOM	Institute of Medicine
J-ART	Japanese Adverse Reaction Terminology

LAIV	Live attenuated influenza vaccine
LRT	Likelihood ratio test
MAH	Market Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MIMS	Manitoba Immunization Monitoring System
MMR	Measles, mumps, and rubella
OR	Odds ratio
OTC	Over-the-counter
P/T	Provincial or territorial
PAEDS	Paediatric Active Enhanced Disease Surveillance
PCV13	Pneumococcal Conjugate Vaccine (13-valent)
PHAC	Public Health Agency of Canada
PRISM	Post-Licensure Rapid Immunization Safety Monitoring
QIV	Quadrivalent inactivated vaccine
RCT	Randomized controlled trial
RR	Relative risk
SIMS	Saskatchewan Immunization Management System
TIV	Trivalent inactivated vaccine
VAERS	Vaccine Adverse Events Reporting Systems
VAESCO	Vaccine Adverse Event Surveillance and Communication Network
VIF	Variance inflation factor
VSD	Vaccine Safety Datalink
WHO	World Health Organization
WHO-ART	WHO's Adverse Reaction Terminology

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To my Egyptian parents, Hala & Mohamed

And my Canadian parents, Erika & Bob

Chapter 1: Introduction

1.1 Vaccines and vaccine safety

Vaccination is the most widely used and effective method for infectious disease prevention (1). The active ingredients in vaccines are biological in nature, namely, the antigen of a pathogenic microorganism. Vaccines are formulated to stimulate the body's immune response to later encounter that specific pathogen, without causing the disease (2). Additional ingredients can be included such as stabilizers to maintain vaccine effectiveness during storage (e.g. cow or pig gelatin), adjuvants to enhance the immune response (e.g. aluminum salts), preservatives to prevent contamination of multi-dose vials (e.g. thimerosal), or antibiotics to prevent bacterial contamination of tissue cultures during manufacturing (e.g. neomycin) (3). Despite the advancements, impact, and widespread use of vaccines, like any pharmaceutical intervention, they are not completely safe and have a potential to cause adverse events following immunization (AEFI) (4).

The Council for International Organizations of Medical Sciences (CIOMS)/World Health Organization (WHO) Working Group on Vaccine Pharmacovigilance provided a general definition for an AEFI as "*any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease* (5)". Frequencies and severity of AEFIs have resulted in their categorization according to their occurrence among individuals vaccinated into: very common (≥10%), common (≥1% and < 10%), uncommon (≥ 0.1% and < 1%), rare (≥ 0.01% and < 0.1%), and very rare (< 0.01%) AEFIs (6).

Over time, while incidence of vaccine-preventable diseases has decreased, anxiety about vaccine safety has risen (7,8). The tolerance for AEFIs is low because vaccines are administered primarily to young, healthy children. Additionally, vaccines are used in mass programs and are given to a large proportion of the population. Also, the fact that people may perceive that vaccines are mandated in some settings such as day care, schools, or in healthcare settings adds to the low tolerance for AEFIs, since people in these settings may not have a choice about vaccination (4).

Proper evaluation of vaccines is necessary to ensure that the benefit of vaccination outweighs risk. In this regard, vaccines are subjected to the highest forms of regulatory safety standards for approval as well as post-marketing safety surveillance. These standards have evolved over the past century based on existing AEFI incidents (9) as well as the impact of fraudulent evidence of associations between vaccines and unrelated events (10). Risk-benefit assessment is a cornerstone in the vaccine life cycle – during development, manufacturing, regulatory approval, and after the vaccine is on the market. An important component of the vaccine risk-benefit analysis is ongoing vaccine pharmacovigilance.

1.2 Vaccine regulation and pharmacovigilance

Vaccine pharmacovigilance is "*the science and activities relating to the detection, assessment, understanding and communication of adverse events following immunization and other vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization*." Its goal is to detect and respond to AEFIs in a timely manner to decrease negative health effects and to minimize any negative impact on vaccinating the population (5). Pharmacovigilance is an ongoing process throughout all phases of the vaccine life cycle (11,12).

1.2.1 Vaccine development

After a disease is targeted for vaccination based on studies determining disease burden and prioritization, extensive non-clinical research concerning the pathogen takes place. The specific antigen and type of immune response are studied first in laboratory and animal settings. If the product formulation works, and is deemed safe, researchers and manufacturers can conduct pre-licensure trials on human subjects (13).

Pre-licensure trials (or clinical trials) are composed of 3 consecutive phases. If the vaccine is poorly tolerated at any stage, further testing may not be done. Phase I is focused solely on safety. Only a small number of healthy adult volunteers are enrolled with numbers as low as 10 individuals. This phase provides preliminary data on the vaccine's tolerability and safety for local and systemic reactions. Based on the small number of participants, the type of adverse

event (AE) detected would generally be common. Phase II is composed of a larger group with hundreds of volunteers. This stage provides a better understanding of the safety profile and defines the dosing requirements. If the vaccine is proven safe during Phase II trials, Phase III, typically double-blinded randomized controlled trials (RCTs), are conducted where there is a definitive demonstration of safety, immunogenicity, and efficacy in a larger study sample – up to thousands of participants (14).

1.2.2 Vaccine approval and licensure

After the vaccine has passed the above stages of vaccine development with sufficient evidence regarding efficacy and safety, it is further assessed to meet licensing standards. The national regulatory authority that approves the vaccine must work independently from manufacturers and has authoritative power. It examines results of pre-licensure clinical trials including how safe the vaccine was based upon the documented AEs, and it provides its own assessment of the evidence. The national regulatory authority also inspects manufacturing facilities and reviews vaccine lots to ensure quality and consistency (15).

In Canada, the Biologics and Genetic Therapies Directorate, under Health Canada (HC), is the federal authority responsible for regulating biological drugs and vaccines. It also determines whether the benefits of the vaccine outweigh its risks and if the risks can be reduced (16). Guidelines on Good Manufacturing Practices (GMPs) apply to vaccine manufacturers to demonstrate process validation – where manufacturing procedures, tests, equipment, and systems perform as intended and produce expected and consistent results (17). Good Manufacturing Practices pertaining to the Food and Drug Act and Regulations are inspected by HC's Health Products and Food Branch Inspectorate. This inspection can take place any time during the vaccine life cycle.

Further, a Lot Review Program in the Biologics and Genetic Therapies Directorate ensures manufacturing consistency where lot-to-lot specifications must comply with those defined when conducting clinical trials before sale in the Canadian market. With every batch, manufacturers are required to test and document safety, purity, and potency profiles. HC monitors results of manufacturers lot testing and can carry out their own testing with more focus on final product monitoring. Results from HC are communicated back to manufacturers (18,19).

1.2.3 Post-marketing vaccine safety monitoring

Phases of vaccine development are within meticulous experimental context, with great care of product supply and storage. These conditions are different from real-world settings. Also, the number of participants in these phases is minute compared to the actual numbers of people exposed to the vaccine after approval. Therefore, regulatory agencies recommend post-licensure safety monitoring for rare AEs (or Phase IV clinical trials). The vaccine product's package insert and monograph include all vaccine safety information and report the frequency of any identified AEFI. Any AEFI not mentioned in the product monograph would be considered an "unexpected AEFI" (16). When unexpected AEFIs are detected, they can trigger a "signal". A signal must be based on information from one or more sources that suggests an association between the vaccine and an event that is new, important, and not previously refuted. This signal demands investigation and, if necessary, remedial action (20).

Evidence of the usefulness of post-marketing vaccine safety surveillance has been demonstrated by identification of a variety of unexpected and rare AEs. For example, a signal of intussusceptions (where part of the intestines prolapses into itself) following a rotavirus vaccine was detected in the United States in 1999 (21,22). Vasovagal syncope with Quadrivalent Human Papillomavirus Recombinant Vaccine, thrombocytopenia (decreased platelet counts) with MMR and other vaccines, and Guillain–Barré syndrome (GBS; a rare condition in which a person's immune system attacks its own peripheral nerves) with A/New Jersey influenza vaccination have also been identified following vaccination through post-marketing surveillance (23–25).

Reporting of AEFIs to national regulatory authorities is mandated for market authorization holders (MAH). In Canada, under the Food and Drug Regulations, MAHs must report AEFIs that occur nationally and internationally through the Canada Vigilance Program (26). MAHs dispatch an annual summary of safety reports along with adverse reaction reports, issue-specific safety reports, and risk management plans to HC's Market Health Products Directorate. The Market Health Products Directorate then conducts risk-benefit analyses and communicates the risks. Health's Canada Health Products and Food Branch Inspectorate continues to perform regular inspections to assess compliance with regulations (16,27).

To achieve a comprehensive vaccine safety profile, ongoing monitoring is done through distinctive post-marketing surveillance systems. Each surveillance system operates differently and has its own advantages.

1.2.3.1 Passive AEFI reporting systems

This system usually relies on voluntary reporting. Here, individuals, healthcare professionals or the public, choose to report an AEFI. Although underreporting is an inherent limitation in the system, spontaneous reporting provides a cost-effective way to detect rare AEFIs in a timely manner (28,29).

The United States has a national, passive reporting system for AEs following US-licensed vaccines called the Vaccine Adverse Event Reporting System or "VAERS". The system is jointly administered by the Centers for Disease Controls and Prevention (CDC) and the US Food and Drug Administration (FDA) (30).

In Canada, healthcare is a provincial or territorial (P/T) responsibility. Therefore, the Public Health Agency of Canada (PHAC) receives reports for AEFIs from P/T public health authorities through the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS). This is the national, voluntary, passive reporting system with reports generated by nurses, physicians, or pharmacists who report to local public health units who then report to P/T public health authorities (31). CAEIFSS differs from VAERS in that consumers (i.e. non-health care professionals) are unable to report into the system (30,32).

On an international level, the WHO Programme for International Drug Monitoring monitors and analyses spontaneous AEFIs from national centers. Currently, the Programme for International Drug Monitoring consists of 131 members (or countries) (33). The member's national pharmacovigilance center submits individual case safety reports to the largest WHO global database called "VigiBase" (34). Administration of the Programme for International Drug Monitoring is the joint responsibility of the WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre, and the WHO Headquarters (35). The program also contains reports of AEs from drugs and traditional medicines (36).

1.2.3.2 Active AEFI reporting systems

Active surveillance systems aim to monitor vaccination AEs in a defined population or health center (37). In this system, it is possible to "actively" query existing information in a timely manner (38) with the advantage of ensuring high case ascertainment (39).

1.2.3.2.1 Population-based active surveillance

This often occurs by data linkage where large administrative databases are used (40). Multiple initiatives to link databases have been put into place for timely detection, higher validation, and earlier management of AEFIs (41). These systems usually have both numerator and a denominator data, which allows calculation of rates. Limitations of data linkage include the need for analytic resources as well as legislative and privacy barriers (42).

The United States developed the Vaccine Safety Datalink (VSD) database that links vaccination data to health outcomes (e.g. outpatient clinics, hospital admissions, emergency room presentations) and demographic data to test hypotheses regarding vaccine-related AEs and to identify safety signals using a specialized type of statistical analyses (rapid cycle analysis) (43,44). Moreover, the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) links data from national health insurance plans and immunization registries to perform distinctive epidemiological studies regarding vaccine safety due to its large population database and geographic diversity (44,45).

Europe has also developed the Vaccine Adverse Event Surveillance and Communication Network (VAESCO) project. The project links large computerized clinical databases with immunization registries and "aims to establish a European collaborative network of regulatory agencies, public health institutes and academia responsible and able to collect and collate information on adverse events following immunization in Europe" (46). Vaccine Adverse Event Surveillance and Communication Network conducted past epidemiological studies for associations between the 2009 H1N1 pandemic influenza vaccine with GBS (47) and narcolepsy (48).

In Canada, a pan-Canadian vaccine registry (Public Health Surveillance System (Panorama)) was also initially designed to link individual-level vaccination data with health events to monitor vaccine safety (49). Unfortunately, the registry has not been adopted by all P/Ts. Therefore, its ability to monitor vaccine safety at a national level is limited. Other

immunization information systems (IIS) exist in some jurisdictions such as Immunization and Adverse Reaction to Immunization (Imm/ARI) in Alberta, Saskatchewan Immunization Management System (SIMS), and Manitoba Immunization Monitoring System (MIMS). Some of these IISs have routine linkage with their province's AEFI surveillance system and some do not (50).

1.2.3.2.2 Hospital-based active surveillance

This system is concerned with all hospital admissions of interest. In Canada, PHAC funds an active surveillance system called the Canadian Immunization Monitoring Program ACTive (IMPACT). IMPACT, commenced in 1991, tracks pediatric admissions for active case finding of unusual events at pediatric tertiary care hospitals across Canada and establishes antecedent receipt of vaccine(s). Events are reported to local public health officials and to CAEFISS (16). A similar model was established in Australia in 2007, the Paediatric Active Enhanced Disease Surveillance (PAEDS) (39).

1.2.3.2.3 Participant-centered/based active surveillance

These systems have active contact with vaccinated individuals to monitor AEFIs. Methods to engage vaccine recipients can be diary cards for lower/middle income countries and SMS or web-based contact in high income countries. The objective of these systems can be to survey a particular population, to investigate AEFIs for specific vaccines, or to look closely for a particular event that may have arisen from a particular signal. These systems have the advantage of capturing minor events that would not be reported by passive systems. Also, collecting information directly from vaccinees renders the data more trustworthy and transparent to the public, especially when results are available for them to see (42).

In Australia, a few systems are in place. AusVaxSafety provides national real-time vaccine safety data for adults and children by actively monitoring pertussis, zoster and influenza vaccines. It is funded by the Australia Government Department of Health (51). Also in Australia, the Follow-up and Active Surveillance of Trivalent influenza vaccine in Mums (FASTMum) program initiated in 2012 involves contacting pregnant women by SMS following TIV vaccination inquiring about possible AEFI (52).

In Canada, the Canadian National Vaccine Safety Network (CANVAS) Network, launched in 2009, conducts annual, participant-centered active surveillance with the objective of

gathering and analyzing safety data online on thousands of vaccinated individuals (adults and children) to provide seasonal influenza vaccine safety information to public health authorities early in the annual influenza vaccination campaign. CANVAS augments passive surveillance for influenza vaccines by providing higher sensitivity and timeliness (53). CANVAS also recruits a control group to identify background rates for events that occur each year among unvaccinated individuals (54). Previous studies have shown that participants were willing to provide information after vaccination through the internet. Self-reported online systems were used in the 2009 H1N1 pandemic to assess the safety of the vaccines (55). A study done to assess the feasibility, acceptability, and response rate for pandemic and seasonal influenza vaccination in 2009/10 showed an online response rate of 88%, and 98.3% were willing to use the online self-report form again (56).

1.3 Standardization of adverse events following immunization (AEFIs) terminologies and case definitions

Given the variety of monitoring systems in place locally, nationally and internationally, using standardized terminologies and definitions for AEFIs allows for consistency in assessments across clinical trials and surveillance systems. This allows for meaningful assessment of data, scientific communication, comparable reporting, enhancement of vaccine quality, and vaccine safety management. A number of terminology systems have been developed to achieve this standardization.

1.3.1 Medical Dictionary for Regulatory Activities (MedDRA) terminologies

MedDRA was developed by the International Council for Harmonisation (57). The scope of the terminologies includes medical, health-related, and regulatory concepts related to medical products of human use, including vaccines. These are also used for classifying medication errors, signs and symptoms of disease, and diagnoses. The terminology is adopted for the coding of AEs by many governmental organizations and the pharmaceutical industry. It includes terms from established terminologies including the US FDA Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART©), WHO's Adverse Reaction Terminology (WHO-ART©),

International Classification of Diseases Ninth Revision (ICD-9), the Clinical Modification of ICD-9 (ICD9-CM©), Hoechst Adverse Reaction Terminology System (HARTS©), and Japanese Adverse Reaction Terminology (J-ART).

Individual case safety reports reported to the WHO VigiBase (mentioned in Section 1.2.3.1) use MedDRA coding. Also, HC, including the Canada Vigilance Program, uses MedDRA terminology to code AEFIs (58).

1.3.2 Brighton Collaboration case definitions

The Brighton Collaboration is an international partnership of scientific experts started in 2000 (59). One of its main objectives is the development of single standardization of case definitions and guidelines specific for AEFIs, although receipt of a vaccine is not a part of the definitions. Their primary purpose is not causality assessment or patient management, but provision of better global comparisons of vaccine safety data from surveillance systems, clinical trials, individual case reports, and epidemiological studies (5,60). Definitions are structured by levels of diagnostic certainty based on resource availability. Healthcare professionals, health officials, and immunization researchers are the target groups for their use. There were limited standardized definitions specific to AEFI before the Brighton Collaboration was established (60).

1.4 Seasonal influenza vaccines

1.4.1 Background on vaccine types in Canada (2012-2016)

Generally, there are two types of influenza vaccines in use in Canada: inactivated influenza vaccines (IIVs) and live attenuated influenza vaccines (LAIVs). The most common route to administer IIVs is through intramuscular (IM) injection in the deltoid muscle (upper arm) for children older than 1 year of age, adults, and the elderly, or the anterolateral aspect of the thigh (front and side of thigh) for young children under 1 year of age. LAIVs are administered intranasal (IN) by spraying the vaccine into the nostrils, for children 2 years of age and older. It cannot be given to children below 2 years of age because of the increased risk of wheezing. A third route of administration is intradermal (ID) where the influenza vaccine is

given in the skin with a micro-needle. This method has not been available in Canada since 2015 (61).

Contemporary IIVs contain split or subunit viruses. Split viruses have a disrupted lipid envelope structure of the virus, while subunit viruses are further purified (62). Formerly, a whole-virus vaccine was inactivated and used in the vaccine, but it was more reactogenic since the viral structure was more intact (63,64). LAIVs contain a live but weakened virus. The LAIV virus is cold-adapted, so can efficiently replicate in a temperature of 25ºC. Since it replicates in cooler temperatures, common and mild AEs are usually nasal (e.g. runny nose and nasal congestion). There are more contraindications for using the LAIV than the IIVs, most of which are related to compromised immune systems. Also, pregnant women, children on aspirin, and individuals with severe asthma must not receive the LAIV (65).

There are 3 types of influenza viruses affecting humans (A, B, and C), but 2 types (A and B) cause seasonal influenza epidemics and require protection through vaccination. Influenza A is divided into subtypes (H and N), and each subtype is further divided into strains (e.g. Influenza A (H1N1) and Influenza A (H3N2)). On the other hand, influenza B is divided into lineages (B/Yamagata and B/Victoria) (66). When influenza vaccines are produced to protect against 3 strains of influenza virus, they are called “trivalent vaccines”: 2 influenza A strains and 1 influenza B lineage. When the second B lineage is added, the vaccines are “quadrivalent”. Influenza vaccines available in Canada relevant to the analysis reported herein are: adjuvanted and non-adjuvanted trivalent inactivated vaccines (TIV), quadrivalent inactivated vaccines (QIV), trivalent LAIVs, and quadrivalent LAIVs. Since the 2009 HIN1 pandemic (67), the 3 strains in trivalent vaccines include 2 influenza A strains, H3N2 and H1N1, and 1 influenza B lineage viruses (Yamagata or Victoria) (68). Quadrivalent vaccines include both influenza B lineages (69).

Only one vaccine in use in Canada is adjuvanted: the MF59-adjuvanted TIV (Fluad®, Novartis). Adjuvants, as mentioned earlier (Section 1.1), are added to the vaccine to produce an enhanced immune response. This is especially important for young children, since their previous exposure to the virus or to previous influenza vaccinations is limited, and for the elderly due to age-related immunosenescence (when the immune response is naturally less efficient as a result of aging) (70,71). Since immunogenicity is improved with adjuvants, fewer vaccine doses are

required which, in turn, improves vaccine supply (72). This dose-sparing capacity of adjuvants is especially important in the face of pandemics (73). Nonetheless, it is generally uncommon to use adjuvants in influenza vaccines because most age groups have been previously exposed to influenza antigens (70) and do not require an enhanced immune response. Currently, seasonal influenza vaccines may contain the oil-in-water MF59 adjuvant which has been proven to be well-tolerated (74,75).

Some of the vaccines come in single dose vials, while some are multi-dose. Those multi-dose preparations contain minute amounts of thimerosal preservative to avoid bacterial contamination (76).

The vaccine is recommended for everyone 6 months of age and older without contraindications to the vaccine, but is particularly recommended for vulnerable high-risk groups at risk of developing complications from influenza infections including: pregnant women, immunocompromised individuals, young children, and the elderly (77).

1.4.2 Seasonal influenza vaccine safety

Influenza vaccine safety is of particular concern to public health authorities because of the vaccines' limited production lead time and their widespread use in the population in a short time period. Due to the continuous evolution of the influenza virus, each year the WHO recommends which strains should be included in the vaccine for the upcoming season (77) and the vaccines are produced very quickly thereafter. After influenza vaccines are approved by HC, mass vaccination campaigns take place.

In 1997, the committee of the European Medicines Agency adopted the Note for Guidance on Harmonisation of Requirements for Influenza Vaccines (CPMP/BWP/214/96) that included undergoing clinical trials every year before the licensure of the seasonal influenza vaccine (78). After the 2009 H1N1 pandemic, the document was withdrawn and as of the 2015/16 influenza season, clinical trials were not part of the vaccine approval process in the European Union. It was found that the level of safety and immunogenicity of the vaccine does not change significantly on an annual basis. Instead, the trials were to be replaced by enhanced post-marketing safety surveillance (79).

1.5 History of influenza vaccines and neurological manifestations

Neurological manifestations, or clinical signs and symptoms caused by nervous system injury or dysfunction (80), have been repeatedly reported as AEs following influenza vaccination. Examples of neurological manifestations include: paresis (muscle weakness) or paralysis, sensation disorders, gait disorders, reflex abnormalities, vertigo, and others. GBS cases were reported after the administration of a non-adjuvanted influenza vaccine in 1976 in New Jersey, USA, resulting in that vaccine's suspension (81). The following year, Furlow published in *The Lancet* a case series of 2 patients who sought medical attention for abnormal sensations in the vaccinated arm following influenza vaccination. Their symptoms occurred within 5 to 10 days from vaccination and persisted for 5 weeks and 2 months, respectively (82). In 1979, the first cohort study was published comparing GBS incidence by influenza vaccination status where the adult vaccinated population had a significantly elevated attack rate (24).

In later years, a different formulation of influenza vaccine (nasal) introduced in Switzerland in October 2000, resulted in reports of Bell's palsy and led to the vaccine's discontinuation. Later, it was shown that there was a "strong case for a causal connection" as those who received the vaccine were at 19 times higher risk to develop Bell's Palsy than those who were not exposed to the vaccine (83–85).

In 2006, a report discussed 3 cases of rapidly progressive chronic inflammatory demyelinating polyneuropathy, a disease closely related to GBS, post-influenza vaccination (86). Additionally, single reports and smaller studies assessed AEFIs of multiple sclerosis and other demyelinating conditions, such as optic neuritis (87–89), all of which led to hypotheses generation. Yet, due to the lack of a control group, there were no firm conclusions regarding associations.

After administration of a 2009 H1N1 pandemic influenza vaccine, unexpected narcolepsy cases were reported in Sweden, Finland, France, Norway, and Portugal. This novel monovalent pandemic vaccine, Pandemrix® (GlaxoSmithKline, Middlesex, UK), was administered to approximately 30 million people in Europe (90,91). Here, the strength of the association has led to recent studies that further investigated the existence of a causal relationship (92). Pandemrix®

was also highly associated with Bell's palsy (93), with previous reports that had also linked the vaccine to the neuro-immunological event (83,84).

A study published in 2013, using data from the American and European pharmacovigilance surveillance systems, showed that acute disseminated encephalomyelitis, an immune-mediated inflammatory disorder of the central nervous system, was most frequently associated with the seasonal influenza vaccine (94). Data on vaccine coverage exclusive to the United States, retrieved from the VAERS database and from the CDC website, demonstrated the mean incidence of acute disseminated encephalomyelitis after vaccination against influenza was estimated to be 0.05 cases per million influenza vaccine doses without major variations among seasons, with higher incidence after the H1N1 vaccine in 2009 at 0.15 cases per million vaccine doses (95).

The Institute of Medicine's (IOM), now called the National Academy of Medicine, Immunization Safety Review Committee reviews evidence from AEFI studies and reaches conclusions on causality. These conclusions are based on three assessments: weight of epidemiological evidence, weight of mechanistic evidence, and overall causality assessment − when the combination of epidemiological and mechanistic evidence suggests a more definitive assessment on causation. The four categories of causation evidence are: convincingly support a causal relationship, favors acceptance of a causal relationship, inadequate to accept or reject a causal relationship, and favors rejection of a causal relationship.

Based on the evidence on possible causal associations between influenza vaccination and AEs, the IOM concluded that data were inadequate to accept or reject a causal relationship between influenza vaccines and multiple sclerosis, chronic inflammatory demyelinating polyneuropathy, GBS (after 1976), optic neuritis, and demyelinating neurological disorders (96,97). Also, a recent Cochrane systemic review included comparative non-randomized studies for associations between influenza vaccines and serious AEs (i.e. events that could have resulted in deaths, life-threatening events, hospitalizations or prolongations of hospitalization, and persistent or significant disabilities) as GBS. No significant associations were found between seasonal IIVs or the 2009 H1N1 pandemic vaccines and GBS (98).

1.6 Anesthesia/paresthesia and influenza vaccination

Anesthesia/paresthesia can be considered a neurological or autoimmune AEFI, or a local symptom at the injection site (93). There is not yet any published case definition for anesthesia or paresthesia by the Brighton Collaboration, although it was planned to be one of the symptoms that would be defined by the Brighton Collaboration (4). PHAC's User Guide to Completion and Submission of the AEFI reports defines "anesthesia" as the loss of normal feeling or sensation, while "paresthesia" as an abnormal physical sensation such as tingling, burning (not necessarily accompanied by redness or skin irritation), prickling, formication (the sensation of crawling insects over the skin), etc. These symptoms usually overlap since numbness is described as loss of sensation that is often accompanied by tingling (32). For this reason, we will refer to them here as anesthesia/paresthesia.

Anesthesia/paresthesia is often a sensory symptom of peripheral neuropathies where peripheral nerves are afflicted (99). Negative sensory sensations include numbness, tingling, prickling, or decreased sensations, while burning is an example of positive sensory sensations (100,101). Any abnormality along the sensory pathway which extends from peripheral nerves to the sensory cortex in the brain can induce these sensations (102). This symptom has also been described as a variant of neuropathic pain (102–106). Studies have shown that anesthesia/paresthesia can directly affect the health-related quality of life of individuals and reduce sleep quality, especially in those who experience pain of higher intensities (107,108). The symptom is also associated with several underlying causes that can be neurologic, cardiovascular, metabolic, autoimmune, and others (109).

In an annual report published by CAEFISS for all vaccines administered in 2012, anesthesia/paresthesia represented the highest AE within the "other events" on the CAEFISS report form at 41.8%, none of which were serious (110). In the United States, a study using 1990-2005 VAERS data for AEs following the receipt of TIV demonstrated that anesthesia/paresthesia was the most commonly reported neurological AE for 18 years of age and older, with a rate of 1.80 per million vaccinations (111).

Monitoring of AEFIs during the 2009 H1N1 pandemic demonstrated an increased frequency of anesthesia/paresthesia reports in European countries (93,112,113), as well as Quebec, Canada (55). The passive surveillance system in Quebec received 328

anesthesia/paresthesia reports between 26 October and 31 December 2009, of whom 96% received a monovalent AS03-adjuvanted vaccine that was manufactured in Canada (Arepanrix®, GSK Canada). Of these reports, 59% anesthesia/paresthesia cases sought medical attention and 3% reported being hospitalized. Some of these cases were followed up as part of a case-control study to investigate risk factors associated with the symptom. Twenty-four out of 181 cases experienced sensations that persisted up to 12 months post-vaccination (114).

A Cochrane review included anesthesia/paresthesia among the "serious and rare harms" underneath the "Neurological and autoimmune disorders" category, as an AEFI post-seasonal or post-pandemic influenza vaccination (98). No meta-analyses were done regarding this AEFI since anesthesia/paresthesia symptoms included in this review were based on a single retrospective population-based cohort study of 1.98 million people in Stockholm (93). The study was done to monitor a number of neurological and autoimmune disorders of interest following Pandemrix®. Results showed an increased risk of low magnitude among vaccinated compared to an unvaccinated group for anesthesia/paresthesia (hazard ratio = 1.11; 95% CI = 1.00, 1.23), all of whom were healthcare workers (HCW) and high-risk groups for complications from influenza, after adjustment for age, sex, socioeconomic status, and healthcare utilization. This study was later extended to other regions in Sweden; results for anesthesia/paresthesia were similar with a hazard ratio of 1.07 (95% CI = 1.02, 1.11) (115).

1.7 Headaches and influenza vaccination

Headaches are one of the most prevalent nervous system disorders in the general population. In 2016, the WHO estimated that, globally, half to three quarters of adults in the previous year had symptomatic headaches. Thirty per cent of those reported migraines (116). Based on the Global Burden of Disease Study of 2013, headache disorders were the third highest cause of years lost due to disability, while migraines alone were the sixth leading cause (117).

According to the International Headache Society, headaches are either primary or secondary. Secondary headaches result from another condition (e.g. infections or inflammations, cancers, immunosuppression, or neurological), while primary headaches have no specific cause (118). Migraines are a common and very disabling primary headache. They could be manifested

with or without an aura which are characterized by “the transient focal neurological symptoms that usually precede or sometimes accompany the headache” (119).

A case definition for headaches as AEFIs does not exist in the national PHAC guide or by the Brighton Collaboration. Headaches as AEFIs are regarded as having “relatively minor medical significance” (120). They are also not considered an unexpected AE following seasonal influenza vaccination. In fact, vaccine monographs include headaches as a frequent systemic effect (121–123), a common neurological disorder (124), or listed without being classified as either a systemic effect or a neurological disorder (65). Table 1.1 displays results from clinical trials available in product monographs for headaches as an AEFI following seasonal influenza vaccination.

Table 1.1: Comparison of percentages of headaches as adverse events following immunization between seasonal influenza vaccine products from clinical trial results as appearing on product monographs

	Age	Follow up time	Percentage of headaches
Agriflu® (125)	3-17 years	4 days	3-13%
	18-64 years	4 days	5- 23%
Fluviral® (126)	5-17 years	4 days	17%
	≥18 years	7 days	20%
FluLaval® tetra (127)	3-17 years	7 days	11- 22%
	≥18 years	7 days	22%
Flumist® (65)	2-17 years	10 days & 14 days	12-13%
	18-59 years	6 days & 14 days	25-37%
Fluzone® high dose (122)	≥65 years	7 days	17%
Fluzone® quadrivalent (123)	1-3 years	7 days	9%
	3-8 years	7 days	23%
	≥18 years	3 days	16%
	≥65 years	7 days	13%
Influvac® (128)	18-59 years	3 days	12-13%
	≥60 years	3 days	2-8%
Intanza® (121)	18-59 years	7 days	30%
	≥60 years	7 days	14%
Vaxigrip® (124)	18-59 years	3 days	1-10%
	≥60 years	3 days	3-6%

Headaches among healthy adults following seasonal influenza vaccination can be recognized as the most commonly reported AEFI as early as Phase I pre-licensure clinical trials (129). A 2018 Cochrane systematic review presented findings from RCTs and quasi-RCTs in individuals aged 16 to 65 that showed an increased risk of headaches with LAIV compared to placebo or no intervention (RR = 1.54; 95% CI = 1.09, 2.18). Parenteral IIVs versus placebo or no intervention showed a lesser risk increase (RR = 1.14; 95% CI = 0.99, 1.30) (98). Clinical trials involving children have also reported headaches as the most common AEFI (130,131).

Surveillance data from VAERS have also shown headaches as the most common AEFI with both LAIVs and IIVs between 1990 to 2014 (132–134). Headaches following seasonal influenza vaccination have been explained as part of systemic reactions and are generally mild, self-limited, and short-termed that typically resolve within 3 days (135–140).

These secondary headaches that are part of systemic reactions are mainly caused by interferon or cytokines in response to influenza antigens. Mode of administration of immunization is, therefore, irrelevant (141). Such responses can produce other systemic reactions in the body including fever, chills, fatigue, muscle pain, and joint pain that occur within 6 to 12 hours of vaccination (142). Despite evidence of expected mild systemic inflammatory response produced from unadjuvanted vaccines (143,144), additional vaccine components may trigger this response, including adjuvants (145,146). Vaccination can also trigger migraines by acting as a psychological stressor (147). Vaccines have also shown to cause anxiety-related symptoms that typically include headaches; these usually appear in geographical clusters (148).

As previously mentioned, most headaches post-vaccination are common and non-serious, but in some RCTs, they have been shown to prevent daily activities (described as grade 3 headaches) (130,131) where proportions reached 2.9% of vaccinees. Some headaches (n = 201; 0.27%) were reported through VAERS as serious AEs following TIVs (132). Typically, however, headaches are only worrisome when associated with other symptoms such as sensory disturbances, muscle weakness, allergic reactions, or tremors, since they can be part of other serious diagnoses.

1.7.1 Headaches with anesthesia/paresthesia and influenza vaccination

Headaches with anesthesia/paresthesia have sometimes been reported together following seasonal influenza vaccination. A study investigating anesthesia/paresthesia and sensory disturbances associated with the 2009 pandemic vaccines reported 38% of anesthesia/paresthesia cases were associated with headaches (114). It is possible that anesthesia/paresthesia is a symptom of an underlying headache or migraine (i.e. an aura). Other conditions where both symptoms can occur simultaneously include Bell's palsy, allergic reactions, and seizures – all of which have been reported following seasonal influenza vaccination (83,150–152). Occasionally, GBS can also include headache as a symptom along with its known clinical picture.

1.8 Seizures and influenza vaccination

Seizures are episodes of neuronal hyperactivity most commonly resulting in sudden, involuntary muscular contractions with or without loss of consciousness, altered sensory disturbances, behavioral abnormalities, or autonomic dysfunction (153). According to the WHO, up to 10% of people worldwide have one seizure during their lifetime (154). Seizures can be associated with fever (i.e. febrile) or without (i.e. afebrile or non-febrile).

Febrile seizures (FS) occur in feverish children between 6 months to less than 60 months of age who do not have an intracranial infection, metabolic disturbance, or history of afebrile seizures. They occur in 2-5% of children within that age group (155). FS often last for less than 15 minutes, are generalized (involve the whole body), and occur once within a 24-hour period. This common type of FS is named "simple FS". On the other hand, complex FS are more prolonged, are focal, and recur within 24 hours (155). The risk of developing epilepsy later in life for children with simple FS is equivalent to that of the general population (156). However, children with multiple recurrent simple FS, had their first FS before 12 months of age, and have a positive family history of epilepsy have a higher risk of developing epilepsy by 25 years of age (157). Contrary to simple FS, which typically are not associated with epilepsy, it is uncertain whether complex FS are followed by epilepsy in the future (158).

Generally, FS are the most common type of seizures observed in infants and children following vaccination (153). Onset of their occurrence depends on components of the vaccine: live attenuated vaccines need more time for viral replication before inducing a response, while

inactivated vaccines can illicit responses as early as 24 hours following vaccination (159). There have been incidents in post-marketing surveillance where seasonal influenza vaccination has been associated with increased reports of seizures.

For the period between 1990 and 2003, VAERS results showed that 28 (17%) reports of children under 2 years of age were from seizures. Of those, 19 (68%) described fever with the seizures within 2 days after administration of TIV. In the same study, seizures represented 10 out of the total 23 serious AEs reported in that age group; 7 out of the 10 were febrile (160). This signal led to another study by the Vaccine Safety Datalink project that also investigated TIV for the same years and for the same age group. After chart review, and a 14-day follow-up period, 22 of 24 (92%) convulsions were found to be febrile. Only 1 FS occurred on day 3 following vaccination. The peak increase in number of FS was found to coincide with the MMR (Measles, Mumps, Rubella) vaccine that is known to result in a 3-fold increase of FS two weeks following vaccine administration (161). Therefore, no alarming signal was confirmed (162). Another population-based case-cross over study of children in the Vaccine Safety Datalink project receiving TIV from 1993 to 1999 demonstrated no medically attended seizures were associated with the vaccine (163).

With regard to the 2009 H1N1 pandemic, the final summary of adverse drug reaction reports in Sweden with Pandemrix® from October 2009 through mid-April 2010 showed the most frequent reported serious neurological AEFI in children was febrile convulsions (17/82), mostly in children under 2 years of age (16/17) (113). In the same year, France also demonstrated that FS were one of the most commonly reported neurological events in children with the pandemic vaccine, Panenza®, at a rate of 1.2 per 100,000 doses (112).

On a more serious note, in the influenza season 2010/11, unexpected high numbers of reports for febrile convulsions in children under 5 years of age arose from Western Australia (164). Initially, decisions were made by the Australian Department of Health to suspend to all influenza vaccination of children less than 5 years of age (152). Later, a final decision was made where vaccination of healthy children under 5 years of age can resume, but not with the Fluvax® or Fluvax® Junior (CSL Biotherapies ('CSL'), Parkville, Australia) that was associated with the AE (165,166). Epidemiological analyses of the vaccine showed a rate of about 5 to 7 febrile convulsions per 1,000 doses in children less than 5 years of age, depending on the Australian

jurisdiction. Lower rates were reported in previous years and the concurrent year for all other TIV products (167). This incident led to a recommendation in the United States against the use of CSL's vaccine product Afluria® in children ages 6 months to 8 years starting from the 2010/11 season (168). Several investigations addressing the biological basis for these seizures took place and the causative factor was most probably in the manufacturing process (169). In the same season, the United States also picked up a signal from VAERS where there was an increased risk of FS in children less than 5 years of age immunized with Fluzone® TIV product (170). An increased risk was also determined by the Vaccine Safety Datalink project for the same season with administration of TIV (171). Febrile convulsions were later added to the nervous system disorders under the title "Data from Post-Marketing Experience" title in the Fluzone® product monograph (172).

Following this incident in Australia, a systematic review on fever, febrile convulsions and serious AEs following inactivated TIVs in children, including the aforementioned CSL vaccines, was published in 2015. The review was based on RCTs and non-RCTs from 2005 to 2012. Results from RCTs demonstrated that the rate of febrile convulsions was 1.1 out of 1,000 vaccinated children (173).

The CDC has identified that young children who receive the IIV along with pneumococcal conjugate vaccine (PCV13), and/or DTaP (diphtheria, tetanus, and acellular pertussis) vaccine concurrently are at an increased risk of developing FS. A study using Vaccine Safety Datalink data of 5 influenza seasons from 2006/07 through 2010/11 showed evidence of a higher risk of FS with concurrent TIV and PCV13 (RR = 3.50; 95% CI, 1.13, 10.85) and with TIV and DTaP (RR = 3.50; 95% CI, 1.52, 8.07) (159). However, no changes in recommendations have been made regarding concomitant vaccine administration (174).

Fever resulting from the inflammatory response following vaccination is known to trigger seizures for children who are prone. Reasons have been studied in animal and human models (175). Firstly, increased brain temperature alters temperature-sensitive ion channels that affect synchronized neuronal activity (176). Another reason is the inflammatory cytokines, specifically interleukin-1β, secreted in the brain which increases excitability of neurons (177). Other studies have implied that genetics influence the susceptibility of developing FS (178).

Convulsive seizures temporally associated with influenza vaccines have not been restricted to young children (95,179). Before the 2009 H1N1 pandemic, a descriptive study assessing AEs passively reported to the VAERS in the United States reported convulsions following the TIV with a rate of 0.28 per million vaccinations for adults 18 years of age or older (111).

Similar to previously mentioned neurological disorders associated with the influenza vaccine, the IOM Immunization Safety Review Committee concluded that data were inadequate to accept or reject a causal relationship between influenza vaccines and seizures (97).

1.9 Justification for the study

Based on recommendations to promote vaccine safety research with particular attentiveness to neurological manifestations following influenza vaccines (96), this proposed project focuses on anesthesia/paresthesia, severe headaches and generalized convulsive seizures (GCS), both febrile and afebrile, that are self-reported via CANVAS after seasonal influenza vaccination to better describe these AEs.

We aimed to investigate the occurrence of anesthesia/paresthesia as an outcome following seasonal influenza vaccination based on the previously detected signals discussed earlier in Canada and other European countries following the 2009 pandemic influenza season. Headaches are routinely investigated during interventional and observational studies following seasonal influenza vaccination; however, associations for severe headaches are not available in the published literature. Here, we aim to detect the presence of an association only for severe headaches that led to prevention of performance of daily activities, absenteeism, or seeking medical attention. Finally, occurrence of seizures was investigated based on the confirmed signal of FS in Australia that led to the discontinuation of a single vaccine product. We were interested in determining the presence of a relationship between seasonal influenza vaccine and GCS based on diagnostic certainty, as described by the Brighton Collaboration case definition for a more standardized way to identify seizures.

Identifying possible AEs is necessary, especially since vaccination against seasonal influenza is currently recommended by the National Advisory Committee on Immunization for

everyone 6 months of age and older without contraindications to the vaccine (180). Investigation of the nature and frequency of these AEs allows further assessment of risks that, in turn, provide policymakers with a framework for generating guidelines and recommendations regarding influenza vaccination. When this is followed by transparent communication of risk and benefit and addressing the concerns of the public through open conversation, trust and confidence towards influenza vaccination may be built. This trust will be of special importance when there is a need to take rapid action as in the face of pandemics that would necessitate vaccinating millions of people in a short period of time (181,182).

1.10 Objectives

The study has the following objectives:

a) To determine the risk of anesthesia/paresthesia following seasonal influenza vaccination from 2012 through 2016 among CANVAS participants.
b) To determine the risk of severe headaches following seasonal influenza vaccination from 2013 through 2016 among CANVAS participants.
c) To determine the risk of febrile and afebrile generalized convulsive seizures following seasonal influenza vaccination from 2013 through 2016 among CANVAS participants.

1.11 Research Questions and Hypotheses

1. Is influenza vaccination associated with an increased risk of occurrence of anesthesia/paresthesia?

   Hypothesis: Given our sample size of 107,565 with a power of 80%, we will be able to detect an absolute difference of 16% in the odds of anesthesia/paresthesia in vaccinees compared to non-vaccinees assuming a proportion of 0.013 in non-vaccinees.
2. Is influenza vaccination associated with an increased risk of occurrence of severe headaches?

Hypothesis: Given our sample size of 97,420 with a power of 80%, we will be able to detect an absolute difference of 12% in the odds of severe headaches in vaccinees compared to non-vaccinees assuming a proportion of 0.026 in non-vaccinees.

3. Is influenza vaccination associated with the occurrence of generalized convulsive seizures?

Chapter 2: Methods

2.1 Data source

Data for this project were extracted from the CANVAS Network for the influenza seasons 2012/13 through 2016/17 (i.e. 2012 through 2016). A summary of influenza vaccines used in Canada throughout this period is shown in Table 2.1. Based on the vaccinees recruited, each year CANVAS had a 99.9% chance to detect events occurring at a rate of 1 in 100, 500, and 1,000 and a 98%, 92%, and 71% chance to observe events at a rate of 1 in 3,000, 5,000 and 10,000, respectively.

2.1.1 Study population

Participants were recruited from hospital vaccination campaigns, pharmacies, physicians' offices, public health clinics or mass vaccination clinics, or other locations (e.g. a participant's workplace or long-term health facilities) in 7 cities in 5 Canadian provinces: Halifax in Nova Scotia, Quebec City and Sherbrook in Quebec, Toronto and Ottawa in Ontario, Calgary in Alberta, and Vancouver in British Columbia.

When this network was launched in 2009, only HCW were recruited as participants. However, starting 2012, the network expanded recruitment to include children 6 months to 14 years of age, and in 2013, adults of all occupations could participate (Table 2.2).

2.1.1.1 Recruitment of vaccinees and controls

Participants were recruited at the time of influenza vaccination and completed an online survey at day 8 after vaccination. Each year's vaccinated participants served as the next year's control group by completing a second survey approximately 12 months after the first survey, but before the start of next influenza vaccination campaign in their jurisdiction (in the following fall). An individual can participate as a control and re-enter the study in the same year as a vaccinee with a different identification number. Each site ran on its own schedule based on when the campaign started locally. Sites launched between early to late October, and all sites finished by mid-November.

All participants provided informed consent and the study had REB approval from Children's & Women's Health Centre of British Columbia (REB # H10-02274) and at each participating site.

2.1.2 Study procedures for vaccinated and control groups

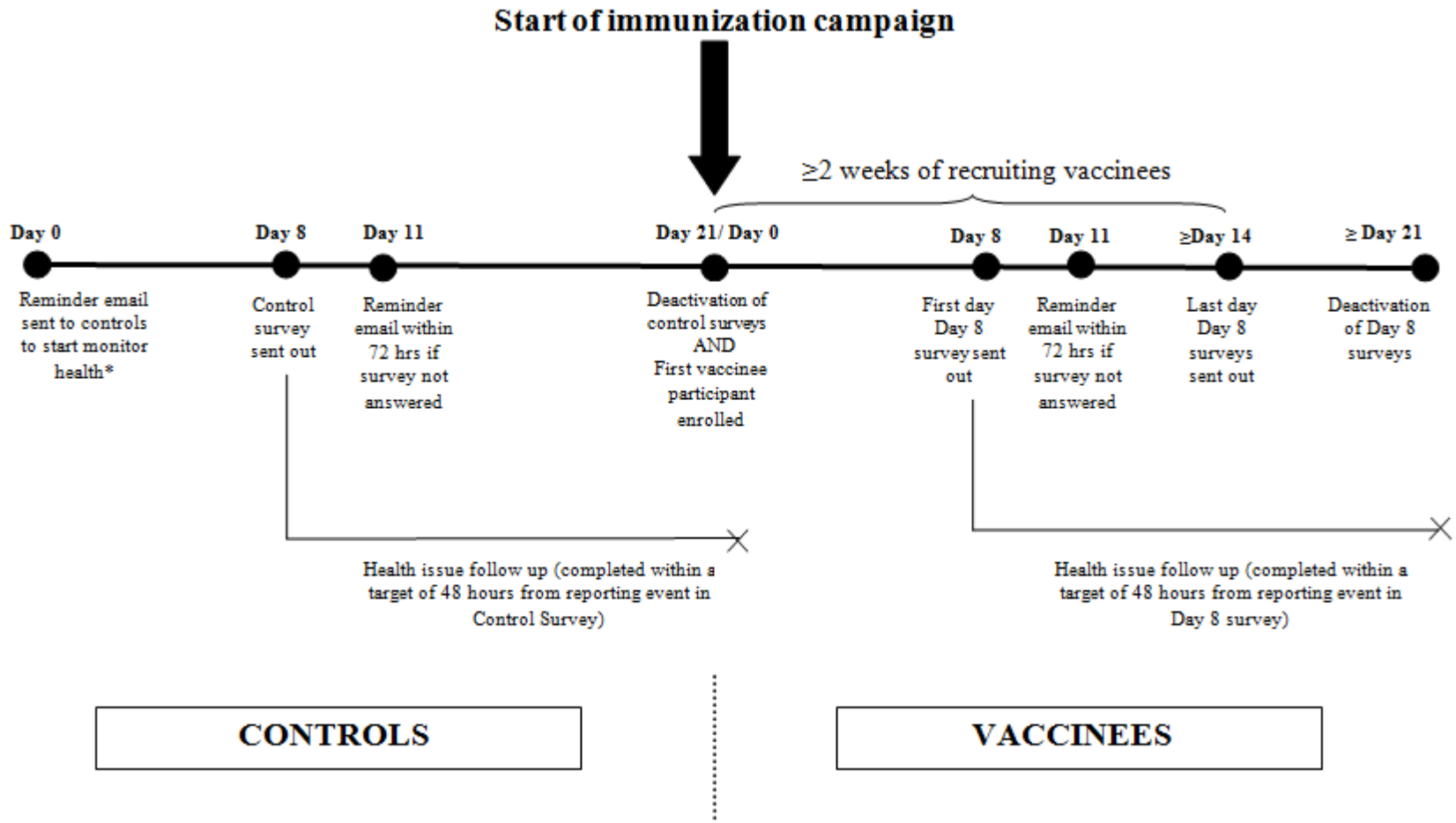
Enrolled vaccinated participants (i.e. vaccinees) were sent an email on day 8 following vaccination (referred to as "Day 8 Surveys") inviting them to respond to a short survey in either English or French languages. Participants accessed the survey by clicking on a link embedded in the email. The survey contained the following questions: demographics (age of the vaccinated child or adult and gender), past influenza vaccination history, and the occurrence of AEs for the first 7 days post-vaccination (Figure 2.1).

Control participants received an email survey about 2 weeks before the start of the seasonal influenza vaccination campaign (referred to as "Control Surveys"), before the vaccine has been made available. The Control Survey collected data about the development of new health problems or worsening of existing health problems in the last 7 days in the respondent or their child(ren). The Control Survey provided information on background rates of health events prior to each season's influenza campaign and provided a baseline rate for health event reports in the absence of influenza vaccination. Starting in 2013, controls received a reminder email 7 days before the control survey was sent to mark the start of the 7-day monitoring period. This email did not reveal any questions that would be asked in the survey they would receive. If vaccinees or controls failed to answer the survey within 72 hours of its receipt, a reminder email was sent automatically (Figure 2.1).

For 2012, vaccinees and controls could report solicited symptoms in the online surveys (i.e. derived from an organized data collection scheme), even if their symptoms were mild. Starting 2013, participants were asked to report solicited symptoms only if these led to work or school absenteeism, prevented their daily activities, or required medical attention (Figure 2.2). A summary of differences in data collection by year is shown in Table 2.2.

Table 2.1: Authorized vaccine preparations used in Canadian National Vaccine Safety Network participants, 2012-2016

Trade name of vaccine	**Authorized Age for Use**	**2012** (183)	**2013** (184)	**2014** (185)	**2015** (61)	**2016** (180)	**Preparation details**
Agriflu® (Novartis)	≥ 6 months	✓	✓	✓	✓	✓	Trivalent Inactivated Vaccines (TIV) - Unadjuvanted - Intramuscular (IM) administered.
Fluviral® (GlaxoSmithKline)	≥ 6 months	✓	✓	✓	✓	✓	
Fluzone® (Sanofi Pasteur)	≥ 6 months	✓	✓	✓	✓	✓	
Vaxigrip® (Sanofi Pasteur)	≥ 6 months	✓	✓	✓	✓	✓	
Influvac® (BGP Pharma ULC or Abbott)	≥ 18 years	✓	✓	✓	✓	✓	
Intanza® (Sanofi Pasteur)	≥ 18 years	✓	✓	✓			TIV - Unadjuvanted - Intradermal (ID) administered.
Fluzone® High-Dose (Sanofi Pasteur)	≥ 65 years					✓	TIV - Unadjuvanted - IM administered.
FluLaval® Tetra (GlaxoSmithKline)	≥ 6 months			✓	✓	✓	Quadrivalent Inactivated Vaccines (QIV) - Unadjuvanted - IM administered.
Fluzone® Quadrivalent (Sanofi Pasteur)	≥ 6 months			✓	✓	✓	
Fluad® (Novartis)	≥ 65 years	✓	✓	✓	✓	✓	TIV - MF59-adjuvanted - IM administered.
Fluad Pediatric® (Novartis)	6-23 months				✓	✓	
Flumist® Quadrivalent (AstraZeneca)	2-59 years				✓	✓	Quadrivalent Live Attenuated Influenza Vaccines (LAIV) - Intranasal spray (IN).
Flumist® Trivalent (AstraZeneca)	2-59 years	✓	✓	✓			Trivalent LAIV - IN spray.



*This email was sent starting 2013.

Figure 2.1: Timeline of Canadian National Vaccine Safety (CANVAS) Network campaign for vaccinees and controls

2.1.3 Follow up of reported events

Adult participants and parents of children reporting an event that prevented daily activities, led to absenteeism from school or work, or required medical attention were contacted by telephone within 48 hours (or more if the nurse was unable to reach the participant). In 2015 and 2016, only participants who reported that they sought medical attention were followed-up by phone (Table 2.2). This change was due to a decrease in resources allocated for the study.

In the follow-up phone call, the research nurse elicited additional information on symptoms, diagnosis, duration, treatment, and outcome of the most concerning symptom they had reported in the survey. The additional follow-up details were entered into an electronic report form. If the event reported was in a vaccinated participant and met criteria for local AEFI reporting, the nurse also filled out a local AEFI report form and submitted it to the local public health unit.

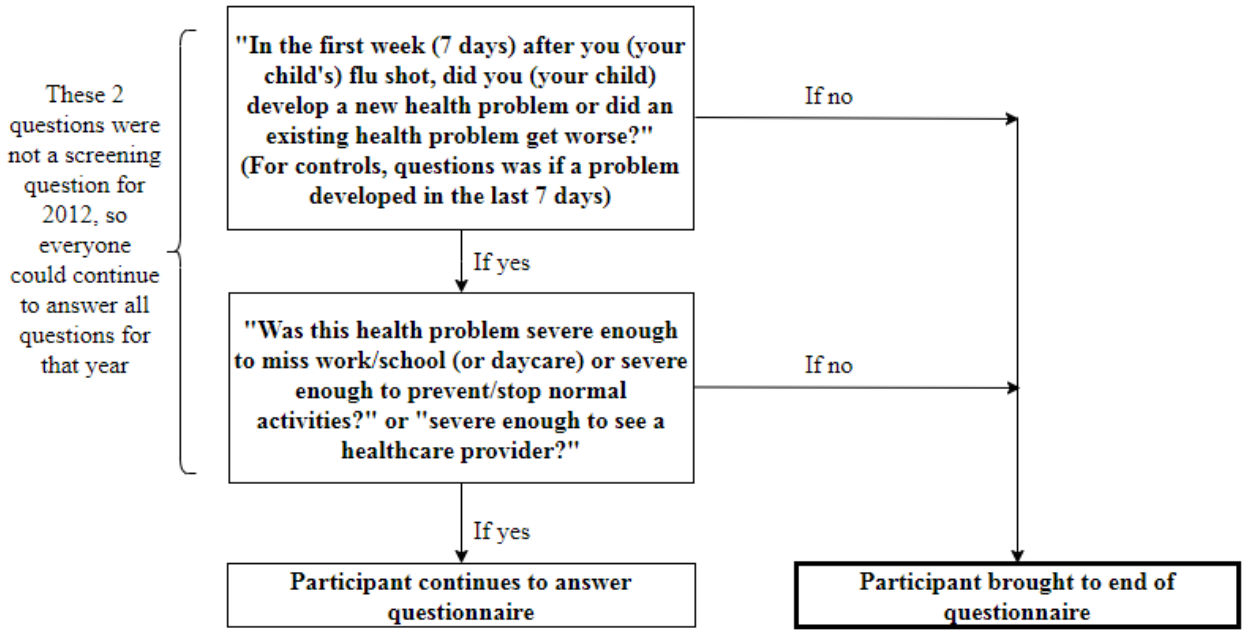


Figure 2.2: Flow of beginning of survey questions, Canadian National Vaccine Safety (CANVAS) Network 2012-2016

Table 2.2: Differences in data collected by year, Canadian National Vaccine Safety (CANVAS) Network, 2012-2016

	2012	2013	2014	2015	2016
Type of respondents					
Adults	HCWs[a] only	HCWs + other adults	✓[b]	✓	✓
Children	Pilot at one site (data not included in this analysis)	Yes (6 months to 14 years of age)	✓	✓	✓
Respondents who could report solicited symptoms					
Mild symptoms	Yes	-	-	-	-
Prevented daily activity/missed school or work	Yes	✓	✓	✓	✓
Sought medical attention	Yes	✓	✓	✓	✓
Had follow-up interviews					
Prevented daily activity/missed school or work	Yes	✓	✓	-	-
Sought medical attention	Yes	✓	✓	✓	✓
Details collected					
Vaccine product known at individual level	Identified[c] (except Ottawa & Calgary)	Identified	✓	✓	✓
Seizures as an event	Unsolicited[d]	Solicited	✓	✓	✓
Headaches as an event	Unsolicited	Solicited	✓	✓	✓

[a]Healthcare workers
[b]A repetition of previous cell
[c]Vaccine product could be described by center
[d]Not derived from organized data collection

2.1.4 Online data collection tool

From 2012 to 2015, data were collected using SimpleSurvey software by OutSideSoft Solutions inc. (Saint-Jean-sur-Richelieu, Quebec). The database was accessed through a secure web application with personal passwords for all sites, providing a secure environment

(encryption, firewalls, frequent backups, and recovery plan). Email addresses were kept in SimpleSurvey until the last email reminder was sent, then all email addresses were stripped from the data and deleted. For better customization of the surveys, financial, and logistical feasibility, in the 2016 influenza season, the survey was moved to REDCap software that was hosted and supported by the BC Children's Hospital Research Institute in Vancouver. The process of data management was similar to that of SimpleSurvey.

2.1.4.1 Validity and acceptability of online self-reported events

For the 2012 CANVAS data, results of a pilot study were published to assess internal validity of self-reported events by parents of children 6 months to 18 years of age. A total 5 out of 63 parents provided incorrectly reported symptoms by comparing what was reported by participants with follow-up telephone calls within 48 hours of reporting (186). A second study with the combined 2011 and 2012 CANVAS data for HCWs showed 30% (40/134) of controls and 9% (33/366) of vaccinees reported having severe events, but follow-up interviews revealed these events did not prevent daily activities/work or require a medical consultation, or a medical condition was pre-existing, or symptoms started prior to the 7 day monitoring period. The proportion of events excluded was significantly higher among controls than vaccinees ($p < 0.001$). This led to the introduction of an early reminder email in 2013 for controls to monitor health for the upcoming 7 days as a measure to enhance validity of control responses (54). Both studies concluded that internet-based reporting was highly feasible and acceptable for pediatric populations as well as adult HCWs.

2.1.4.2 Representativeness of online tool

An additional sub-study of the 2012 CANVAS data was conducted to determine the representativeness of health events reported by online responders. Control participants who did not complete their online questionnaire (i.e. non-responders) were 78.8% (6,979/9,458) and vaccinee non-responders were 36.2% (4,343/12,010) of corresponding enrolled participants. A random 10% of the enrolled non-responders were contacted by telephone 5-10 days after the reminder email was sent to compare event rates and general characteristics of participants. Results showed that the rate of severe events were similar between responders and non-responders for vaccinees (27/994; 2.7%; $p = 0.62$) and controls (36/921; 3.9%; $p = 0.84$). As for characteristics, in the control group, no difference was observed regarding age or gender. For

vaccinees, non-responders were older ($p < 0.001$), but there was no difference in gender (54). Results indicate overall representativeness of online response.

2.2 Merging of data for secondary data analysis

For the purposes of this project, we created a merged dataset for all years from 2012 through 2016. Although the project was launched in 2009, data were not available from before 2012. Children from 2012 were not included in this project because that year was a pilot study to determine the general feasibility of including children. It took place in one site (Calgary, Alberta), and the survey was too different from the remaining years to be included. Only variables related to our objectives were included in the analysis.

2.3 Analytic sample

From 2012 to 2016, 220,000 people were enrolled in the main CANVAS study; control response proportions ranged from 13% to 50%, while the range of participation for vaccinees was 60% to 74%. The total study sample people who actually participated in the study were 107,642. This number is the total number of surveys received from vaccinees and controls. Although vaccinees are the same individuals participating as controls the following influenza season, individual subject IDs were not linked. Fifty-four participants reported that the event occurred 8 days or more after vaccination (or more than 8 days prior to receiving the Control Survey) and were excluded. Of the remaining 107,588, there were 13 individuals who answered "other" for gender and were excluded because this category was only collected starting in 2016.

The final analytic sample sizes were different for anesthesia/paresthesia than for headaches or GCS. For anesthesia/paresthesia, of the 107,575 participants, 10 individuals were excluded due to missing responses on potential confounding variables. For headaches or seizures, of the 107,575 participants, 10,146 participants enrolled in 2012 were excluded because the symptom was not solicited in that year. An additional 9 individuals were excluded due to missing responses on confounding variables.

The final analytic sample size for investigating anesthesia/paresthesia was 107,565, while for headaches or seizures was 97,420 – 99.93% and 90.50% of the original combined dataset for anesthesia/paresthesia and headaches or GCS, respectively (Figure 2.3 & Figure 2.4)

The number of participants increased annually, from 2012 through 2016. The largest sample was obtained from the 2016 dataset (n = 29,855) which represented 27.7% of the total participants for anesthesia/paresthesia, and 30.6% of the sample for headaches or GCS. The sample size was higher in vaccinees than controls each year (Figure 2.5).

2.4 Effect size calculation

Based on our sample size, with an 80% power, we could detect an odds ratio (OR) of 1.16, assuming a proportion of 0.013 in controls, for anesthesia/paresthesia, and an OR of 1.12, assuming a proportion of 0.026 in controls, for severe headaches between vaccinees and controls. Proportions in controls were obtained from published literature (54).

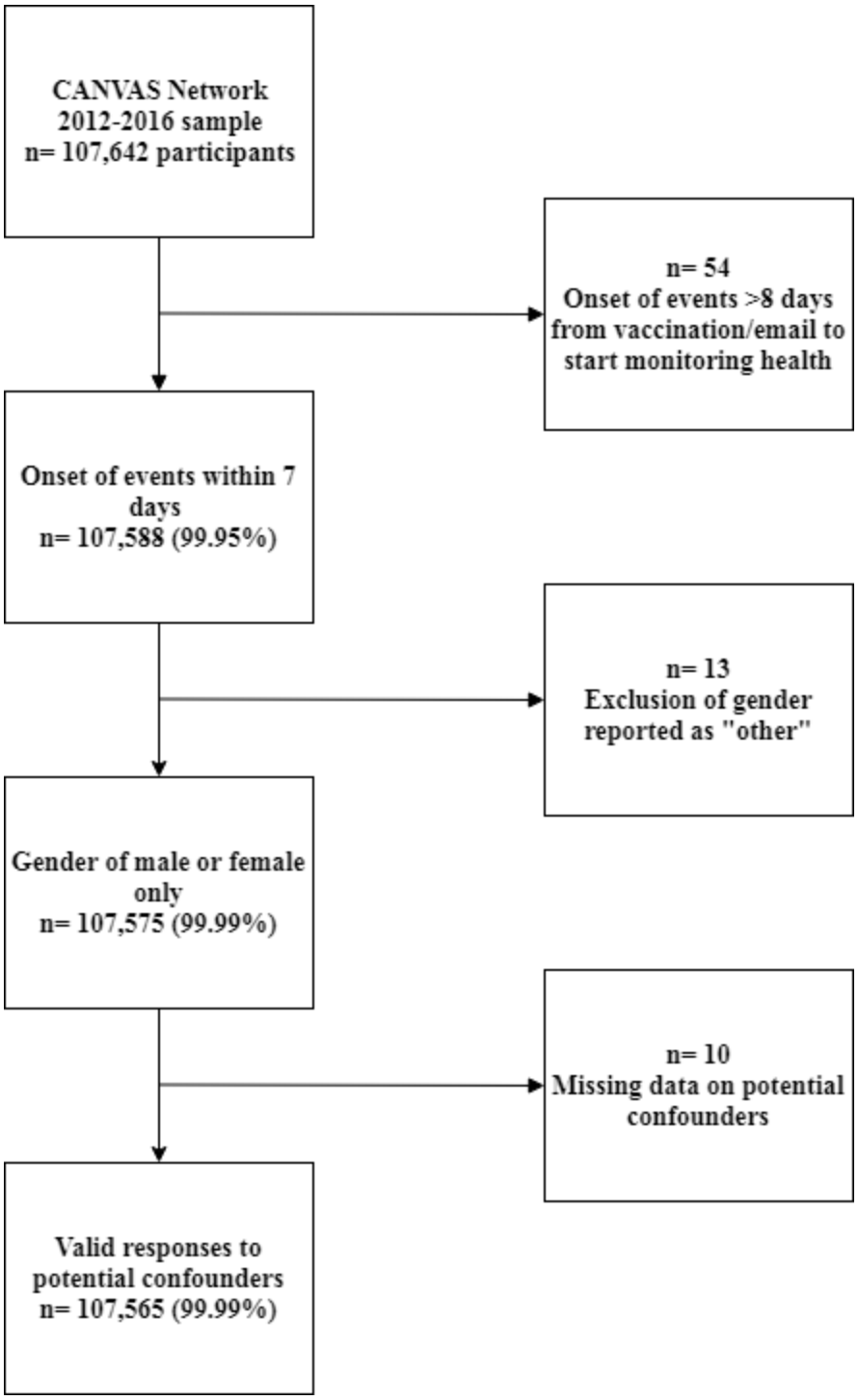


Figure 2.3: Analytic sample from Canadian National Vaccine Safety (CANVAS) Network 2012-2016 for analysis of relationship between seasonal influenza vaccination and occurrence of anesthesia/paresthesia

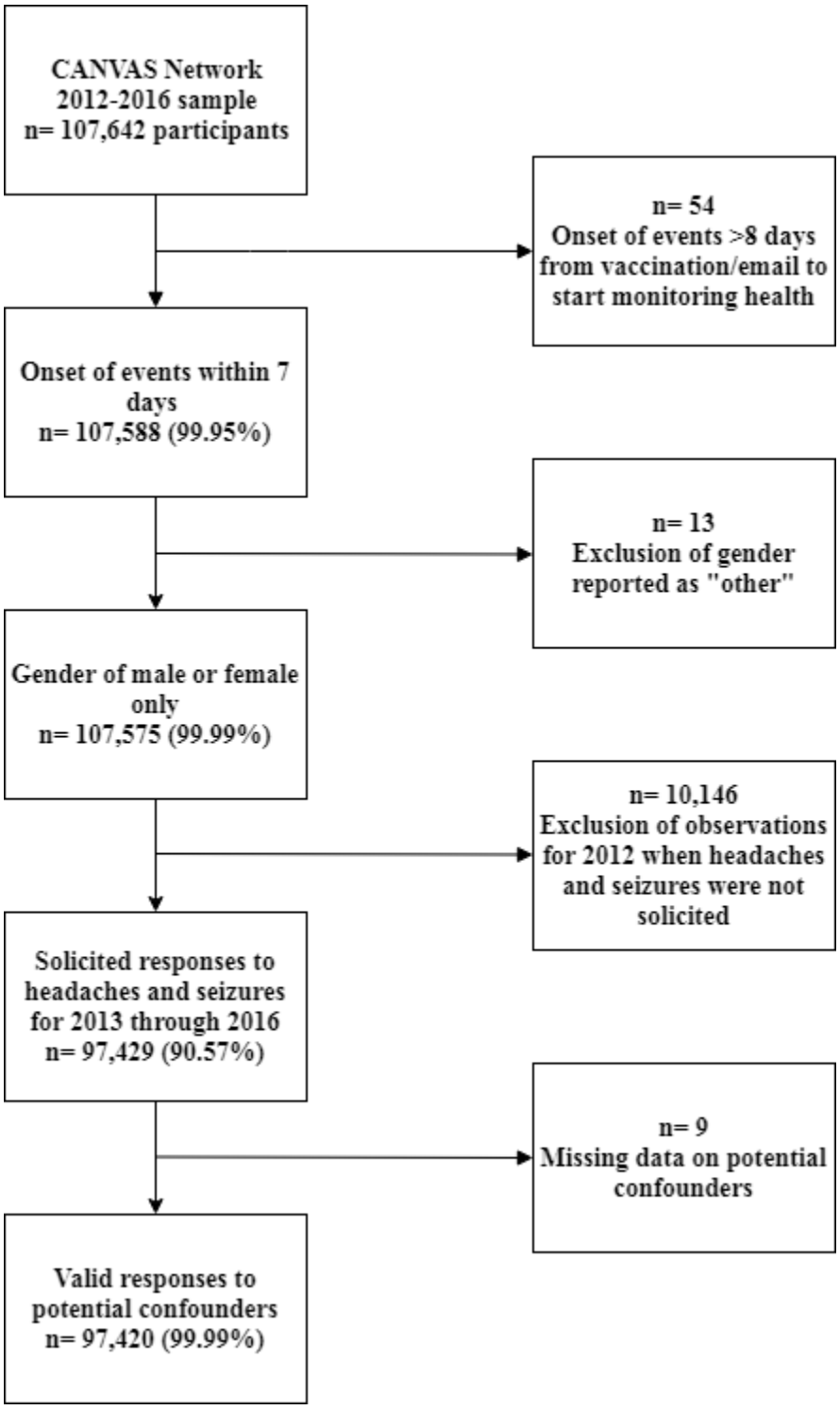
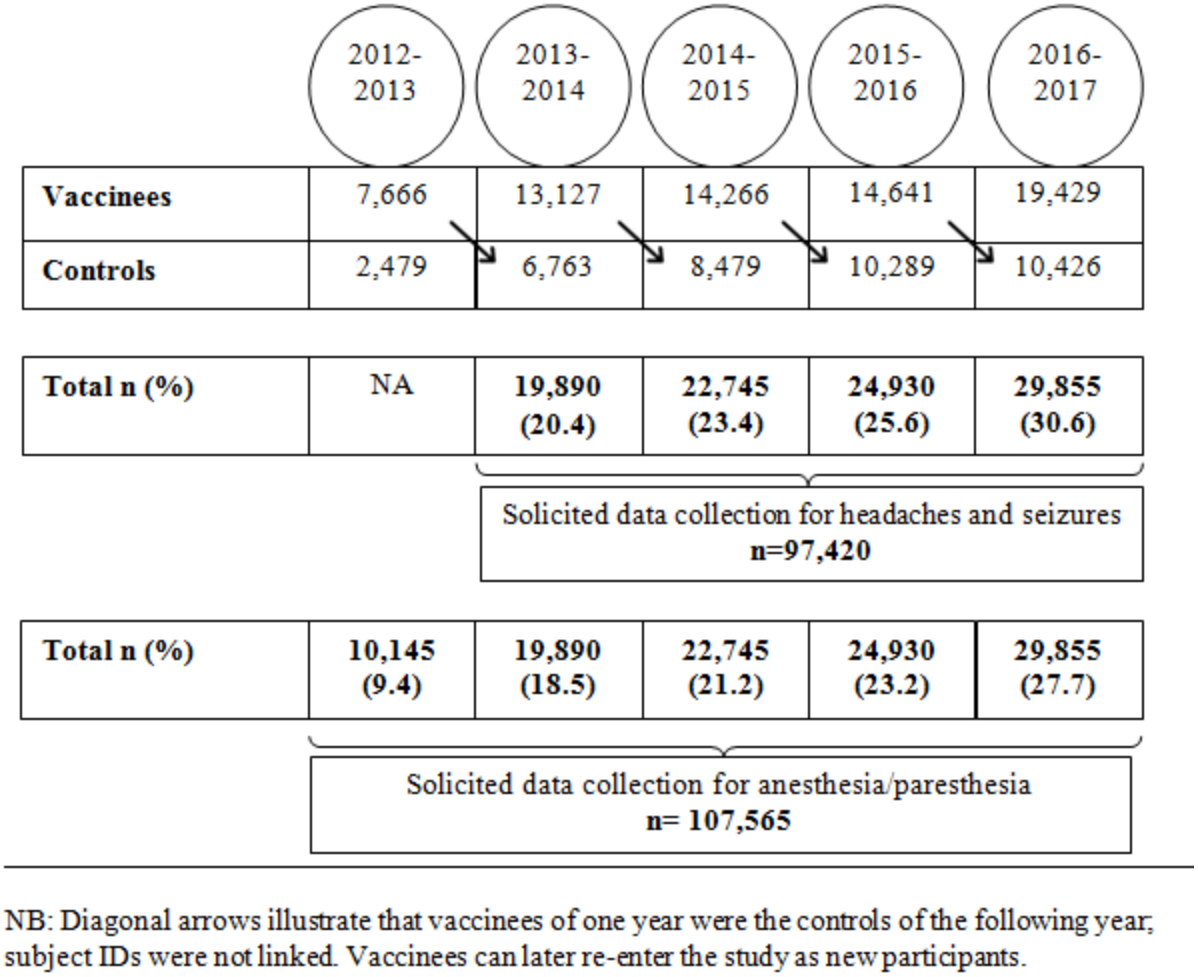


Figure 2.4: Analytic sample from Canadian National Vaccine Safety (CANVAS) Network 2013-2016 for analysis of relationship between seasonal influenza vaccination and occurrence of severe headaches or GCS



NB: Diagonal arrows illustrate that vaccinees of one year were the controls of the following year; subject IDs were not linked. Vaccinees can later re-enter the study as new participants.

Figure 2.5: Sample size by year, Canadian National Vaccine Safety (CANVAS) Network, 2012-2016

2.5 Study variables

2.5.1 Dependent variables and case definitions

All reported outcomes must have been newly developed or already existing but worsened; were severe enough to miss work/school, prevent normal daily activities, or severe enough to require medical attention; and occurred in the first 7 days after vaccination or 7 days after the start of the health monitoring process for controls. All outcomes were all self-reported and binary in nature (i.e. either experienced or did not experience the symptom).

A) Anesthesia/paresthesia

The definition of this outcome was numbness, tingling, pins and needles, decreased sensation, or burning sensation anywhere in the body. For participants in 2012 and 2013, to report anesthesia/paresthesia and its related information, the symptom must have occurred within the past 24 hours of receiving the vaccine (Figure 2.6) or within 24 hours after the start of the health monitoring process for controls (Figure 2.7). This short time period used by CANVAS was based on conclusions from a study where shorter onsets of anesthesia/paresthesia following vaccination suggest a more causal role; however, for temporal roles, onsets would be expected to be over a period of days (114). As for the remaining years, the outcome could be reported if it had occurred within 7 days of vaccination or 7 days prior to receiving the Control Survey with a question that follows about the 24 hour time frame (Figure 2.8 & Figure 2.9).

Missing information throughout the years for details related to anesthesia/paresthesia was likely due to differences in the branching of the questionnaire (Figure 2.6, Figure 2.7, Figure 2.8, and Figure 2.9).

B) Headaches

Headaches were a broad term that reflected any type/cause of headache (e.g. migraine headaches, tension headaches, cluster headaches, sinus headaches, etc.) all occurring within the described 7-day period. Headaches were not solicited in 2012. There were no differences in data collection from 2013-2016 for this outcome.

We further described anesthesia/paresthesia without headaches, headaches without anesthesia/paresthesia, and if both were present together.

C) Generalized Convulsive Seizures (GCS)

Based on the questions in the follow-up telephone interviews, it was possible to further classify seizures based on the Brighton Collaboration case definition for GCS (5). The definitions identify different levels of GCS based on diagnostic certainty. Table 2.3 describes these levels with level 1 being most certain and level 5 being the least. For 2013, data from interviews did not include the type of generalized muscle involvement and, therefore, GCS could only be classified up to level 4. Starting 2014, details in the follow-up questionnaire allowed classification of subjects from level 1 diagnostic certainty onwards. This classification was

conducted during the data analysis stage, not during data collection. Seizures were not solicited in 2012.

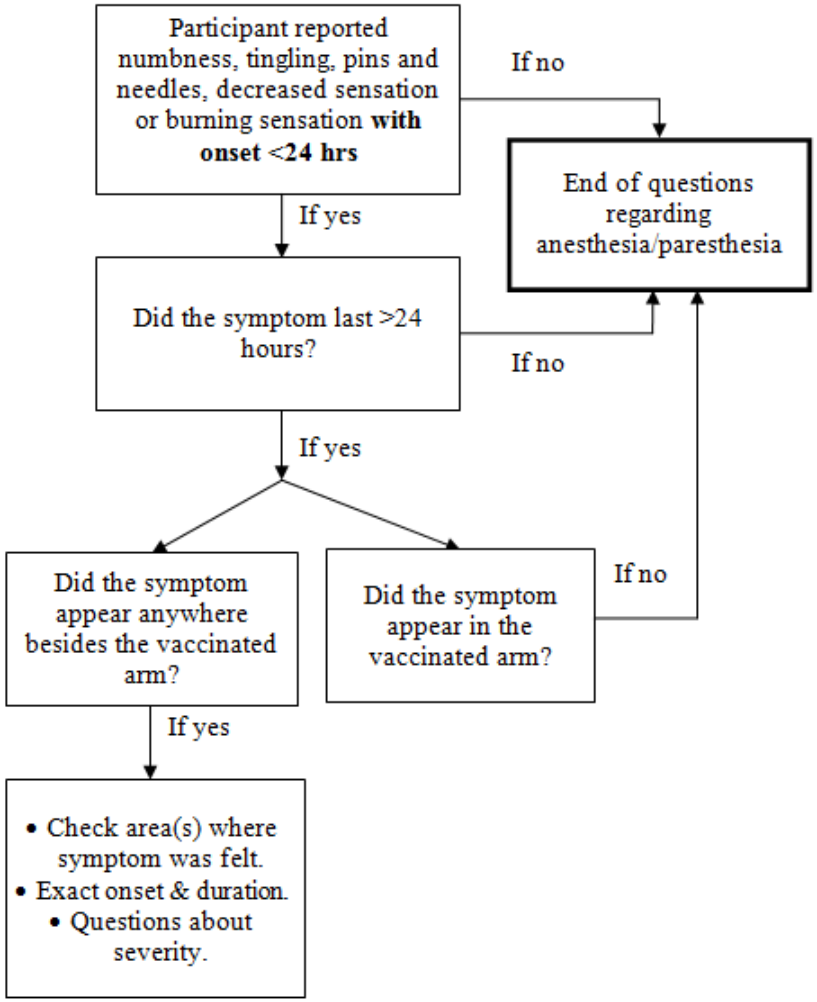


Figure 2.6: Anesthesia/paresthesia flow of questionnaire for vaccinees, Canadian National Vaccine Safety (CANVAS) Network, 2012 and 2013

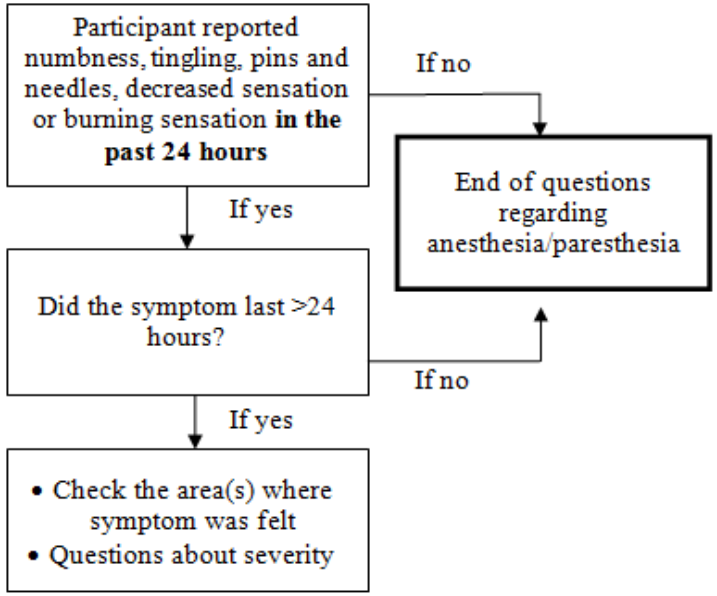


Figure 2.7: Anesthesia/paresthesia flow of questionnaire for controls, Canadian National Vaccine Safety (CANVAS) Network, 2012 and 2013

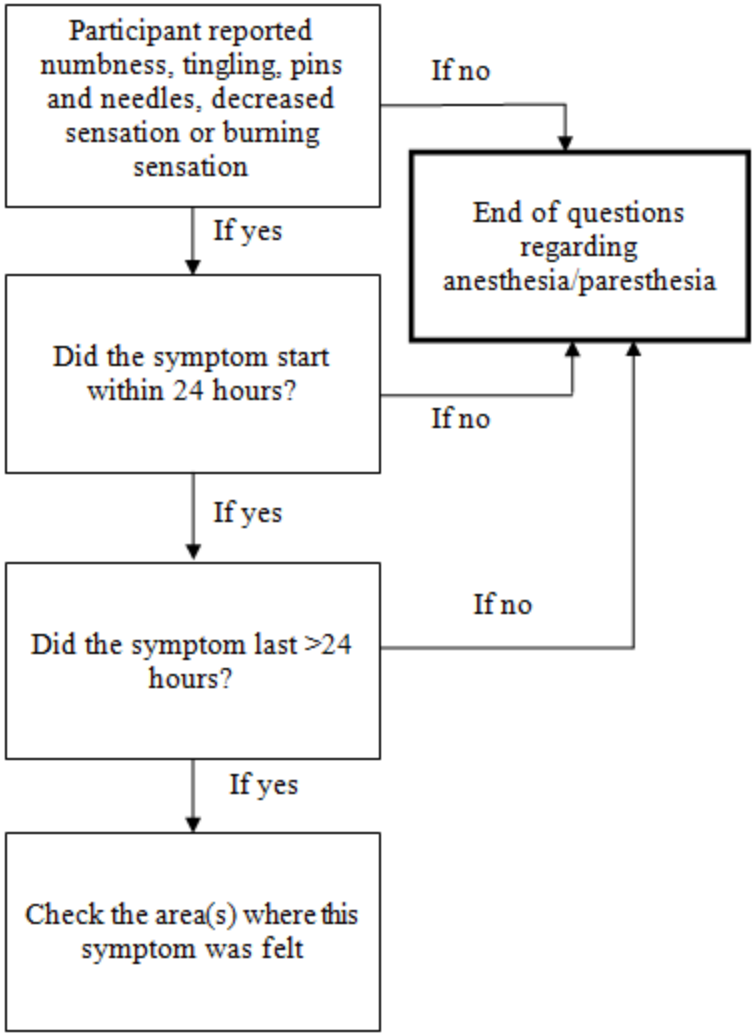


Figure 2.8: Anesthesia/paresthesia flow of questionnaire for vaccinees, Canadian National Vaccine Safety (CANVAS) Network, 2014-2016

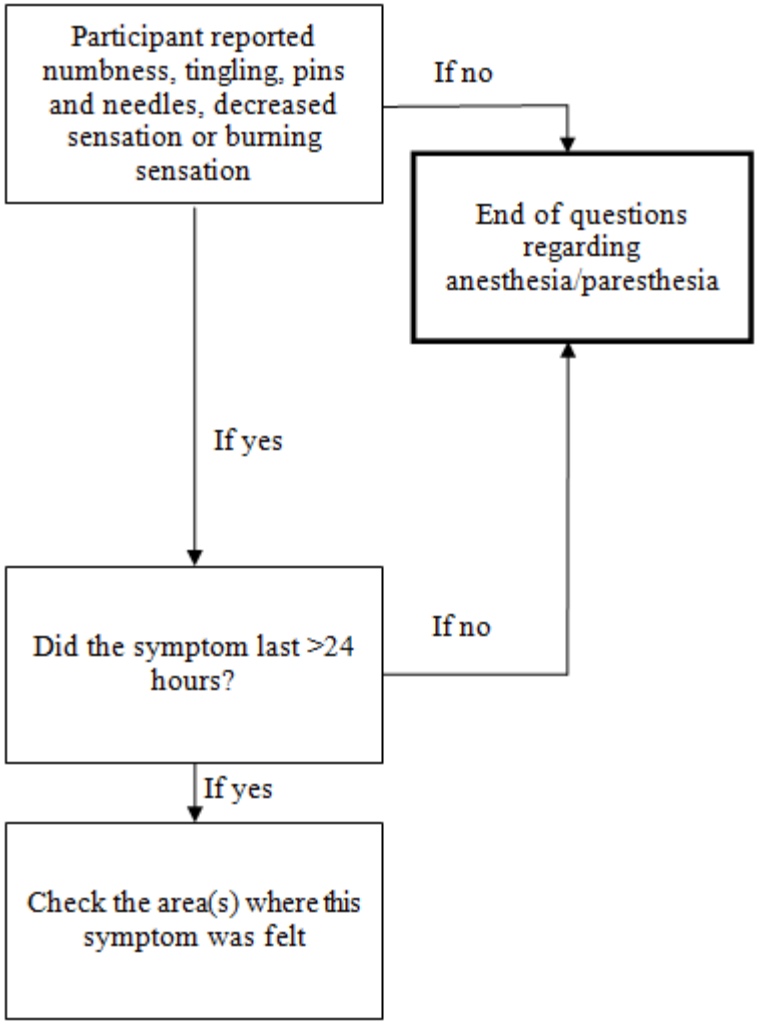


Figure 2.9: Anesthesia/paresthesia flow of questionnaire for controls, Canadian National Vaccine Safety (CANVAS) Network, 2014-2016

Table 2.3: Levels of certainty for generalized convulsive seizures based on the Brighton Collaboration case definition

Level 1 (most certain)	Witnessed sudden loss of consciousness AND generalized[a], tonic[b], clonic[c], tonic-clonic[d], or atonic motor[e, f] manifestations.
Level 2	History of unconsciousness[g] AND generalized, tonic, clonic, tonic-clonic, or atonic motor manifestations.
Level 3	History of unconsciousness AND other generalized motor manifestations[h].
Level 4	Insufficient evidence to meet case definition: when information (i.e., inclusion and/or exclusion criteria) is missing.
Level 5	Not a case of GCS: if an exclusion criterion is met or investigation reveals a negative finding of a necessary criterion for classification in levels 1–3 (e.g., unconsciousness, generalized motor manifestations).

[a] Synonymous: bilateral, more than minimal muscle involvement.
[b] A sustained increase in muscle contraction lasting a few seconds to minutes.
[c] Sudden, brief (< 100 msec) involuntary contractions of the same muscle groups, regularly repetitive at a frequency of about two to three contraction/s.
[d] A sequence consisting of a tonic followed by a clonic phase.
[e] A sudden loss of tone in postural muscles, often preceded by a myoclonic jerk and precipitated by hyperventilation.
[f] In the absence of: hypotonic hyporesponsive episode (as defined by the Brighton Collaboration), syncope, and myoclonic jerks.
[g] The sudden loss of consciousness was not observed, but the patient was found unconscious (i.e., unreactive to verbal and painful stimuli).
[h] Less specific descriptions such as shaking, trembling, shivering, quivering.

There was a discrepancy regarding level 1 diagnostic certainty between the stated Brighton Collaboration criteria and the data collected in CANVAS. In CANVAS, the nurse asked if the seizure was witnessed by a healthcare professional, while Brighton Collaboration case definition entails the sudden loss of consciousness be witnessed. In this study, we make an assumption that these two elements are the same.

Fever ≥38°C, was described if associated with the GCS regardless of the level of certainty. We cannot be confident if the fever reported to the nurse was measured by a device or if it was unmeasured; and a question concerning accurate measurement was not asked. As long as an associated fever ≥38°C was reported to the nurse, it was accepted as such. According to the

Brighton Collaboration case definition of fever: “The value of ≥38ºC is accepted as reflecting an abnormal elevation of temperature, irrespective of device, anatomic site, age, or environmental conditions. While it is recognized that this value is to some extent arbitrary, it is based upon a conservative interpretation of definitions proposed and used by clinicians, investigators, and the public at large (187).” Fever in the context of seizures was described as febrile, afebrile, or as a missing value. Fever was not a defining factor in categorization of GCS.

2.5.2 Main explanatory variable

Vaccination status

This is our main exposure variable of interest describing whether the participant has received the influenza vaccine that influenza season, or if they were unvaccinated. This variable was binary in nature: vaccinee or control.

2.5.3 Other independent variables

These are potential confounders that were conceptually thought of as associated with vaccination, and a risk factor to the development of anesthesia/paresthesia or headaches. All of these variables were categorical in nature, either binary or nominal.

A) Age group

Age was presented as 5 different groups: 6 months-4 years of age, 5-14 years of age, 15-29 years of age, 30-59 years of age, and > 59 years of age. Participants were considered children when less than 15 years of age. We considered age as a potential confounder because as individuals get older, they are more liable to develop peripheral neuropathies since their nervous system also ages. Additionally, older age groups have a higher prevalence of systemic disorders that can affect the whole body and can also lead to neuropathies, such as Diabetes Mellitus (188). As for headaches, new cases of primary headache decrease with age, while those of secondary headache increase (189).

B) Gender

Described as male or female. Further classifications (i.e. “other”) were included only in 2016, so this variable remained dichotomous for the purpose of this study. This variable was chosen as a potential confounder as studies have shown that females generally experience more severe, more frequent, and longer durations of pain (190), including headaches and migraines

(191), especially when self-reported (192). Neuropathic pain is also more common in females (193).

C) Year

While the year is listed as a calendar year, it represents the influenza season (e.g. year 2012 represents influenza season of 2012/13). This variable is considered a potential confounder since every year the influenza vaccine is subject to change in its components as previously described.

D) Center

These were represented by names of cities where participants submitted their surveys. These were Sherbrooke, Quebec City, Halifax, Ottawa, Toronto, Calgary, and Vancouver. Not all jurisdictions use the same vaccines in a given year. Also, different centers can actively enroll participants with different characteristics. For example, Vancouver is one of the sites that mainly recruits adults in the healthcare profession.

2.5.4 Other descriptive variables

Table 2.4 includes a list of variables with their descriptions that were included in describing the outcomes under study.

Table 2.4: Variables included in the descriptive analysis, Canadian National Vaccine Safety Network, 2012-2016.

	Definition	Data	Relevant participants	Notes
Previous vaccination history	Whether or not the vaccinee had previously received an influenza vaccine before enrollment in the study	Dichotomous: Yes/No	Vaccinees only	-
Vaccine product used	The trade name of the vaccine product given to the vaccinee at enrollment	Nominal: Table 2.1 summarizes all influenza vaccine products available in a given year from 2012-2016	Vaccinees only	Data were entered by means of the center or by the vaccinees themselves when filling their surveys (depending on the center and year). They were given this information at vaccination
Body regions for anesthesia/ paresthesia	The reported affected body area where anesthesia/paresthesia took place	Nominal: - Face only; - Leg only; - Lower arm only; - Neck only; - Trunk only; - Scalp only; - Upper arm only; - Leg at side of vaccination only; - Lower arm at side of vaccination only; - Vaccinated upper arm	Individuals who reported anesthesia/ paresthesia as an outcome AND the outcome had occurred within 24 hours from vaccination/ the health monitoring process for controls AND the outcome must have lasted > 24 hours	-

	Definition	Data	Relevant participants	Notes
		only; - More than 1 site		
Time interval to develop the event (onset)	It was the time between vaccination/start of health monitoring process for controls and experiencing the symptom	-	All vaccinees and controls with an outcome	For 2012 and 2013, onset of reported anesthesia/paresthesia could only have happened within 24 hours
Grade of severity	-Describes the intensity of the outcome -This is not synonymous to "serious" AEs referred to by International Committee for Harmonization E2A Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting which is comprised of AEs or reactions that result in death, persistent or significant disability, a congenital anomaly, require hospitalization or elongation of hospital	Nominal: To simplify descriptions, we used 3 grades to describe severity: - **Grade 1:** participants who reported missing work/school or could not perform their normal daily activities (but did not seek medical attention); -**Grade 2**: participants who reported seeking medical attention (but did not miss work/school and could perform their normal daily activities); -**Grade 3:** participants who missed work/school	All vaccinees and controls with an outcome	Missing values from this variable were from year 2013 where the survey design made it possible to not specify the grade of severity. However, all included outcomes could only be severe. To report this variable for anesthesia/paresthesia in 2012, participant must have symptoms of anesthesia/paresthesia with onset < 24 hours, a duration > 24 hours, and the symptom must appear anywhere besides the vaccinated arm

	Definition	Data	Relevant participants	Notes
	stay, is life-threatening, or require intervention to prevent permanent impairment or damage (120)	or could not perform normal daily activities in addition to seeking medical attention		
Type of medical care sought	Where participants went to seek medical attention	Nominal: - General practitioner; - Emergency room; - Hospital; - Other (identified)	Vaccinees or controls who sought medical attention when reporting severity	-
Duration of hospital admission	Time stayed at hospital	Discrete count	Vaccinees or controls who were hospitalized	-
Diagnoses descriptions	These were reported by participants who sought a medical consultation	Text	Vaccinees or controls who sought medical attention	-

2.6 Statistical analyses

Descriptive statistics were used to summarize the overall study sample and descriptions related to each outcome under study. Inferential statistics were used to test our hypotheses. Missing or incomplete data were not replaced. Analyses were performed using SAS software, Version 9.4 of the SAS System for Windows. Copyright © 2002-2012 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA. Measures of potential impact and their confidence intervals (CI) were calculated using OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version 3.01, updated 2013/04/06.

2.6.1 Descriptive statistics

We described the frequencies and proportions of “age group”, “gender”, “center”, and “year” by vaccination status for the overall sample. For vaccinees only in the total sample, previous vaccination history and type of vaccine product used at enrollment were also described. The same descriptions were repeated for participants reporting outcomes, in addition to time interval to develop the event (i.e. onset) and the event duration. Exclusive to anesthesia/paresthesia, we described the body areas affected by the symptom as reported by participants.

Outcomes were summarized using frequencies and proportions for each outcome individually. However, the small count of individuals who experienced GCS made it difficult to describe in terms of proportions; so, only frequencies and individual case descriptions were used.

Grade of severity was described for each outcome by vaccination status (if the participant with the outcome was a vaccinee or control). Type of medical attention sought and diagnoses received were described for anesthesia/paresthesia without headaches, headaches without anesthesia/paresthesia, and for both symptoms together.

For anesthesia/paresthesia and headaches, all reported events from the Day 8 and Control surveys were included in the analyses. For GCS, only reviewed events through follow-up interviews, that were medically attended and could be categorized at a specific Brighton level, were analysed. Using reviewed events of anesthesia/paresthesia and headaches was not possible

as the events must have been severe enough to require medical attention, which was not always expected for these two symptoms.

2.6.2 Inferential statistics

For objectives 1 and 2, we built a main effects multivariable logistic regression model to determine the effect of vaccination on the occurrence anesthesia/paresthesia or headaches. Separate models were built for each outcome. ORs along with their 95% CIs were calculated. The models were built using purposeful selection of covariates as described by Hosmer et al. (194,195). Purposeful variable selection is summarized in the following order:

1) A univariable analysis for each of our independent variables was modeled with the outcome of interest. ORs with 95% CIs were estimated for each analysis. Categories with zero frequency cells were eliminated. Cells with small frequencies were combined with other categories.
2) We used the likelihood ratio test (LRT) to calculate *p*-values for the univariable analyses. Variables whose *p*-values were more than a set cut-off of 0.25 were excluded from our modeling process.
3) We fit the first multivariable model using the selected statistically significant variables from step 2.
4) We then identified variables with a significant alpha level above 0.1. Then, we identified the covariate with the largest *p*-value greater than 0.1 to be excluded first.
5) We fit a reduced model after excluding the variable identified from step 4. These two models were then compared using the partial LRT to ensure that the reduced model fit as well as the original in terms of residual error. AIC values were also used for comparisons. The model with the lesser AIC value was better.
6) The model built in step 5 was based on statistical significance. We further checked for confounding by comparing changes in estimates of all coefficients between the reduced model and the fuller model from step 3. If any change in estimate was > 10%, we retained the variable in the model. This is because variables act differently in the presence of other variables, and so are important to provide a needed adjustment. If the change in estimate was not > 10%, the variable was excluded.

7) If the variable was excluded, we repeated the steps from step 4 onwards.

Our main explanatory variable remained in the model regardless of its statistical significance since it was the variable under investigation. Multicollinearity was assessed for the final regression models. Dependence or redundancies among covariates was a possibility where the same information was provided through more than one variable. The presence of multicollinearity was detected using the variance inflation factor (VIF). A variable is dependent on other covariates if its VIF is greater than 10. The tolerance statistic was also examined, which is a reciprocal of the VIF. Values below 0.2 indicate multicollinearity. If multicollinearity was detected, we would include the variable that was more significantly associated with outcome (196).
Goodness-of-fit of the models was described by the deviance which compares our fitted model with a more complex or saturated model. Because our models have a small number of explanatory variables, all of which are categorical, it was possible to group our data into unique possibilities (or unique profiles) by cross-classifying all levels of our explanatory variables. The saturated model has 1 parameter for each of the unique profiles. For these unique profiles, the observed and expected frequencies for each of the outcomes of the dependent variable were calculated based on our fitted model. The resulting statistic would be a deviance statistic. If the *p*-value was above 0.05, then there was no evidence to reject the null hypothesis, which is that the fitted model is correct (197).

We calculated attributable fraction as a measure of potential impact. As recommended in the literature, we calculated impact numbers among vaccinees for outcomes that were significantly associated with seasonal influenza vaccination, since they are only useful in such situations (198). This measure was calculated by subtracting the odds of the outcome in the control group from the odds of the outcome in the vaccinees and dividing by odds of the outcome in the vaccinated group.

For objective 3, the extremely small sample size with GCS prevented the construction of a model. Instead, we determined independence/dependence of GCS from vaccination using a 2-tailed Fisher's exact test since expected cell counts were less than 5 in 2 cells of the 2x2 table. An OR could not be calculated because 1 cell had zero observations. Statistical significance was assessed using an error level of 0.05.

2.6.3 Secondary analyses

Firstly, we modeled effect modification to examine differential effects of potential confounders on outcomes in vaccinees as compared to controls. For anesthesia/paresthesia as an outcome, we aimed to determine the presence of a measurable effect of vaccination by different centers of reporting. This analysis was carried out after finding higher proportions of anesthesia/paresthesia reports and stronger associations in univariable and multivariable analyses for Vancouver compared to other centers. For headaches, we constructed different models for all potential confounders as effect modifiers, considering we had a greater number of participants with the outcome. Interaction terms were added to the final model that resulted from the previous section (Section 2.6.2). We determined ORs for different levels of covariates and calculated *p*-values for partial LRTs to conclude if models with an effect modifier were better than the reduced model.

Secondly, we investigated the effect of individual vaccine products that could have been specifically associated with the occurrence of anesthesia/paresthesia or headaches in vaccinees. We did not include year 2012 in this part of the analysis for anesthesia/paresthesia because vaccine products were not as well-identified as the rest of the years. We built separate multivariable logistic regression models for each outcome. Potential confounders were included based on the final achieved model from the previous section (Section 2.6.2). For anesthesia/paresthesia, we only modeled Fluviral® and Agriflu® since they were used throughout centers, unlike other products (Appendix B). They were also mainly used in Vancouver which, as previously explained, was more associated with anesthesia/paresthesia when compared to other centers. On the other hand, all vaccine products were modeled for headaches. To adjust for multiple comparisons using Bonferroni's correction, the significance level was set to 0.005.

Chapter 3: Results

3.1 Study Sample

For the influenza seasons between 2012 and 2016, 107,565 individuals participated in CANVAS and were included in this study. Vaccinees represented almost two-thirds of the participants (n = 69,129; 64.3%). Almost half of the vaccinees (46.5%) and half of the controls (48.0%) were between 30 and 59 years of age, while children represented the smallest group. The majority of participants were female in both groups at almost 65%. The province of Quebec had the highest proportions of participants with one-third of all surveys from Sherbrooke for vaccinees and controls (31.3% and 33.8%, respectively). Each year, the number of participants increased. Fluviral® represented more than 40% of all vaccine products used throughout the years. Among vaccinees, 65,078 (94.1%) reported being previously vaccinated at least once in their lives before enrolling in this study. Table 3.1 summarizes participant characteristics.

To investigate headaches and GCS, only influenza seasons from 2013 to 2016 were included in our study sample. The description of this sample was similar to what was previously seen from 2012 to 2016. The table summarizing participant characteristics from 2013 to 2016 is attached in Appendix A.

3.2 Descriptive Statistics

3.2.1 Anesthesia/paresthesia

The overall number of participants who reported anesthesia/paresthesia to CANVAS from 2012 through 2016 was 104 (0.10%) individuals. The proportion in vaccinees was slightly lower than controls (0.09% versus 0.11%).

Table 3.1 displays the differences in characteristics between vaccinees and controls with our outcomes of interest. Vaccinees with anesthesia/paresthesia were mainly adolescents and adults 15 years of age and older. There was only 1 child vaccinee between 5 to 14 years of age, and none were below 5 years of age. Controls with anesthesia/paresthesia were mainly older at 30 to 59 years of age (31/18,435; 0.17%). In both groups, the percentage of females reporting

anesthesia/paresthesia was higher compared to males. Although Sherbrooke had the highest number of participants in this study overall, it had the lowest proportions of anesthesia/paresthesia reports. Reports from Vancouver were higher (11/7,587; 0.14% in vaccinees and 17/5,552; 0.31% in controls) than at other reporting centers. There was no noticeable trend in reporting for vaccinees by year; nonetheless, controls of 2012 had the highest proportion of anesthesia/paresthesia reported (9/2,479; 0.36%). Among vaccinees, the highest proportions of anesthesia/paresthesia were reported with FluLaval® (1/250; 0.40%) and Fluad® (2/600; 0.33%).

Eighty (out of 104) individuals reported both the time interval from the beginning of the health monitoring to development of symptoms (i.e. onset of the symptom) and duration. Onset occurred most frequently within 24 hours of receiving the influenza vaccine (28/51) or within 24 hours of the beginning the health monitoring process for controls (13/29). The distribution of duration of anesthesia/paresthesia did not vary between vaccinees who developed it in the first 24 hours and those who reported it within 2 to 3 days after vaccination (Table 3.2). The majority of controls who also reported onset within 3 days of monitoring their health reported the symptom to be still present on Day 8.

The sensation of anesthesia/paresthesia by body region is shown in (Table 3.3). Out of the 104 individuals reporting anesthesia/paresthesia, 65 individuals did not report the affected body region. Among those who reported on body region, most vaccinees (13/18) experienced anesthesia/ paresthesia in two or more body regions. Half of the vaccinees reported anesthesia/paresthesia in the vaccinated upper arm in addition to another site. The vaccinated upper arm and the lower arm at the side of vaccination were commonly reported together (3/9) when compared to other reports of multiple sites. In controls, the leg was the most frequent site in reports, both as an isolated region (8/22) or combined with other areas of the body (5/7).

3.2.1 Headaches

Headaches were reported by 1,361 (1.40%) participants; 907 (1.48%) versus 454 (1.26%) in vaccinees and controls, respectively. Table 3.1 summarizes headaches reported by participants. Proportions of headaches were higher in vaccinees than in controls for all age groups with the highest proportions occurring in participants between 5 to 14 years of age

(79/4,052; 1.95%) and 15 to 29 years of age (164/8,450; 1.94%) followed by older adults 30 to 59 years of age (483/26,965; 1.79%). The highest proportion in controls was among those 30 to 59 years of age (277/16,659; 1.66%). Similar to anesthesia/paresthesia, headaches were most commonly reported by females and higher reporting occurred in Vancouver. The majority of reports were from vaccinees in 2016 and 2015 (332/19,429; 1.71% and 225/14,641; 1.54%, respectively), and in 2013 for controls (103/6,763; 1.52%). Fluzone® was the most commonly used product by individuals with headaches (122/4,699; 2.60%).

For individuals who reported the onset and duration of headaches (n = 1,084), onset occurred most frequently within the first 3 days of receiving the influenza vaccine (601/776), while almost two-thirds of controls reported headaches started on the fourth day onwards from monitoring their health (202/308). The distribution of duration of headaches was similar to what was found with anesthesia/paresthesia for vaccinees and controls; it did not vary across strata for vaccinees, but a majority of controls reported headaches to still be present when filling out their survey (Table 3.2).

Table 3.1: Number and percentage of anesthesia/paresthesia and headaches events within each stratum by vaccination status, Canadian National Vaccine Safety (CANVAS) Network, 2012-2016

N = Total number where denominators are calculated
n = Numerators with the outcome in a specific category

	Vaccinees			Controls		
	Total	**Anesthesia/ paresthesia**	**Headache[a]**	**Total**	**Anesthesia/ paresthesia**	**Headache[a]**
	N = 69,129	**n = 63 (0.09)**	**n = 907 (1.48)**	**N = 38,436**	**n = 41 (0.11)**	**n = 454 (1.26)**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Age Group						
> 59 years	**19,785** (28.6)	16 (0.08)	151 (0.79)	**11,322** (29.5)	7 (0.06)	66 (0.60)
30-59 years	**32,151** (46.5)	29 (0.09)	483 (1.79)	**18,435** (48.0)	31 (0.17)	277 (1.66)
15-29 years	**10,331** (14.9)	17 (0.16)	164 (1.94)	**4,779** (12.4)	3 (0.06)	65 (1.51)
5-14 years	**4,052** (5.9)	1 (0.02)	79 (1.95)	**2,685** (7.0)	0 (0.0)	39 (1.45)
6 months-4 years	**2,810** (4.1)	0 (0.0)	30 (1.07)	**1,215** (3.2)	0 (0.0)	7 (0.58)
Gender						
Male	**24,312** (35.2)	12 (0.05)	204 (0.92)	**13,162** (34.2)	10 (0.08)	113 (0.90)
Female	**44,817** (64.8)	51 (0.11)	703 (1.79)	**25,274** (65.8)	31 (0.12)	341 (1.46)
Center						
Sherbrooke	**21,624** (31.3)	10 (0.05)	222 (1.07)	**12,989** (33.8)	4 (0.03)	89 (0.70)
Quebec City	**11,426** (16.5)	13 (0.11)	81 (0.82)	**5,344** (13.9)	5 (0.09)	42 (0.85)
Halifax	**5,177** (7.5)	5 (0.10)	90 (2.10)	**3,062** (8.0)	6 (0.20)	54 (2.08)
Ottawa	**5,150** (7.4)	4 (0.08)	72 (1.53)	**2,443** (6.4)	5 (0.20)	42 (1.78)
Toronto	**7,615** (11.0)	9 (0.12)	124 (1.75)	**3,832** (10.0)	2 (0.05)	47 (1.30)
Calgary	**10,550** (15.3)	11 (0.10)	179 (1.89)	**5,214** (13.6)	2 (0.04)	76 (1.46)

[a] Denominators for proportions were calculated from Appendix A

	Vaccinees			Controls		
	Total	**Anesthesia/ paresthesia**	**Headache[a]**	**Total**	**Anesthesia/ paresthesia**	**Headache[a]**
	N = 69,129	**n = 63 (0.09)**	**n = 907 (1.48)**	**N = 38,436**	**n = 41 (0.11)**	**n = 454 (1.26)**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Vancouver	**7,587** (11.0)	11 (0.14)	139 (2.59)	**5,552** (14.4)	17 (0.31)	104 (2.25)
Years						
2012	**7,666** (11.1)	7 (0.09)	NA	**2,479** (6.4)	9 (0.36)	NA
2013	**13,127** (19.0)	12 (0.09)	145 (1.10)	**6,763** (17.6)	9 (0.13)	103 (1.52)
2014	**14,266** (20.6)	8 (0.06)	205 (1.44)	**8,479** (22.1)	9 (0.11)	91 (1.07)
2015	**14,641** (21.2)	15 (0.10)	225 (1.54)	**10,289** (26.8)	7 (0.07)	137 (1.33)
2016	**19,429** (28.1)	21 (0.11)	332 (1.71)	**10,426** (27.1)	7 (0.07)	123 (1.18)
Vaccine product						
Fluviral®	**29,382** (42.5)	25 (0.09)	380 (1.33)	**NA**	NA	NA
Agriflu®	**10,197** (14.8)	9 (0.09)	148 (1.53)	**NA**	NA	NA
Vaxigrip®	**9,015** (13.0)	8 (0.09)	49 (1.15)	**NA**	NA	NA
Influvac®	**8,169** (11.8)	11 (0.13)	114 (1.40)	**NA**	NA	NA
Flumist®	**4,720** (6.8)	1 (0.02)	75 (1.59)	**NA**	NA	NA
Fluzone®	**4,699** (6.8)	5 (0.11)	122 (2.60)	**NA**	NA	NA
Other/unknown	**2,092** (3.0)	1 (0.05)	9 (1.51)	**NA**	NA	NA
Fluad®	**600** (0.9)	2 (0.33)	5 (0.83)	**NA**	NA	NA
FluLaval®	**250** (0.4)	1 (0.40)	5 (2.00)	**NA**	NA	NA
Intanza®	**5** (0.0)	0 (0.00)	0 (0.00)	**NA**	NA	NA
Previously vaccinated						
Yes	**65,078** (94.1)	56 (0.09)	843 (1.46)	**NA**	NA	NA

[a] Denominators for proportions were calculated from Appendix A.

Table 3.2: Reported time interval till the development of anesthesia/paresthesia or headaches, Canadian National Vaccine Safety (CANVAS) Network, 2012-2016

Onset and duration of symptom		Anesthesia/paresthesia		Headaches	
		Vaccinee n = 51	Control n = 29	Vaccinee n = 776	Control n = 308
		n (%)	n (%)	n (%)	n (%)
Within 24 hrs		**28 (54.9)**	**13 (44.8)**	**345 (44.5)**	**26 (8.4)**
Duration	Lasted 1-10 hrs	2 (7.1)	0 (0.0)	23 (6.7)	1 (3.9)
	Lasted 11-24 hrs	4 (14.3)	1 (7.7)	66 (19.1)	4 (15.4)
	Lasted 2-3 days	7 (25.0)	0 (0.0)	87 (25.2)	1 (3.9)
	Lasted 4-5 days	6 (21.4)	0 (0.0)	60 (17.4)	2 (7.7)
	Lasted >= 6 days	4 (14.3)	0 (0.0)	37 (10.7)	1 (3.9)
	Still present	5 (17.9)	12 (92.3)	72 (20.9)	17 (65.4)
Within 2-3 days		**11 (21.6)**	**7 (24.1)**	**256 (33.0)**	**80 (26.0)**
Duration	Lasted 1-10 hrs	0 (0.0)	0 (0.0)	4 (1.6)	1 (1.3)
	Lasted 11-24 hrs	2 (18.2)	0 (0.0)	33 (12.9)	6 (7.5)
	Lasted 2-3 days	1 (9.1)	2 (28.6)	56 (21.9)	19 (23.8)
	Lasted 4-5 days	3 (27.3)	0 (0.0)	45 (17.6)	3 (3.8)
	Lasted >= 6 days	2 (18.2)	0 (0.0)	29 (11.3)	0 (0.0)
	Still present	3 (27.3)	5 (71.4)	89 (34.8)	51 (63.8)
Within 4-5 days		**11 (21.6)**	**2 (6.9)**	**129 (16.6)**	**95 (30.8)**
Duration	Lasted 1-10 hrs	0 (0.0)	0 (0.0)	3 (2.3)	1 (1.1)
	Lasted 11-24 hrs	2 (18.2)	0 (0.0)	14 (10.9)	5 (5.3)
	Lasted 2-3 days	2 (18.2)	0 (0.0)	29 (22.5)	11 (11.6)
	Lasted 4-5 days	0 (0.0)	0 (0.0)	19 (14.7)	18 (19.0)
	Lasted >= 6 days	0 (0.0)	0 (0.0)	8 (6.2)	4 (4.2)
	Still present	7 (63.6)	2 (100.0)	56 (43.4)	56 (59.0)
Within 6-7 days		**1 (2.0)**	**7 (24.1)**	**46 (5.9)**	**107 (34.7)**
Duration	Lasted 1-10 hrs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Lasted 11-24 hrs	0 (0.0)	0 (0.0)	8 (17.4)	2 (1.9)
	Lasted 2-3 days	0 (0.0)	0 (0.0)	11 (23.9)	6 (5.6)
	Lasted 4-5 days	0 (0.0)	1 (14.3)	5 (10.9)	25 (23.4)
	Lasted >= 6 days	0 (0.0)	0 (0.0)	2 (4.4)	22 (20.6)

Table 3.3: Reported sites of anesthesia/paresthesia by vaccination status, Canadian National Vaccine Safety (CANVAS) Network, 2012-2016

Sites[a]	Vaccinees n = 18	Controls n = 22
	n (%)	n (%)
Scalp only	0 (0.0)	0 (0.0)
Face only	0 (0.0)	1 (4.5)
Neck only	1 (5.6)	0 (0.0)
Trunk only	0 (0.0)	3 (13.6)
Vaccinated upper arm only	0 (0.0)	NA
Upper arm only	0 (0.0)	1 (4.5)
Lower arm at side of vaccination only	0 (0.0)	NA
Lower arm only	0 (0.0)	2 (9.1)
Leg at side of vaccination only	4 (22.2)	NA
Leg only	0 (0.0)	8 (36.4)
More than 1 site including vaccinated upper arm	9 (50.0)	NA
More than 1 site (excluding vaccinated upper arm for vaccinees)	4 (22.2)	7 (31.8)

[a] 65 individuals reporting anesthesia/paresthesia did not respond to this question.

3.2.1 Grade of severity, types of medical attention sought, and diagnoses received for anesthesia/paresthesia and headaches

As displayed in Table 3.4, almost half of the participants who reported anesthesia/paresthesia and its grade of severity sought medical advice (42/91). There was no significant difference between vaccinees and controls as to grade of severity of anesthesia/paresthesia. However, there was a significant difference for those who experienced headaches as to Grade 1 ($p < 0.005$).

Most participants who sought medical attention were adults (15 years of age and older). The only children (< 15 years of age) who sought a consultation were those with headaches without anesthesia/paresthesia and these individuals accounted for only 10% of individuals with that outcome (Appendix C).

Diagnoses received for our outcomes covered a diversity of physiological systems, most of which were non-neurological. For example, we see 17 out of 22 with anesthesia/paresthesia and 213 out of 242 with headaches received diagnoses other than neurological.

Among the participants who sought medical advice and experienced anesthesia/paresthesia, 17 vaccinees and controls had the symptom without headache. Most visited a general practitioner or an emergency room. Eleven out of the 17 participants reported their diagnosis from a healthcare provider. Two vaccinees received a neurological diagnosis: one with Guillain-Barré syndrome and another with a possible inflamed sciatic nerve.

On the other hand, those who reported headaches without anesthesia/paresthesia and sought medical advice reached out to a more diverse selection of healthcare professionals (Table 3.5). Vaccinees and controls in the headache group were frequently diagnosed with a respiratory illness or an ear/throat diagnosis. Nonetheless, there was a variety of neurological diagnoses besides isolated headaches and migraines provided for these participants. The most common diagnosis was vertigo which can also result from an inner ear disorder (Table 3.6).

A total of 32 (0.03%) vaccinees and 20 (0.02%) controls reported both headache and anesthesia/paresthesia symptoms. Out of the 27 who reported both symptoms and sought medical advice, one control participant reported seeing a neurologist (Table 3.5). Three vaccinees were diagnosed with a respiratory illness, and one was diagnosed with migraine (Table 3.6).

Table 3.4: Reported grade of severity by participants who reported anesthesia/paresthesia and headaches Canadian National Vaccine Safety (CANVAS) Network, 2012-2016

Severity	Anesthesia/paresthesia[a]			Headaches		
	Vaccinee n = 69,129	Control n = 38,436	*p*-value	Vaccinee n = 61,463	Control n = 35,957	*p*-value
	n (%)	n (%)		n (%)	n (%)	
Grade 1[b]	28 (0.04)	16 (0.04)	0.930	707 (1.15)	327(0.91)	**<0.005**
Grade 2[c]	11 (0.02)	7 (0.02)	0.780	37 (0.06)	27 (0.08)	0.381
Grade 3[d]	21 (0.03)	15 (0.04)	0.457	163 (0.27)	99 (0.28)	0.768

[a] Only participants reporting severity anesthesia/paresthesia must have occurred within 24 hours of vaccination/beginning monitoring health event, and must lasted more than 24 hours.
[b] Participants who reported missing work/school or could not perform their normal daily activities.
[c] Participants who reported seeking medical attention.
[d] Participants who missed work/school or could not perform normal daily activities in addition to seeking medical attention.

Table 3.5: Types of medical consultations reported by participants with anesthesia/paresthesia without headaches, headaches without anesthesia/paresthesia, and both anesthesia/paresthesia and headaches, Canadian National Vaccine Safety (CANVAS) Network, 2012-2016

Consultation[a]	Anesthesia/ paresthesia without headaches			Headaches without anesthesia/ paresthesia			Both		
	Vaccinee n = 11	Control n = 6	*p*-value	Vaccinee n = 192	Control n = 121	*p*-value	Vaccinee n = 19	Control n = 8	*p*-value
	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
GP	6 (54.5)	4 (66.7)	1.000	144 (75.0)	101 (83.5)	0.111	10 (52.6)	6 (75.0)	1.000
ER[b]	4 (36.3)	1 (16.7)	0.600	27 (14.1)	13 (10.7)	0.361	3 (15.8)	1 (12.5)	0.651
Hospital[c]	0 (0.0)	0 (0.0)	NA	1 (0.5)	0 (0.0)	1.000	0 (0.0)	0 (0.0)	NA
Other:									
Healthlink (811)	1 (0.1)	0 (0.0)	1.000	6 (3.1)	1 (0.8)	0.328	3 (15.8)	0 (0.0)	0.286
Nurse	0 (0.0)	0 (0.0)		4 (2.1)	0 (0.0)		2 (10.5)	0 (0.0)	
Pharmacist	0 (0.0)	1 (16.7)		6 (3.1)	2 (1.7)		1 (5.3)	0 (0.0)	
Specialist[d]	0 (0.0)	0 (0.0)		4 (2.1)	4 (3.3)		0 (0.0)	1 (12.5)	

GP: General practitioner
ER: Emergency room
[a] 18 participants with headaches without anesthesia/paresthesia had more than 1 consultation, 17of which involved a GP.
[b] 1 participant was transferred by ambulance and also reported a seizure.
[c] Duration is 5 days due to gastrointestinal diagnosis.
[d] Chest doctor/eye doctor/ear, nose, and throat doctor/neurologist/chiropractor/infectious disease specialist.

Table 3.6: Diagnoses reported by participants after their medical consultations for anesthesia/paresthesia, headaches, or both anesthesia/paresthesia and headaches, Canadian National Vaccine Safety (CANVAS) Network, 2012-2016

Diagnoses[a]	Anesthesia/ paresthesia without headaches		Headaches without anesthesia/ paresthesia		Both	
	Vaccinee n = 8	Control n = 3	Vaccinee n = 136	Control n = 92	Vaccinee n = 6	Control n = 5
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Neurological diagnoses						
Cluster headache	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)
Febrile seizure	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Guillain-Barré syndrome	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Migraine	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (16.7)	0 (0.0)
Neuralgia	0 (0.0)	0 (0.0)	1 (0.7)	1 (1.1)	0 (0.0)	0 (0.0)
Possible inflamed Sciatic nerve	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vertigo	0 (0.0)	0 (0.0)	1 (0.7)	4 (4.3)	0 (0.0)	0 (0.0)
Atypical benign headache	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Viral meningitis	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory diagnoses[a]	2 (25.0)	0 (0.0)	59 (43.4)	42 (45.7)	3 (50.0)	0 (0.0)
Ear/throat infection[b]	0 (0.0)	0 (0.0)	27 (19.9)	15 (16.3)	0 (0.0)	0 (0.0)
Viral/bacterial infection[c]	0 (0.0)	2 (66.7)	15 (11.0)	9 (9.8)	1 (16.7)	1 (20.0)
Eye infection/inflammation[d]	0 (0.0)	0 (0.0)	2 (1.5)	1 (1.1)	0 (0.0)	1 (20.0)
Cardio-vascular diagnoses[e]	0 (0.0)	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)	1 (20.0)
Gastrointestinal diagnoses[f]	0 (0.0)	0 (0.0)	3 (2.2)	2 (2.2)	0 (0.0)	1 (20.0)
Urinary tract diagnoses[g]	0 (0.0)	1 (33.3)	1 (0.7)	5 (5.4)	0 (0.0)	0 (0.0)
Allergic reaction[h]	1 (12.5)	0 (0.0)	6 (4.4)	1 (1.1)	1 (16.7)	0 (0.0)
Arthralgia/arthritis	1 (12.5)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)
Other[i]	0 (0.0)	0 (0.0)	4 (2.9)	4 (4.3)	0 (0.0)	1 (20.0)
Undetermined[j]	2 (25.0)	0 (0.0)	12 (8.8)	5 (5.4)	0 (0.0)	0 (0.0)

[a] Common cold, bronchitis, influenza, pneumonia, sinusitis, cough, asthma, upper respiratory tract infection, laryngitis, fibrocystic lung disease.
[b] Streptococcal throat infection, tonsillitis, ear infection, otitis, pharyngitis.
[c] Varicella Zoster Virus (Chicken pox/shingles), coxsachie virus, adenovirus, unidentified.
[d] Blepharitis (inflamed eyelids), iritis, conjunctivitis, infection.
[e] High blood pressure and low blood pressure
[f] Dehydration due to gastrointestinal virus, gastroenteritis, viral gastroenteritis, flu bug, gastritis.
[g] Pyelonephritis, urinary tract infection.
[h] Oculo-respiratory syndrome, reaction to the influenza vaccine, allergy.
[i] Lower back pain, insomnia, localized vaccine reaction, perioral dermatitis, aerophagia (excess air swallowing) and gastroparesis (reduced abdominal muscle motility), iritis (inflamed iris), posttraumatic disorder, query thyroiditis, and 1 person did not wish to disclose the diagnosis.
[j] Consultant unsure of diagnosis, awaiting investigations, awaiting specialist's appointment.

3.2.1 Generalized convulsive seizures (GCS)

There were 7 individuals reporting seizures from 2013 through 2016, 6 of whom were vaccinees. Four of the 7 were reported in 2016, 4 were female, and 4 of the reports were from the province of Quebec (3 from Sherbrooke and 1 from Quebec City). Three participants with seizures reported grade 1 severity, and 4 reported grade 3.

Full details of the event were only captured for 3 participants. For the remaining participants: 1 was lost to follow-up, 2 did not see a healthcare provider and therefore were ineligible for follow-up, and 1 described only lower back pain as a concern in the follow up phone call with no record of a seizure in the interview.

Table 3.7 describes seizures that occurred in the 3 eligible individuals as identified through the follow-up interviews. These 3 met the Brighton Collaboration case definition for GCS. The seizures occurred in females and were from the vaccinated group. They were previously vaccinated at least once.

Table 3.7: Descriptions of generalized convulsive seizures for participants in the Canadian National Safety (CANVAS) Network, 2013-2016

Participant	#1	#2	#3
Vaccine product	Vaxigrip®	Fluviral®	Flumist®
Age	> 59 years	6 months-4 years	6 months-4 years
Interval between vaccination and onset of symptoms	4 days	6-7 days	3 days
Duration of episode	3 hours	4 minutes	1 day

Participant	#1	#2	#3
Diagnosis received	Epileptic fit	Febrile seizure	Idiopathic generalized epilepsy
History of seizure	Yes	No	No
Type of medical attention	ER[a]	Ambulance+ER	ER + Hospitalized[b]
Fever ≥38ºC	No	Yes	No
Anesthesia/paresthesia	Yes	No	No
Headache	No	Yes	No
Criteria for Brighton Collaboration classification:			
Witnessed seizure[c]	Yes	No	No
History of loss of consciousness	Yes	Yes	Yes
Type of motor manifestation	NA	Tonic-clonic	Tonic-clonic
Level of GCS according to Brighton Collaboration case definition	*Level 4*	*Level 2*	*Level 2*

[a] Emergency room.
[b] The hospitalized participant entered the hospital and was released the following day.
[c] This variable is collected in the Canadian National Vaccine Safety (CANVAS) Network as a seizure witnessed by a healthcare professional, while in Brighton Collaboration case definition it states witnessed sudden loss of consciousness.

3.3 Inferential statistics

3.3.1 Research objective 1: The association of seasonal influenza vaccine with risk of occurrence of anesthesia/paresthesia

Table 3.8 presents the univariable analyses of the main explanatory variable (vaccination status) as well as potential confounders (age group, gender, center, and year) modeled with the outcome of the occurrence of anesthesia/paresthesia. For the "age group" variable, we combined the 5-14 years of age category with the 15-29 years of age category because there was only 1 child participant in the 5-14 age group with anesthesia/paresthesia. We eliminated the youngest age group (6 months to 4 years of age) from this analysis because it had no participants with anesthesia/paresthesia.

For our main explanatory variable, the OR was 0.86 (95% CI = 0.58, 1.28). CIs of ORs for the age groups of 5-29 and 30-59 years of age, when compared to the age group of 59 years of age and above, suggested no significant difference between ages that report anesthesia/paresthesia. ORs for reporting anesthesia/paresthesia in all centers, especially Vancouver, was significantly higher when compared to Sherbrooke. There was no significant difference in reporting anesthesia/paresthesia for all years when compared to 2016.

Based on the LRT that compares each of the univariable analyses to the null model, "age group", "gender", and "center" variables were statistically significant candidates for the multivariable analysis as their *p*-values were less than our set cut-off point of 0.25. "Year" did not meet the statistical criteria to remain in the model. Since "vaccination status" was the main explanatory variable, it was kept in the model.

A multivariable model was then created without the variable "year". Results of the model are shown in Figure 3.1. Looking at the *p*-values of this model, and according to our set cut-off of 0.1 to retain the variable, both categories in the age group variable were not statistically significant. There were no other variables with a *p*-value above 0.1, so "age group" was the only variable to be excluded. Again, "vaccination status" remained in our model because it was the main explanatory variable under investigation.

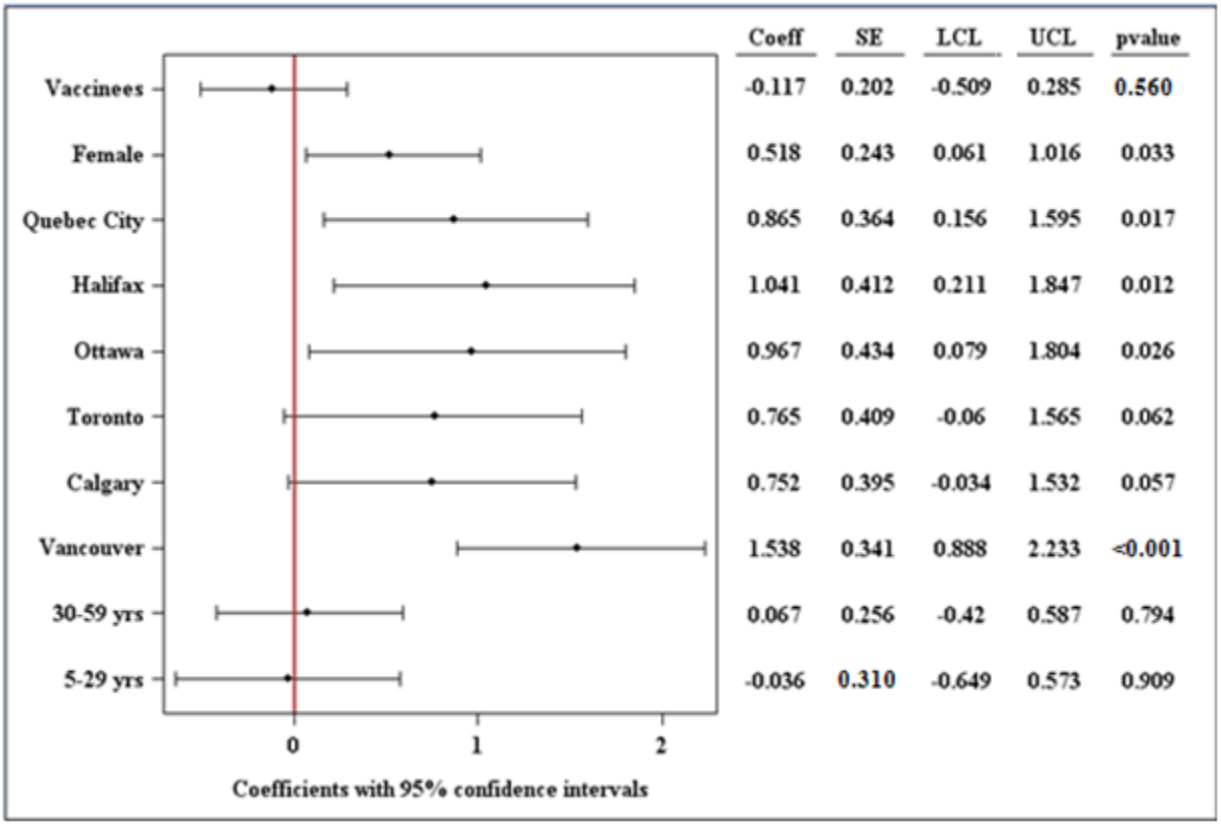
Comparing the more parsimonious model ("year" and "age group" excluded) to the fuller model (only "year" excluded) was important to be sure that neither model fit significantly better than the other. Results of the partial LRT yielded a *p*-value of 0.911. The result was not significant at $p < 0.05$, so we failed to reject the null hypothesis and concluded that there was no significant difference between the reduced and full models in terms of deviance. AIC values also decreased from 1631.338 to 1627.524 from the fuller to the reduced model. To further explore if "age group" confounded the effect of any of the other covariates, we assessed the change in coefficients for all variables in the model, demonstrated in Table 3.9. All changes in coefficients were less than 10%.

Figure 3.2 shows the results of the multivariable logistic regression model. Since none of the *p*-values for coefficients was > 0.1, we considered this to be the final model. The OR of the effect of vaccination on reporting anesthesia/paresthesia was 0.89 (95% CI = 0.60, 1.32) adjusting for center of reporting and gender, *p*-value = 0.552.

None of the VIF in Table 3.10 exceeded 10 (and none of the tolerance statistics were below 0.2), so it was concluded that there were no problems of multicollinearity between the variables in the model. A goodness-of-fit test was done to determine if the model fit the data. There was a deviance of 25.608 with 19 degrees of freedom. The *p*-value for the deviance was 0.142, meaning our data fit the model.

Table 3.8: Univariable logistic regression analysis of covariates associated with anesthesia/paresthesia among participants, Canadian National Vaccine Safety (CANVAS) Network, 2012-2016

	Coefficient	Standard error	Odds ratio (95% confidence interval)	*p*-value
Vaccination status				
Controls	-	-	Reference	**0.463**
Vaccinees	-0.148	0.201	0.86 (0.58, 1.28)	
Age Group				
> 59 years	-	-	Reference	
30-59 years	0.473	0.245	1.61 (0.99, 2.60)	**0.135**
5-29 years	0.263	0.302	1.30 (0.72, 2.35)	
Gender				
Male	-	-	Reference	**0.004**
Female	0.660	0.240	1.93 (1.21, 3.10)	
Center				
Sherbrooke	-	-	Reference	
Quebec City	0.936	0.357	2.55 (1.27, 5.13)	
Halifax	1.154	0.403	3.17 (1.44, 6.98)	
Ottawa	1.033	0.427	2.81 (1.22, 6.49)	**< 0.001**
Toronto	0.824	0.403	2.28 (1.04, 5.02)	
Calgary	0.781	0.385	2.18 (1.03, 4.65)	
Vancouver	1.641	0.328	5.16 (2.72, 9.81)	
Year				
2016	-	-	Reference	
2015	-0.062	0.285	0.94 (0.54, 1.64)	
2014	-0.223	0.308	0.80 (0.44, 1.46)	0.362
2013	0.117	0.289	1.12 (0.64, 1.98)	
2012	0.479	0.314	1.61 (0.87, 2.98)	



***Reference groups**: Center (ref: Sherbrooke); Age group (ref: > 59 yrs)
yrs: years
Coef: Parameter coefficient.
UCL: Upper confidence limit.
LCL: Lower confidence limit.
SE: Standard error.

Figure 3.1: Results of multivariable regression model with all covariates significant from univariable analyses, Canadian National Vaccine Safety (CANVAS) Network, 2012-2016

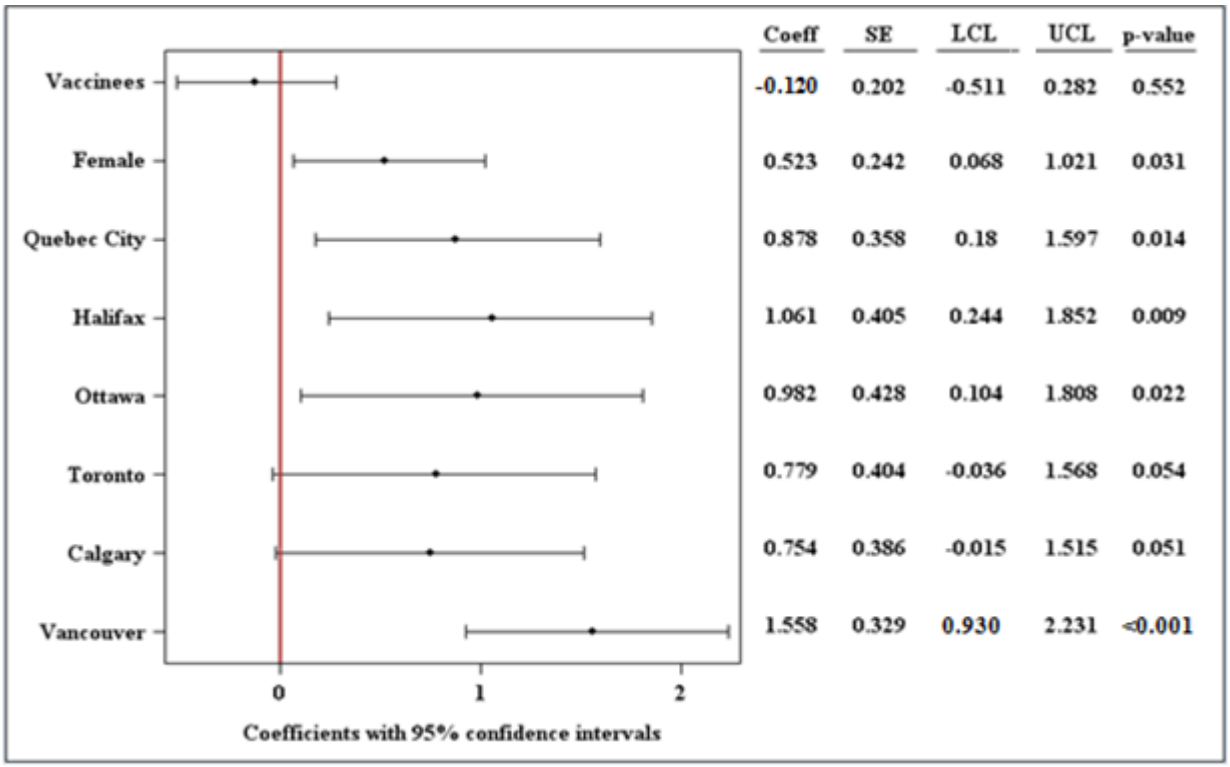
Table 3.9: Estimated change in coefficients between full (Figure 3.2) and reduced models (Figure 3.1)

	Change in Coefficients
Vaccination status	
Controls	-
Vaccinees	2.6%
Gender	
Male	-
Female	1.0%
Center	
Sherbrooke	-
Quebec City	1.5%
Halifax	1.9%

Ottawa	1.6%
Toronto	1.8%
Calgary	0.3%
Vancouver	1.3%

Table 3.10: Multicollinearity diagnostics for the final multivariable logistic regression model for anesthesia/paresthesia, Canadian National Vaccine Safety (CANVAS) Network, 2012-2016

Variable	Degrees of freedom	Variance inflation factor (VIF)	Tolerance (1/VIF)
Vaccination status	1	1.00063	0.99937
Center	1	1.00844	0.99163
Gender	1	1.00805	0.99202



***Reference group**: Center (ref: Sherbrooke)
Coef: Parameter coefficient.
UCL: Upper confidence limit.
LCL: Lower confidence limit.
SE: Standard error.

Figure 3.2: Final multivariable logistic regression analysis of the relationship between vaccination status and the occurrence of anesthesia/paresthesia, Canadian National Vaccine Safety (CANVAS) Network, 2012-2016

3.3.2 Research objective 2: The association of seasonal influenza vaccine with risk of occurrence of headaches

Table 3.11 shows the results of the univariable logistic regression analyses for the main explanatory variable, vaccination status, and the potential confounders. There were no categories with zero counts, so we did not delete or combine any categories. All variables were candidates for the multivariable model using the *p*-value cutoff < 0.25. Therefore, the multivariable model included all covariates.

For our main explanatory variable, the point estimate of the OR, 1.17, showed a preliminary increased risk of headaches after seasonal influenza vaccination with a 95% CI (1.05, 1.31) indicating that the increase was significant. When compared to seniors (> 59 years of age), all age groups showed a significant increased chance in the occurrence of headaches, except for children below 5 who did not show any significant difference. With the exception of Quebec City, ORs showed significantly higher odds of headaches in all reporting centers when compared to Sherbrooke, with the highest odds in Vancouver (2.65; 95% CI = 2.24, 3.14). All years showed decreased odds of headache occurrence when compared to 2016, with CIs not crossing 1 indicating that headaches were significantly more reported in 2016 than in previous years.

Results of the multivariable model are shown in Figure 3.3. All of our variables were significant based on our set cut-off of 0.1, except for the age category of 6 months to 4 years of age ($p = 0.234$). The partial LRT for exclusion of the age group variable yielded a *p*-value of < 0.001. The AIC was also higher in the reduced model (14036.211) when compared to the full model (13912.028). Therefore, the fuller model (with “age group” included) had significantly lower residual deviance, and so age group was kept in the multivariable logistic regression model. The OR of the effect of vaccination on reporting severe headaches in the final model was 1.21 (95% CI = 1.08, 1.36) adjusting for age group, gender, center of reporting, and year; *p*-value = 0.001.

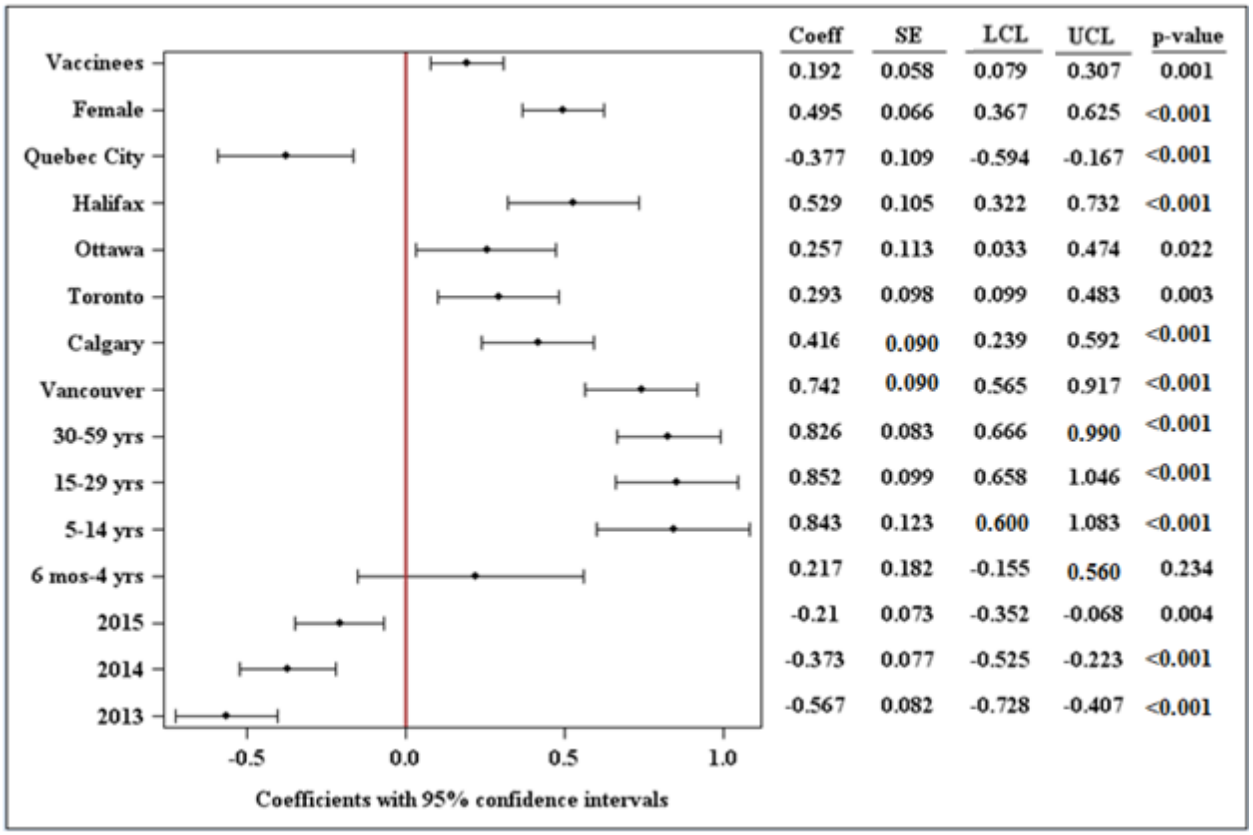
None of the VIF in Table 3.12 exceeded 10 (and none of the tolerance statistics were below 0.2), so it was concluded that there were no problems of multicollinearity between the variables in the model. A goodness-of-fit test was done to determine if the model fit the data.

There was a deviance of 548.079 with 517 degrees of freedom. The *p*-value for the deviance was 0.166, meaning our data fit the model.

The calculated attributable fraction among vaccinees indicates that 14.6% (95% CI = 4.4, 23.8) of all severe headaches among vaccinees are due to the seasonal influenza vaccine.

Table 3.11: Univariable logistic regression analysis of covariates associated with headaches among participants, Canadian National Vaccine Safety (CANVAS) Network, 2013-2016

	Coefficient	Standard error	Odds ratio (95% confidence interval)	*p*-value
Vaccination status				
Controls	-	-	Reference	**0.006**
Vaccinees	0.158	0.058	1.17 (1.05, 1.31)	
Age Group				
> 59 years	-	-	Reference	
30-59 years	0.898	0.077	2.46 (2.11, 2.86)	
15-29 years	0.929	0.095	2.53 (2.10, 3.05)	< **0.001**
5-14 years	0.904	0.115	2.47 (1.97, 3.09)	
6 months-4 years	0.251	0.179	1.29 (0.91, 1.82)	
Gender				
Male	-	-	Reference	< **0.001**
Female	0.613	0.065	1.85 (1.63, 2.09)	
Center				
Sherbrooke	-	-	Reference	
Quebec City	-0.115	0.107	0.89 (0.72, 1.10)	
Halifax	0.820	0.102	2.27 (1.86, 2.77)	
Ottawa	0.553	0.110	1.74 (1.40, 2.16)	< **0.001**
Toronto	0.547	0.096	1.73 (1.43, 2.08)	
Calgary	0.627	0.085	1.87 (1.59, 2.21)	
Vancouver	0.974	0.086	2.65 (2.24, 3.14)	
Year				
2016	-	-	Reference	
2015	-0.049	0.071	0.95 (0.83, 1.09)	**0.031**
2014	-0.160	0.075	0.85 (0.74, 0.99)	
2013	-0.204	0.080	0.82 (0.70, 0.95)	



***Reference groups**: Center (ref: Sherbrooke); Age group (ref: > 59 yrs); Year (ref: 2016)
yrs: years; mos: months
Coef: Parameter coefficient.
UCL: Upper confidence limit.
LCL: Lower confidence limit.
SE: Standard error.

Figure 3.3: Final multivariable logistic regression analysis of the relationship between vaccination status and the occurrence of headaches, Canadian National Vaccine Safety (CANVAS) Network, 2013-2016

Table 3.12: Multicollinearity diagnostics for the final multivariable logistic regression model for headaches, Canadian National Vaccine Safety (CANVAS) Network, 2013-2016

Variable	Degrees of freedom	Variance inflation factor (VIF)	Tolerance (1/VIF)
Vaccination status	1	1.00063	0.99937
Center	1	1.01807	0.98226
Gender	1	1.01173	0.98841
Age group	1	1.01169	0.98845
Year	1	1.01201	0.98813

3.3.3 Research objective 3: The association of seasonal influenza vaccine with the occurrence of generalized convulsive seizures (GCS)

There were 3 participants who reported GCS out of the 97,420 participants from 2013-2016, all of whom were vaccinees. Although no controls reported seizures, the difference between groups was not statistically significant using a Fisher's exact test (p = 0.3014). No OR could be reported because no event occurred in the control group.

3.4 Secondary analyses

For anesthesia/paresthesia, effect modification of the main effect was investigated with center as the effect modifier after finding a high statistical significance in the univariable and multivariable analyses for Vancouver. Results of the interaction was not significant (p = 0.136) meaning that we could not reject the null hypothesis that the effects of vaccination on anesthesia/paresthesia was equivalent for different centers. Partial LRT also showed no significance when compared to our final model (p = 0.094).

For headaches, after determining an overall significant effect following vaccination, we examined effect modification of all potential confounders (center, gender, year, and age group) with vaccination and determined ORs for different levels of covariates using separate models. Table 3.13 shows different ORs and the results of partial LRTs. Despite significance in some categories, partial LRT showed none of the models with effect modifiers were significantly better than the reduced model previously described.

There was no significant association between any particular vaccine product and the occurrence of anesthesia/paresthesia or headaches, after we set the significance level at 0.005 based on Bonferroni correction to account for multiple comparisons (Table 3.14 & Table 3.15).

Table 3.13: Effect modification of the association between seasonal influenza vaccination and headaches by center, gender, year, and age group, Canadian National Vaccine Safety (CANVAS) Network, 2013-2016

	Odds ratio (95% confidence interval)	*p*-value of partial LRT
Center as effect modifier		0.097
Vaccinee vs Control at Center = Calgary	1.29 (0.98, 1.69)	
Vaccinee vs Control at Center = Halifax	0.97 (0.69, 1.37)	
Vaccinee vs Control at Center = Ottawa	0.88 (0.60, 1.30)	
Vaccinee vs Control at Center = Quebec City	1.07 (0.74, 1.56)	
Vaccinee vs Control at Center = Sherbrooke	**1.59 (1.24, 2.03)**	
Vaccinee vs Control at Center = Toronto	1.37 (0.97, 1.92)	
Vaccinee vs Control at Center = Vancouver	1.08 (0.83, 1.40)	
Gender as effect modifier		0.949
Vaccinee vs Control at Gender = Female	**1.26 (1.11, 1.44)**	
Vaccinee vs Control at Gender = Male	1.06 (0.84, 1.34)	
Year as effect modifier		0.250
Vaccinee vs Control at Year = 2013	0.91 (0.70, 1.17)	
Vaccinee vs Control at Year = 2014	**1.35 (1.05, 1.73)**	
Vaccinee vs Control at Year = 2015	1.15 (0.93, 1.42)	
Vaccinee vs Control at Year = 2016	**1.41 (1.15, 1.74)**	
Age group as effect modifier		0.681
Vaccinee vs Control at Age Group = 6 months-4 years	1.91 (0.84, 4.37)	
Vaccinee vs Control at Age Group = 5-14 years	1.37 (0.93, 2.02)	
Vaccinee vs Control at Age Group = 15-29 years	1.29 (0.96, 1.72)	
Vaccinee vs Control at Age Group = 30-59 years	1.11 (0.96, 1.29)	
Vaccinee vs Control at Age Group => 59 years	**1.38 (1.03, 1.85)**	

LRT: Likelihood ratio test; comparing to reduced model with age group, gender, center, and year as confounders.

Table 3.14: Adjusted odds ratios of multivariable logistic regression model on the effect of influenza vaccine products compared to controls on the occurrence of anesthesia/paresthesia, Canadian National Vaccine Safety (CANVAS) Network, 2013-2016

	Odds ratio (95% confidence interval)	*p*-value*
Vaccine product		
Fluviral®	1.02 (0.63, 1.65)	0.940
Agriflu®	0.93 (0.44, 1.95)	0.849

Table 3.15: Adjusted odds ratios of multivariable logistic regression model on the effect of influenza vaccine products compared to controls on the occurrence of headaches, Canadian National Vaccine Safety (CANVAS) Network, 2013-2016

	Odds ratio (95% confidence interval)	*p*-value*
Vaccine product		
Fluviral®	1.07 (0.89, 1.30)	0.282
Agriflu®	1.04 (0.87, 1.26)	0.661
Vaxigrip®	1.34 (0.98, 1.83)	0.063
Influvac®	1.12 (0.90, 1.41)	0.310
Flumist®	1.15 (0.86, 1.53)	0.360
Fluzone®	1.28 (1.02, 1.61)	0.035
Other/unknown	0.73 (0.37, 1.42)	0.350
Fluad®	0.80 (0.33, 1.96)	0.624
FluLaval®	0.79 (0.32, 1.94)	0.610

*To account for multiple comparisons, we set the significance level at 0.005 based on Bonferroni correction

Chapter 4: Discussion

4.1 Anesthesia/paresthesia as an outcome

4.1.1 Investigating the association between seasonal influenza vaccination and anesthesia/paresthesia

This study was done using post-marketing surveillance data to investigate a hypothesis based on anesthesia/paresthesia signals following the 2009 pandemic vaccine in Quebec, Canada and other European countries (93,112–114). Based on published studies in peer-review health journals, this is the first study to measure the association between seasonal influenza vaccination and the occurrence of anesthesia/paresthesia using multi-year data (2012-2016). In this study, anesthesia/paresthesia was a rare AEFI, with 0.09% of vaccinees developing the symptom. A higher proportion (0.11%) of controls reported this event. Our OR estimate of 0.86 indicates that we fail to reject the null hypothesis and conclude that seasonal influenza vaccination is not associated with increased odds of developing anesthesia/paresthesia. Nonetheless, the wide CI around our OR (0.58 - 1.28) indicates that our sample size did not have sufficient power to precisely estimate the association of such a rare event.

It is possible that the 2009 signal was associated with the adjuvant AS03 which was used by 96% of individuals who reported anesthesia/paresthesia in Quebec and was a component of the pandemic vaccine, Pandemrix®, used in Sweden and France. The signal could also be due to surveillance bias, or may be a reflection of a Weber effect, an epidemiological phenomenon where new products have higher initial reporting rates post-marketing (199).

Studies in the literature reporting anesthesia/paresthesia as an AEFI have been based mainly on passive reporting. The two population-based cohort studies in Sweden that measured associations with Pandemrix® were positive but weak, with hazard ratios of 1.11 (95% CI = 1.00, 1.23) and 1.07 (95% CI = 1.02, 1.11). Increased risk in vaccinees in that study was observed in a predominantly high-risk population (children with multifunctional disorders; pregnant women; patients with chronic heart or lung disease, diabetes mellitus, chronic liver failure, chronic renal failure, or immunosuppression; people with extreme obesity (body mass index > 40); and patients with neuromuscular disease affecting breathing capacity). The excess risk was explained as a possible local symptom at the injection site. Since these studies included millions of

participants and follow-up time was up to two years, their results had more power to detect a rare association, should one exist, than did our study. In fact, the CI we observed encompasses those of the other studies. Unfortunately, these studies did not investigate clinical features of the symptom to get a better understanding of the nature of this AEFI.

Vancouver had the highest proportions of anesthesia/paresthesia reports for both vaccinees and controls. Also, univariable and multivariable analyses showed a high association between Vancouver as a reporting center and the occurrence of anesthesia/paresthesia. However, we did not find the effect of vaccination on our outcome modified by reporting center. We investigated this finding further for vaccinees, to determine whether vaccine products used in Vancouver may have contributed to the increase. The types of vaccine products used in the Vancouver were Fluviral® (59.7%) and Agriflu® (34.5%). Running a separate multivariable logistic model to determine an association between either vaccine and the occurrence of anesthesia/paresthesia showed no significant association. The high association seen between Vancouver, compared to other centers, and the occurrence of anesthesia/paresthesia could be a result of other factors not accounted for in our analysis such as differences in underlying co-morbidities.

Our results showed seasonal influenza immunization to be protective against anesthesia/paresthesia. However, it is unlikely that seasonal influenza immunization is associated with a protective effect for developing anesthesia/paresthesia. The decreased risk may be a result of the healthy vaccinee effect. This happens when healthy people tend to be immunized (i.e., vaccines not administered when an individual is unwell or recently diagnosed with a new condition). Capturing anesthesia/paresthesia in 2012 and 2013 was also restricted to those who experienced the symptom within 24 hours from vaccination. Based on the BCCDC, the temporal criteria for anesthesia/paresthesia as an AEFI for inactivated vaccines is 0-15 days while for live attenuated vaccines is up to 42 days (200). Thus this shorter, stringent temporal requirement could have led to an underestimation of vaccinated participants with these symptoms.

4.1.2 Describing the nature of anesthesia/paresthesia reported in our study sample

Most reports from vaccinees and controls were received from 30-59 year old females. The same pattern was seen in the study in Quebec that included 328 anesthesia/paresthesia cases

from their passive surveillance system during the 2009 pandemic influenza season. This was explained as a possible hormonal or physiological relationship between women in this age group and the occurrence of anesthesia/paresthesia (114).

In the same Quebec study, 177 (54%) reported onset within 24 hours of vaccination. Similarly, in our study, onset in more than half of vaccinees was within the first 24 hours. This front-loading of events was further investigated since for years 2012 and 2013 only anesthesia/paresthesia within 24 hours was collected. However, after excluding these two years (i.e. 2012 and 2013), this same pattern was still observed. Interestingly, the highest proportion of controls with anesthesia/paresthesia also reported onset within 24 hours of the start of their monitoring period. What was seen in our study could be from the small sample size of vaccinees (n = 51) and controls (n = 29) reporting onset and duration that may make this skewed distribution misleading.

As for duration, to have comparable duration periods for comparisons between vaccinees and controls, we examined participants whose onset of anesthesia/paresthesia was within the first 3 days of the monitoring period. For vaccinees, there were no noticeable differences in the distribution of durations reported. However, if anesthesia/paresthesia were to be confused with localized pain, we would have to expect a more condensed distribution in duration with most symptoms resolving within 3 days of vaccination (201). In the control group, the vast majority reported that the symptom was still present at the end of the monitoring period, indicating symptoms of longer durations. This qualitative finding that vaccinees and controls reported different durations is interesting, given that no association was found in our study. Nonetheless, there is a potential of measurement bias in both onset and duration reporting. This is because, starting 2014, we could not tease out onsets and durations of anesthesia/paresthesia from any other reported symptom that could be associated with anesthesia/paresthesia; and more than 60% of our anesthesia/paresthesia reports were from 2014 to 2016. This bias could skew the distribution to reflect perhaps onsets and durations of more severe symptoms that were associated with anesthesia/paresthesia.

Half of our vaccinated participants who reported the anatomical areas affected by anesthesia/paresthesia experienced the symptom at the injection site along with other areas, meaning that the effect was more generalized than local and refutes the possibility of confusing

the definition of localized pain with anesthesia/paresthesia as mentioned earlier. Similar results were reached in the Quebec study where various sites were reported in more than half of the participants.

In our study, nearly half of the participants reporting anesthesia/paresthesia sought medical attention. We did not observe any differences between vaccinees and controls as to grade of severity. Participants of 2012 and 2013 were only able to report grade of severity of anesthesia/paresthesia if it had lasted for more than 24 hours, which could be worrisome for either group. Also, it is possible that other associated symptoms in vaccinees and controls were what had led to the medical consultations.

The symptom was reported in conjunction with many different disease processes where diagnoses received varied between physiological systems as respiratory, neurological, renal, and more. None were diagnosed as having anesthesia/paresthesia as an isolated diagnosis. This means that anesthesia/paresthesia is a non-pathognomonic symptom rather than a disease. One of the diagnoses received was GBS, which is a very rare neurological severe AE that could be attributable to the seasonal influenza vaccine. On the other hand, in the aforementioned study that took place in Sweden, the excess risk for anesthesia/paresthesia was explained as a possible constitution of a local symptom (for example, pain, redness, swelling, tingling); there was no evidence in the study to support that claim (93). Since our data was self-reported, it is worth noting that it is difficult to rely fully on entries of diagnoses, since some were provisional diagnoses and some participants were unsure of their condition. It was also possible that diagnoses reported were part of co-morbidities familiar to the participant, instead of diagnoses related to the selected symptom.

4.2 Headaches as an outcome

4.2.1 Investigating the association between seasonal influenza vaccination and headaches

We aimed to investigate if a relationship exists in the CANVAS data (2013-2016) between seasonal influenza vaccination and the occurrence of headaches. Using a multivariable

logistic regression analysis, our results show an increase in odds of 21 per cent following vaccine exposure when compared to non-vaccinees. We can reject our null hypothesis, and conclude that our results show a difference between vaccinees and controls in terms of risk of developing headaches following seasonal influenza vaccination. The presence of an association in this study was in alignment with results of a recent meta-analysis from RCTs when vaccinees were compared to placebos (or nothing) that demonstrated an association between seasonal influenza vaccination and all headaches regardless of severity or seriousness (98). Although, the association was not dependent on center of reporting, we saw a higher and more significant odds in the occurrence of headaches after vaccination in Sherbrooke. No specific vaccine product was associated with headaches, including those mainly used in Sherbrooke (Fluviral® (57.8%), Vaxigrip® (16.6%) and Agriflu® (11.6%)). Other factors not investigated in this study could be responsible for such findings. For example, perhaps in Sherbrooke participants received concomitant vaccines that contributed to this observed association.

The proportion of headaches in our sample for vaccinees who could not perform normal daily activities, experienced absenteeism, or sought medical attention after using any vaccine product within 7 days of vaccination was 1.48%, rendering headaches as a common AEFI, according the WHO classification for frequency and severity vaccine reactions (6). Information on headaches as an AEFI is commonly collected in clinical trials. Comparing our proportion to grade 3 headaches from clinical trials (i.e. headaches that prevented daily activities), our proportions were similar, indicating the reliability of this reported event through CANVAS.

The calculated attributable fraction among vaccinees indicates that if vaccinees were not actually vaccinated with the seasonal influenza vaccine, there would be a 14.6% reduction in headaches in this group. Calculating attributable fraction assumes causation between exposure and outcome. Since, headaches as an inflammatory response following vaccination are biologically plausible, we consider this to be a valid measure.

4.2.2 Describing the nature of headaches reported in our study sample

In our study, similar to evidence from clinical trials, headaches were least common in the oldest age group (> 59 years of age) of vaccinees and most common in young adult (15-29 years of age) vaccinees (202–204). Controls had slightly more reports in the older adult group (30-59

years of age). It is possible that the highest reports in our controls were under 41 years of age as prevalence of headaches is known to decrease after age 40 (205). Females reported more headaches than males as expected from the literature, especially with self-reported data (190–192).

In accordance to what is known of headaches as a systemic inflammatory reaction, onset of headaches in our study occurred within the first 24 hour following vaccination (142,206). Controls, however, had an opposite pattern. Typically, we expect an equal distribution of onset among strata for controls. Instead, we saw headaches occur more with delayed onsets. This could be due to better recall of later than earlier events, although this was not seen with anesthesia/paresthesia in the control group. The pattern of duration was similar to anesthesia/paresthesia for both vaccinees and controls (i.e. no observable differences between strata for vaccinees, while most headaches were still present for controls). We expect headaches to last up to 3 days from onset as seen in clinical trials and surveillance studies, but since these were severe headaches, they could have had the potential to last longer. Again, reporting onset and duration for headaches had the same issue of measurement bias as discussed with anesthesia/paresthesia where onset and duration could only be reported once for all symptoms in the survey. It is plausible that reported onset and duration may not reflect just headache if associated with other symptoms.

The majority of participants reporting headaches did not seek medical advice. Differences in grade of severity of headaches between vaccinees and controls were seen in light of vaccinees' inability to perform daily activities and/or absenteeism. The impact of such a finding can affect future vaccine compliance, especially when the degree of severity of a potential AEFI is not communicated to an individual at the time of vaccination. The majority of medical diagnoses were related to respiratory illnesses, possibly based on the symptoms of the systemic reaction following the vaccine that include low grade fever, muscle soreness, and nausea.

4.3 Generalized convulsive seizures (GCS) as an outcome

Our third objective was to investigate the risk of occurrence of GCS following seasonal influenza vaccination. GCS as a very rare AEFI (< 0.01%) in our data, constrained us to

conservatively conclude the absence of an association following vaccination. A larger sample size is required to be able to investigate GCS as an outcome and calculate a difference in risk.

There were some discrepancies between Brighton Collaboration definitions and how questions were laid out in the follow-up interviews. Firstly, the highest level of diagnostic certainty (level 1) case definition in Brighton Collaboration is based on seizures associated with "witnessed sudden loss of consciousness"; however, our data collected information on seizures witnessed by a healthcare professional. Such a restriction to whom witnessed the event made it more difficult to be captured as a GCS, since seizures are generally of short duration and are difficult to be witnessed by a healthcare provider outside of a medical setting. This may have led to an underestimation of individuals that could be classified as level 1. Secondly, levels 2 and 3 of Brighton Collaboration definitions require information on history of unconsciousness (i.e. unreactive to verbal and painful stimuli), where CANVAS follows up data collected history of seizures.

The applicability of the Brighton Collaboration case definition for GCS in this context was challenging. There was no access to medical records or a method of extracting reliable detail on motor manifestations. Two of the participants identified the type of generalized motor manifestation to be tonic-clonic. We recognize that such technical terms may not be familiar to a lay person with no medical background, especially since Brighton Collaboration case definitions are meant for use by medical health professionals. However, we accepted such entries when reported by participants.

4.3.1 Describing the nature of generalized convulsive seizures (GCS) reported in our study sample

Febrile seizures temporally related to vaccination occur within 24 hours of inactivated vaccines and 5 to 14 days following live attenuated vaccines (207,208). In this study, one child participant classified as GCS was administered an inactivated vaccines and developed a seizure after 6-7 days. Additionally, seizures are not likely to last more than 11 minutes (209). Longer durations mean the seizure is likely to extend to a condition called "status epilepticus" which is a seizure that lasts more than 30 minutes, or two or more seizures without full recovery of consciousness between them (209,210). Our data showed that a participant had GCS that

persisted for 3 hours, and a child had GCS that lasted 1 day till resolved. Inaccuracies from self-reported data are noticeable with such descriptions that are possible, but highly unlikely, and are a limitation in our results. This was also evident when the parent of the child with the prolonged GCS reported that the episode was not witnessed.

One child participant developed an afebrile seizure after a live attenuated vaccine 3 days following vaccination. Literature does not conclude associations between vaccination and afebrile seizures, although reports following vaccination exist (211,212). Again, since this is self-reported data, fever may or may not have been present, especially since there is no evidence of using a device to accurately measure temperature.

One of the participants classified with GCS in this study was older than 59 years of age, had a previous seizure, and was diagnosed as having an epileptic convulsion. Reports of epileptic convulsions in adults followed the use of Pandemrix® monovalent vaccine in the 2009 pandemic, but epidemiological studies showed no increased risk (213). Therefore, it is likely that this is a coincidental event following vaccination.

4.4 Strengths of the study

Unlike other observational studies and surveillance systems, CANVAS includes events from control groups not yet subject to vaccination. These data provide background rates and allow for accurate calculation of risk. With passive post-marketing surveillance systems, denominators used are from immunization registries or doses distributed. These provide imprecise estimates, since they do not exactly translate to an exposed population (214).

CANVAS is an active surveillance system which overcomes the issue of underreporting of events, delayed reporting, and inconsistent or incomplete reporting. Unlike post-marketing passive surveillance, active surveillance entails additional effort to search for and identify individuals with AEFIs. Therefore, less reliance is placed on motivation of individuals and individuals are more likely to report their events.

Generally, data collection methods and survey questions were consistent throughout the years. This made multi-year analysis possible due to the similar variable definitions used from year to year. The data being consistently collected within a 7-day period

also allowed pooling of the data together, and the limited timing supposedly did not pose an issue regarding recall in both groups. This pooling of data made it possible to account for different confounders with a larger sample.

Our study had the advantage of analyzing five years of data across Canada, adjusting for multiple factors that could falsely alter the true relationship between vaccination and our outcomes, and comparing results to a group that was not exposed to the vaccine. These factors give more credibility to our results in detecting temporal associations following vaccination.

4.5 Limitations of the study

There were a number of limitations in our study. Although self-reported CANVAS data has its advantages, it still brings some skepticism regarding the validity and reliability of the data, especially since participants were not trained on high quality surveillance reporting. Initially, participants with any severe event were re-contacted by a nurse to review and confirm the condition reported online. Due to the growing number of participants and the established validity of the data examined through nurse follow-up interviews with published studies from previous seasons, telephone follow-up for all participants in the survey was stopped after 2014 (54). Starting 2015, only those with medically-attended events were contacted for the follow up. These interviews were the only method of review that took place to ensure that what was reported online matched the chief complaint for which medical attention was sought. Therefore, for this study, no validation of events took place by contacting the individual's healthcare provider or comparing medical records, even for medically attended events.

Another limitation lies in how controls were chosen. Controls of one year were vaccinees of the previous year. Therefore, the assumption of independence for building a logistic regression model was not met. Because the data were unidentifiable, we could not match individuals' surveys from one season to the next. Violation of this assumption led to underestimated errors and *p*-values. Coefficients also lost some efficiency by not accounting for dependence in the data, but would be well-estimated regardless, given our sample size.

No quality check was done to ensure that vaccinees from the previous year have not been vaccinated in the current year when enrolled as controls. However, this scenario could only

happen if a participant was administered an influenza vaccine in another province, since control surveys were sent out before provincial influenza vaccines were available.

For rare events, CANVAS had limited power to detect associations. For example, in our study, the analysis of anesthesia/paresthesia resulted in large CIs, and we were unable to undertake statistical testing for GCS where only 3 vaccinees had the outcome.

In addition, over the years of CANVAS surveillance, controls have been less likely to complete the survey than the vaccinated individuals. Of the original 220,000 people enrolled in the main CANVAS study, control response proportions ranged from 13% to 50%, while the range of participation for vaccinees was 60% to 74%. This issue of non-response may indicate a difference in traits and reported outcomes between participants and non-participants. This is a source of selection bias that may change the results towards or away from the null depending on individuals' responses. Generally, one would expect that those with events would be more likely to respond. This issue was investigated using 2012 CANVAS data only, but no further studies were carried out since.

Other sources of biases arose from the limited questions collected in surveys. For example, we did not have any data regarding concomitant vaccinations received at the time, any underlying health condition at start of follow-up, medication history, or ethnicity. Inability to include these variables in our model could result in unmeasured confounding and could bias our results. Without knowledge of underlying conditions, we were unable to assess for healthy vaccinee effect, which, if present, would result in underestimation of the risk of events in vaccinees.

Although surveys were consistent throughout the years, they were not always identical. Reasons were related to study resources, modifying the questionnaire to be more detailed or concise in certain areas, or based on participant feedback. Examples include changes in categorization of age groups due availability of a high dose vaccine for the elderly (Fluzone® High-Dose (Sanofi Pasteur)), and details collected on seizures. What specifically posed a disadvantage were changes in order of questions regarding severity of anesthesia/paresthesia since it could not be collected for all participants of 2012 and 2013. This was explained in detail in an earlier section (section 2.5.1). For that reason, a limited number of participants with anesthesia/paresthesia in this study could report their severity.

Because our data were based on severe events, we can compare our results to studies with similar criteria. For example, we can relate to clinical trials reporting grade 3 of an event (i.e. one that prevents daily activities). For other surveillance systems we will have lower rates if we compare to reports of any event. For example, a phase 3 clinical trial investigating different types of seasonal influenza vaccines reported headaches to be about 20%. However, grade 3 headaches in the same study were ~ 1% (137). Other surveillance systems could be structured to describe any event in addition to serious events (defined as reactions that result in death, persistent or significant disability, require hospitalization or elongation of hospital stay, or is life-threatening) which does not match our definition of a severe event. Therefore definitions need to be considered when comparing our findings to other studies.

Finally, there was a difference in the data collection period between vaccinees and controls. This may pose a problem if there was discordance in infectious diseases between these weeks. However, pooling data from multiple years and using a regression model should make up for this issue if one exists.

4.6 Public health significance and recommendations

Although vaccination is one of the greatest measures of disease prevention, no vaccine is absolutely safe or free from adverse reactions. Careful post-marketing vaccine surveillance is important in completing a vaccine's safety profile through measuring known adverse events, recognizing events not determined in clinical trials, and identifying groups where vaccines could be contraindicated. Active post-marketing surveillance systems, such as CANVAS, for influenza vaccines are of special importance since vaccines in current use are manufactured to reflect strain requirements for each season, and necessarily differ from influenza vaccines produced in earlier seasons. They are also given in large quantities over a short time period.

In our study, we found no increased risk of occurrence of anesthesia/paresthesia following seasonal influenza vaccination. On the other hand, we found an increased risk in the development of severe headaches, but with no increased risk with any specific vaccine. For GCS, we could not detect any association largely because there were not enough participants who developed the outcome in our study sample.

Anesthesia/paresthesia is not a recognized AE following seasonal influenza vaccine. Our results provide further evidence to support this lack of recognition. Anesthesia/paresthesia is known to be associated with a wide range of underlying disorders from nervous system disorders, circulatory disorders, metabolic disorders, infections, autoimmune diseases, nutrient deficiencies, skin disorders, toxins, psychological, or hereditary disorders. Our study supported this finding as seen by the different diagnoses reported by those with anesthesia/paresthesia symptoms. For this reason, we find anesthesia/paresthesia symptoms to be non-specific for neurologic disorders. If we intend to look at the symptom in further studies to determine neurologic disorders, we recommend looking at all associated symptoms and diagnoses when possible to identify those events that may be associated with a neurologic disease. Therefore, symptoms of anesthesia/paresthesia should not be solely used to suppose neurologic disease. Additionally, although, there was no significant association between seasonal influenza vaccination and the occurrence of anesthesia/paresthesia, there seemed to be qualitative differences between vaccinees and controls as to the duration of the symptom and similarities to its onset and areas of the body being affected. We recommend continued research towards investigating clinical features of the symptom following vaccination, especially since we see a front-loading of events at earlier onsets in the vaccinated group. This may be suggestive of a vaccine event that we were not powered to detect.

The increased risk of headaches was not unexpected because it is part of the body's systemic process in response to a new viral antigen, and it is recorded on the vaccines' monographs as a common AEFI. Of course, few individuals read these monographs before they are administered a vaccine, and they may not be previously educated about influenza vaccine AEs. Therefore, this information needs to be communicated to healthcare providers and vaccinees. Finding a difference between vaccinees and controls as to prevention of daily activities/absenteeism can affect vaccine compliance and hesitancy, especially when the severity of an AEFI is not well communicated. Headaches are an expected systemic inflammatory response; its non-recognition can result in unnecessary stress, anxiety, and cost to the health care system. Over-the-counter (OTC) analgesics (i.e. pain relievers) help reduce headaches following vaccination. However, there is no consensus in the literature to whether analgesics could blunt the body's immune response to the vaccine (215). Lower antibody responses have been reported

with use of analgesics especially when novel antigens are introduced from vaccine (216,217). So, before communicating recommendations for use of analgesics after influenza vaccination, research is needed to generate evidence-based decisions on this topic. Moreover, there is a list of interactions and contraindications for different OTC analgesics for individuals who have chronic conditions, whom are also highly encouraged to be vaccinated against influenza. Until recommendations are concluded, educating recipients to expect systemic effects may help increase their tolerance and reduce health care visits.

As for GCS, our surveillance system had the capacity to detect only a small number of cases, so we could not investigate an association because of the infrequency of the event. We found Brighton Collaboration case definitions to be difficult to apply to self-reported events. To be fair, these definitions were designed for healthcare professionals with the advantage of medical chart review and were not designed for application to self-reported events. Therefore, for participant-based surveillance, we do not recommend the use of Brighton Collaboration case definitions to classify GCS.

This study demonstrated that self-reporting is an efficient method for surveillance of AEFIs. Detecting an association for headaches and none for anesthesia/paresthesia implies differences in reporting of subjective symptoms making it possible to rely on the public to distinguish their own symptoms somewhat accurately. Also, the system was efficient in detecting GBS which is a very rare neurological AE associated with anesthesia/paresthesia. To enhance the benefit of the system, we recommend linking each personal ID every time the same individual rejoins for a survey. This will account for correlation and dependence in the data, and therefore decrease erroneous statistical inferences when conducting multi-year analyses.

Although our study investigated an association for anesthesia/paresthesia and GCS, our sample size was too low to detect associations with sufficient power. Using the infrastructure and capacity of the CANVAS system, it could be feasible to take part in international collaborations to overcome statistical power issues for vaccine safety studies and investigate rare and serious events if a common protocol is used. Similar collaborations previously took place to assess the risk of GBS following the 2009 HIN1 pandemic monovalent vaccines, and feasibility of the project was demonstrated (218). Unifying and developing ideal case

definitions, that are feasible in a self-reported system is first necessary for such efforts to succeed.

As to investigating causal relationships, the last immunization safety review on influenza vaccines and neurological complications was published in 2004 by IOM. More updated revisions are necessary to evaluate the evidence on possible causal associations between immunization and AEFIs. There are also a limited number of studies for causality assessment on vaccine safety (219). Such studies are of particular importance in the face of false allegations and misinterpretations that vaccines cause certain AEFIs, which can easily undermine vaccine coverage rates and public trust in vaccines.

Finally, ongoing monitoring of AEFIs remains crucial for vaccine safety since their perceived risk is the main threat for successful vaccination programs. Also, pharmacovigilance is incomplete without proper communication of results, as per its definition (20). We need to ensure that vaccine safety results are communicated to stakeholders within the field of public health and to those being vaccinated.

Chapter 5: Conclusion

This study contributes different pieces of information for each of our select neurological outcomes: anesthesia/paresthesia, severe headaches, and GCS. Although we did not find a significant association between seasonal influenza vaccination and anesthesia/paresthesia, we observed qualitative differences and similarities between vaccinees and controls as to onset, duration, and areas affected in the body. We suggest further research on the clinical features of the symptom in vaccinees. We support that anesthesia/paresthesia is not an AE following seasonal influenza vaccination, with merits no additional counceling to the public or health care providers.

We found an increased risk of severe headaches in vaccinees. This increased risk was similar to associations described in previous studies for all headaches following seasonal influenza vaccination. The proportions in vaccinees were also similar to severe headaches from clinical trials. A higher proportion of vaccinees with severe headaches were prevented from perfoming daily activities or work/school absenteeism when compared to the non-vaccinated group. Such information needs to be communicated with healthcare providers and the public prior to vaccination, explaining such a possibility. This possibility needs to be clarified and explained in comparison to severity of influenza infection. Transparent communication is important to increase the public's confidence in vaccines. Evidence-based recommendations are necessary concerning the use of analgesics before or after administration of the vaccine.

Finally, our data could did not detect an association between the seasonal influenza vaccine and the occurrence of GCS. Larger sample sizes are needed to investigate this very rare AEFI. We used the Brighton Collaboration case definition for GCS to identify cases; however, there is a need for standardized validated tools that define GCS cases when self-reported.

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Appendices

Appendix A Table of characteristics of vaccinees and controls in the Canadian National Vaccine Safety (CANVAS) Network, 2013-2016

	Vaccinees n = 61,463	Controls n = 35,957
	n (%)	n (%)
Age Group		
> 59 years	19,186 (31.2)	11,087 (30.8)
30-59 years	26,965 (43.9)	16,659 (46.3)
15-29 years	8,450 (13.7)	4,311 (12.0)
5-14 years	4,052 (6.6)	2,685 (7.5)
6 months-4 years	2,810 (4.6)	1,215 (3.4)
Gender		
Male	22,280 (36.2)	12,532 (34.9)
Female	39,183 (63.8)	23,425 (65.1)
Center		
Sherbrooke	20,696 (33.7)	12,629 (35.1)
Quebec City	9,836 (16.0)	4,930 (13.7)
Halifax	4,285 (7.0)	2,591 (7.2)
Ottawa	4,709 (7.7)	2,366 (6.6)
Toronto	7,075 (11.5)	3,606 (10.0)
Calgary	9,496 (15.4)	5,214 (14.5)
Vancouver	5,366 (8.7)	4,621 (12.9)
Year		
2013	13,127 (21.4)	6,763 (18.8)
2014	14,266 (23.2)	8,479 (23.6)
2015	14,641 (23.8)	10,289 (28.6)
2016	19,429 (31.6)	10,426 (29.0)
Vaccine product		
Fluviral®	28,490 (46.4)	NA
Agriflu®	9,657 (15.7)	NA
Vaxigrip®	4,276 (7.0)	NA
Influvac®	8,169 (13.3)	NA
Flumist®	4,720 (7.7)	NA
Fluzone®	4,699 (7.7)	NA
Other/unknown	597 (1.0)	NA
Fluad®	600 (1.0)	NA

FluLaval®	250 (0.4)	NA
Intanza®	5 (0.0)	NA
Previously vaccinated	57,795 (94.0)	NA

Appendix B Doses administered to all who participated as vaccinees stratified by center, Canadian National Vaccine Safety (CANVAS) Network, 2013-2016[a]

Vaccine product	Calgary	Halifax	Ottawa	Quebec City	Sherbrooke	Toronto	Vancouver	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Fluviral®	3,953 (41.6)	1,111 (25.9)	84 (1.8)	6,073 (61.7)	11,971 (57.8)	2157 (30.5)	3,141 (58.5)	**28,490 (46.4)**
Agriflu®	315 (3.3)	516 (12.0)	1,811 (38.5)	504 (5.1)	2,394 (11.6)	2,636 (37.3)	1,481 (27.6)	**9,657 (15.7)**
Vaxigrip®	1 (0.0)	1 (0.0)	2 (0.0)	0 (0.0)	3,438 (16.6)	832 (11.8)	2 (0.0)	**4,276 (7.0)**
Influvac®	10 (0.1)	6 (0.1)	2,783 (59.1)	3,107 (31.6)	995 (4.8)	1265 (17.9)	3 (0.1)	**8,169 (13.3)**
Flumist®	2,499 (26.3)	0 (0.0)	0 (0.0)	152 (1.6)	1,732 (8.4)	23 (0.3)	314 (5.9)	**4,720 (7.7)**
Fluzone®	2,224 (23.4)	2,182 (50.9)	27 (0.6)	0 (0.0)	136 (0.7)	87 (1.2)	43 (0.8)	**4,699 (7.6)**
Other/ Unknown	71 (0.8)	386 (9.0)	0 (0.0)	0 (0.0)	30 (0.1)	26 (0.4)	84 (1.6)	**597 (1.0)**
Fluad®	415 (4.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	184 (3.4)	**600 (1.0)**
FluLaval®	6 (0.1)	83 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	48 (0.7)	113 (2.1)	**250 (0.4)**
Intanza®	2 (0.0)	0 (0.0)	2 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	**5 (0.0)**
Total	**9,496 (15.4)**	**4,285 (7.0)**	**4,709 (7.7)**	**9,836 (16.0)**	**20,696 (33.7)**	**7,075 (11.5)**	**5,366 (8.7)**	**61,463 (100.0)**

[a] Vaccine products for year 2012 were not identified at an individual level in every province, so were not included in this table.

Appendix C Age distribution of types of medical consultations reported by all participants for anesthesia/paresthesia without headaches, headaches without anesthesia/paresthesia, and both outcomes, Canadian National Vaccine Safety (CANVAS) Network, 2012-2016

	Consultation[a]	6 months-4 years n (%)	5-14 years n (%)	15-29 years n (%)	30-59 years n (%)	> 59 years n (%)
Anesthesia/ paresthesia without headaches	**General practitioner (GP)**	0 (0.0)	0 (0.0)	2 (40.0)	3 (75.0)	5 (62.5)
	Emergency room (ER)[b]	0 (0.0)	0 (0.0)	3 (60.0)	1 (25.0)	1 (12.5)
	Hospital[c]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (25.0)
n = 17	***Total***	**0 (0.0)**	**0 (0.0)**	**5 (29.4)**	**4 (23.5)**	**8 (47.1)**
Headaches without anesthesia/ paresthesia	**General practitioner (GP)**	11 (91.7)	18 (94.7)	27 (62.8)	154 (81.5)	35 (70.0)
	Emergency room (ER)[b]	1 (8.3)	1 (5.3)	15 (34.9)	16 (8.5)	7 (17.0)
	Hospital[c]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
	Other	0 (0.0)	0 (0.0)	1 (2.3)	19 (10.0)	7 (17.0)
n = 313	***Total***	**12 (3.8)**	**19 (6.1)**	**43 (13.7)**	**189 (60.4)**	**50 (16.0)**
Both n = 27	**General practitioner (GP)**	0 (0.0)	0 (0.0)	1 (3.7)	11 (40.7)	4 (40.0)
	Emergency room (ER)[b]	0 (0.0)	0 (0.0)	0 (0.0)	4 (25.0)	0 (0.0)
	Hospital[c]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	6 (60.0)
	Total	**0 (0.0)**	**0 (0.0)**	**1 (3.7)**	**16 (59.3)**	**10 (37.0)**