SEASONAL INFLUENZA VACCINE SAFETY IN CHILDREN AND PREGNANT PEOPLE: CROSS-SECTIONAL ANALYSIS FROM 2013/2014 TO 2019/2020

by

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Abstract

Introduction: The Canadian National Vaccine Safety (CANVAS) network collects seasonal influenza vaccine safety data from adults and children across Canada each year. Health events are evaluated between a vaccinated group and an unvaccinated group using data from online surveys. This thesis aims to describe the rate of severe health events and the most severe symptoms following seasonal influenza vaccination compared to an unvaccinated group of children and pregnant people. In addition, it aims to determine the agreement between symptoms reported in the online survey and a follow-up telephone report.

Methods: Uncorrelated data from the CANVAS network were analyzed from 2013/2014 to 2019/2020. The outcome of interest was a severe health event that prevented/stopped daily activities, missed school, or required medical consultation. Incidence rate ratios and logistic regressions were conducted for both groups of interest to determine the association between vaccination status and severe health events. The sensitivity, specificity, and kappa estimate were calculated to determine the agreement for the most severe symptom, diagnosis, and treatment.

Results: The unadjusted rate ratio for severe health events in children who received the inactivated influenza vaccine (IIV) compared to unvaccinated children was 1.22 (1.10, 1.34). However, no differences were observed in children who received the live attenuated influenza vaccine (LAIV) compared to an unvaccinated child group. The adjusted odds ratio (OR) for severe health events in children who received IIV compared to unvaccinated children was 1.11 (1.00, 1.25), and 1.11 (0.95, 1.29) in children who received LAIV compared to unvaccinated children. The agreement between child responses in the self-report online survey and the

telephone report was moderate-to-high in both vaccinated and unvaccinated participants combined. The unadjusted rate ratio for severe health events in vaccinated pregnant people compared to unvaccinated pregnant people was 1.00 (0.64, 1.58). The adjusted OR for severe health events in vaccinated compared to unvaccinated pregnant people was 0.95 (0.59, 1.53).

Conclusions: The findings show no association between the seasonal influenza vaccine and severe health events in children and pregnant people in Canada. There was moderate to high agreement of child responses between the online survey and the telephone report.

Lay Summary

This study explored the safety of the yearly influenza shot in children and pregnant people in Canada. The study found no increase in health events between vaccinated and unvaccinated children and pregnant people. It showed that similar symptoms were reported in an online survey and over the telephone for child participants. This study shows that the yearly flu vaccines are safe for kids and pregnant people.

Preface

The Canadian National Vaccine Safety (CANVAS) Network provided data for this thesis. The literature review, data cleaning, data analyses, and the interpretation of the study results were completed by Jimmy Lopez. I was provided guidance by my supervisor, Dr. Julie Bettinger, and my committee members, Dr. Monika Naus, and Dr. Patti Janssen.

This study was conducted in collaboration with other sites in the CANVAS network:

- Louis Valiquette, Centre Hospitalier Universitaire de Sherbrooke
- Otto Vanderkooi, Alberta Children's Hospital, University of Calgary
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- Anne McCarthy, Ottawa Hospital General Campus

Research ethics approval was obtained at the primary coordination centre, at the Children's & Women's Health Centre of British Columbia[1], and each participating research site in the CANVAS network.

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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
CI	Confidence Interval
F/P/T	Federal/Provincial/Territorial
HC	Health Canada
IAV	Influenza A virus
IBV	Influenza B virus
IM	Intramuscular injection
IMPACT	Canadian Immunization Monitoring Program ACTive
IIV	Inactivated influenza vaccine
IIV3	Trivalent inactivated influenza vaccine
IIV4	Quadrivalent inactivated influence vaccine
IRR	Incidence Rate Ratio
LAIV	Live attenuated influenza vaccine
LAIV3	Trivalent Live attenuated influenza vaccine
LAIV4	Quadrivalent Live attenuated influenza vaccine
LRT	Likelihood Ratio Test
OR	Odds Ratio
PHAC	Public Health Agency of Canada
VVWG	Vaccine Vigilance Working Group
WHO	World Health Organization

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Dedication

To my family and friends.
Thank you for your constant support over the years.

Chapter 1: Background

1.1 Seasonal Influenza Vaccines

Vaccination is the most effective measure in preventing and controlling seasonal influenza infection and severe health outcomes. [1, 2] Vaccination against seasonal influenza provides individual-level protection and reduces community-level transmission. In high-risk groups, such as children, vaccination reduces the risk of laboratory-confirmed influenza infection and may also reduce the risk of influenza-like illness. [3] Similarly, in pregnant women, it reduces the risk of laboratory-confirmed illness. [4] Given the increased risk of influenza-associated morbidity and hospitalization in children [5, 6] and pregnant women [7, 8], both high-risk groups are prioritized to receive the seasonal influenza vaccine in Canada. [1]

Influenza can spread between people via aerosol, contact transmission, or droplets. The incubation period is approximately 2 days, but this can range between 1-to-4 days. Influenza virus can be categorized into types A, B, C, and D, with types A and B commonly circulating in humans. Influenza A virus (IAV) is categorized into subtypes based on the antigenic properties of two surface proteins. The surface proteins are referred to as hemagglutinin (HA) and neuraminidase (NA). Influenza B virus (IBV) is categorized into lineages instead, commonly referred to as Yamagata and Victoria. [1, 9] Influenza viruses frequently undergo genetic mutations that provide an opportunity for novel strains of the virus to emerge and evade immunity from prior infection or vaccination. [10]

Two critical features continue to limit the vaccine's ability to provide long-term protection. Firstly, the influenza virus mutates over time, known as antigenic drift. [11] Secondly, vaccine-induced antibodies wanes over time, which have been observed to occur in the same seasonal influenza season. [12-15] The composition of the seasonal influenza vaccine is

updated each year to better match circulating strains of the virus in order to provide continued protection.

1.2 Seasonal Influenza Vaccine Composition in Canada from 2013/2014 to 2019/2020

During the 2013/2014 to 2019/2020 influenza seasons in Canada, there were 2 types of seasonal influenza vaccines administered to children and pregnant women: 1) the inactivated influenza vaccine (IIV), and 2) the live attenuated influenza vaccine (LAIV). [16-23]

IIVs are made using a killed version of the influenza virus, whereas LAIVs use a weakened form of the influenza virus. The weakened components of the virus in LAIVs are cold-adapted and sensitive to temperature. Therefore, it can replicate at cooler temperatures to elicit an immune response. [24-26] Both seasonal influenza vaccine types are formulated either with a trivalent or a quadrivalent composition, depending on the manufacturer's product. Trivalent inactivated influenza vaccines (IIV3) and trivalent live attenuated influenza vaccine (LAIV3) consists of 3 different influenza viruses. This typically includes 2 subtypes of the IAV and 1 lineage of the IBV. The quadrivalent inactivated influenza vaccines (IIV4) and the quadrivalent live attenuated influenza vaccine (LAIV4) consist of 4 different influenza viruses. The quadrivalent formulation contains two subtypes of IAV and two lineages of the IBV. [1, 27]

The World Health Organization (WHO) provides recommendations for the composition of the following year's influenza vaccines every February. These recommendations are specific to the northern hemisphere, and they are based on the most common circulating strains of the virus. [27] Vaccine manufacturers update the composition of their influenza vaccine products or develop a new seasonal influenza vaccine product, which is guided by the WHO recommendations.

During Canada's 2013/2014 to 2019/2020 influenza seasons, the IIV3 and IIV4 were either manufactured as an unadjuvanted standard dose or contained the MF59 adjuvant. [28] A standard dose consists of 15 µg of HA per strain, and it is administered in a 0.5 mL dose. For children, an adjuvanted dose consists of 7.5 µg of HA per strain and is administered in 0.25mL. A standard dose of the IIV is manufactured into a split virus vaccine or a subunit vaccine. Split influenza vaccines contain a whole inactivated virus that is split using a detergent, ether, or a combination of both methods. Subunit vaccines only have part of the pathogen, using purified HA and NA. [22] An adjuvanted dose with MF59 consists of oil in water emulsion that is used to improve the immune response in infants and children. [29, 30]

1.3 Route of Influenza Vaccine Administration

Seasonal influenza vaccines were administered through intramuscular injection (IM) and intranasal spray from 2013/2014 to 2019/2020. [16-23] The route of vaccination is dependent on the vaccine product. IM injection is recommended in the anterolateral side of the thigh for toddlers (6-to-12 months of age) and in the deltoid muscle (below the subcutaneous layer) for children (1-to-17 years old). FluMist® LAIV is the only product that uses intranasal spray to administer the vaccine inside the nostril of children aged 2-to-17 years old. [24-26]

1.4 Vaccine Regulation and Monitoring in Canada

1.4.1 Clinical Trials and Vaccine Authorization in Canada

1.4.1.1 New Seasonal Influenza Vaccines Seeking Initial Authorization

In Canada, vaccine manufacturers (i.e., sponsors) are responsible for conducting clinical trials (or randomized control trials) for completely new seasonal influenza vaccines (that had

never received market authorization). This process ensures a thorough assessment of the vaccine's efficacy and safety profile before receiving market authorization in Canada. [31] Vaccine manufacturers that bring a new vaccine product to market are required to submit a clinical trial application to Health Canada (HC). [32] It is critical that all clinical trials follow the Division 5 of the Food and Drugs Regulations and Good Clinical Practices. [33] Vaccine manufacturers are able to proceed with their clinical trial once their application receives approval, which is obtain through a No Objection Letter. [31]

A clinical trial that evaluates a new seasonal influenza vaccine in Canada consists of 4 phases. Phase 1 trials are conducted in a small group of healthy participants to examine the vaccine's safety profile, establish its initial dosing, and monitor for side effects. Phase 2 trials include a larger sample (>100), which evaluates the seasonal influenza vaccine's safety, immunogenicity, dosing, and delivery method. Phase 3 trials involve recruiting thousands of participants and continue evaluating the vaccine's safety profile and efficacy. Vaccine manufacturers can apply for market authorization for sale in Canada if their final analysis from phase 3 trials demonstrates sufficient safety and efficacy. The study is terminated if the candidate seasonal influenza vaccine does not demonstrate a strong safety profile or is not efficacious at any stage of the clinical trial. [34] The Biologic and Radiopharmaceutical Drugs Directorate of HC reviews the application to determine if the benefits of the product outweighs the risk, and if the vaccine meets the requirements of HC for market authorization. [35] Newly approved seasonal influenza vaccines receive a Notice of Compliance and a Drug Identification Number. [31] As part of receiving market authorization, vaccine manufacturers are required to conduct phase 4 trials to monitor the seasonal influenza vaccine's long-term safety profile. This consists

of conducting annual summary reports of the vaccine and notifying HC if there are any changes in the vaccine's risk-benefit profile. [34]

1.4.2 Seasonal Influenza Vaccines Requiring Annual Authorization

Seasonal influenza vaccines that previously obtained market authorization in Canada are eligible for an expedited review for changes to their vaccine product. This is granted given the short time interval between the new recommendations for the seasonal influenza vaccine composition (provided by the WHO) and the start of the influenza season later in the year. The expedited review process does not require vaccine manufacturers to conduct new clinical trials for updating their vaccine product. Since most vaccine manufacturers from 2013/2014 to 2019/2020 had already received market authorization for their seasonal influenza vaccine products, they were deemed eligible for the expedited review process. Vaccine manufacturers liaise with the Biologic and Genetic Therapies Directorate Office of Regulatory Affairs of HC to indicate new changes to their seasonal influenza vaccine product. This includes changes to the strains in the vaccine product and changes to the product. [36]

1.4.3 Seasonal Influenza Vaccine Recommendations in Canada

Canada's National Advisory Committee on Immunization (NACI) serves as an expert advisory committee that provides evidence-based recommendations to the Public Health Agency of Canada (PHAC) for vaccines in use or vaccines seeking approval. [37] During the 2013/2014 to 2019/2020 influenza seasons, NACI provided recommendations for the seasonal influenza vaccine in Canada. [16-22] The use of vaccine products can still vary between provincial and territorial programs since the provincial and territorial health authorities decide the vaccine

product(s) and the quantities to purchase. PHAC assists in coordinating and overseeing the distribution of influenza vaccines. [38]

1.4.4 Recommendations for Infants and Children in Canada from 2013/2014 to 2019/2020

From 2013/2014 to 2019/2020, infants and children were recommended a full dose of the unadjuvanted IIV3[2]. Starting in the 2014/2015 influenza season, recommendations for this age group expanded to the unadjuvanted IIV4. [17] From 2015/2016 to 2019/2020, infants were also eligible to receive the MF59-adjuvanted IIV3 (Fluad Pediatric™). Children aged 2-to-17 years old were eligible to receive LAIV3 (FluMist®) and LAIV4 (FluMist® Quadrivalent) from 2013/2014 to 2014/2015 and 2015/2016 to 2019/2020, respectively. Children (under 9 years old) who receive the seasonal influenza vaccine for the first time are advised to receive 2 doses of the vaccine, with a minimum 4-week interval between doses. In each subsequent year following receipt of the first seasonal influenza vaccine, such children are recommended for only one dose of the vaccine. Children 9 years and older are recommended 1 dose of the seasonal influenza vaccine regardless of prior vaccine history. From 2013/2014 to 2019/2020, NACI recommended the IIV4 as the preferred vaccine for infants aged 6-to-23 months. However, the unadjuvanted and adjuvanted IIV3 were recommended if the IIV4 was unavailable. [18-22] NACI also recommended the use of LAIV in healthy children aged 2-to-17 years old as the preferred vaccine [16]. In 2017, new recommendations no longer supported a preference between the IIVs and the LAIVs. [20] NACI did not recommend the seasonal influenza vaccine to children with contraindications due to the vaccine's potential for negative adverse events (AE). Children with severe asthma or with medically attended wheezing (7 days before vaccination) are not

[2] IIV4s were not available at this time

recommended the LAIV. In addition, children who are immunocompromised are not recommended the LAIV; however, IIVs are considered safe for use. [17, 18, 20-22]

Table 1 describes the recommendations for infants and children for each seasonal influenza vaccine product in Canada from 2013/2014 to 2019/2020. During this time period, several seasonal influenza vaccine products were newly authorized for use in children. During the 2014/2015 influenza season, Flulaval™ Tetra and FluZone® Quadrivalent received approval for use in children aged 6 months and older in Canada. [17] In 2015/2016, Fluad Pediatric™ was also licensed for use in Canada in children 6-to-23 months of age. In addition, FluMist® changed their live attenuated vaccine from a trivalent formulation to a quadrivalent formulation. [18] In 2017, HC authorized the approval of Influvac to extend to children aged 3-to-17 years old. [39] Lastly, during the 2019/2020 influenza season, Afluria Tetra was newly licensed to be administered to children 5 years and older. [40] Although multiple seasonal influenza vaccine products were available each year, the type and composition of the vaccine administered to children depended on the vaccine product's availability.

1.4.5 Recommendations for Pregnant Women in Canada from 2016/2017 to 2019/2020

During the 2016/2017 to 2019/2020 influenza seasons, NACI recommended that pregnant women receive either IIV3 or IIV4. [19-22] During this study period, there was insufficient evidence to support the use of the LAIV in pregnant women due to the theoretical risk of an AE in the fetus. However, the LAIV is approved for use in mothers who are breastfeeding. [6, 19-22] Table 2 summarizes NACI recommendations for the seasonal influenza vaccine in pregnant women from 2016/2017 to 2019/2020. During the 2019/2020 influenza

season, Afluria Tetra was newly licensed to be administered to adults (including pregnant women). [40]

Table 1. Seasonal influenza vaccine recommendations for infants and children in Canada, from 2013/2014 to 2019/2020.

Vaccine Manufacturer: Product Name	Novartis/ Seqirus: Fluad Pediatric®	GSK: Fluviral®	Novartis/ Seqirus: Agriflu®	Sanofi Pasteur: Vaxigrip®	Sanofi Pasteur: Fluzone®	BGP Pharma ULC: Influvac®	Seqirus: Afluria® Tetra	GSK: Flulaval® Tetra	Sanofi Pasteur: Fluzone® Quadrivalent	AstraZeneca: FluMist®	
Vaccine Type	IIV3	IIV3	IIV3	IIV3	IIV3	IIV4	IIV4	IIV4	IIV4	LAIV3*	LAIV4*
Authorized Age for Use	6-23 months	≥ 6 months	≥ 6 months	≥ 6 months	≥ 6 months	≥ 3 years	≥ 5 years	≥ 6 months	≥ 6 months	2-17 years	2-17 years
2013/2014		X	X	X	X					X	
2014/2015		X	X	X	X			X	X	X	
2015/2016	X	X	X	X	X			X	X		X
2016/2017	X	X	X	X	X			X	X		X
2017/2018	X	X	X	X	X			X	X		X
2018/2019	X	X	X			X		X	X		X
2019/2020	X	X	X			X	X	X	X		X

IIV3: Trivalent inactivated influenza vaccine
IIV4: Quadrivalent inactivated influenza vaccine
LAIV3: Trivalent live attenuated influenza vaccine
LAIV4: Quadrivalent live attenuated influenza vaccine
*Not recommended for children with severe asthma, medically attended wheezing, current receipt of asthma or asthma containing therapy and immune compromising conditions (except with stable HIV infection)

Table 2. Seasonal influenza vaccine recommendations for pregnant women in Canada, from 2016/2017 to 2019/2020.

Vaccine Manufacturer: Product Name	GSK: Fluviral®	Novartis/ Seqirus: Agriflu®	Sanofi Pasteur: Vaxigrip®	Sanofi Pasteur: Fluzone®	Abbott: Influvac®	Seqirus: Afluria®	GSK: Flulaval® Tetra	Sanofi Pasteur: Fluzone® Quadrivalent
Vaccine Type	IIV3	IIV3	IIV3	IIV3	IIV3	IIV4	IIV4	IIV4
2016/2017	X	X	X	X	X		X	X
2017/2018	X	X	X	X	X		X	X
2018/2019	X	X			X		X	X
2019/2020	X	X			X	X	X	X

IIV3: Trivalent inactivated influenza vaccine
IIV4: Quadrivalent inactivated influenza vaccine

1.5 Vaccine Safety Surveillance

Pharmacovigilance is a process that aims to detect, assess, understand and prevent AE or other associated drug problems. [41] The WHO defines an adverse event following immunization (AEFI) as "any untoward medical occurrence which follows immunization, and which does not necessarily have a causal relationship with the usage of the vaccine". [42] A critical feature of an AEFI is that it follows a temporal relationship (in which the vaccine precedes the AE); however, it is not intended to establish cause and effect. [43] In Canada, a common AEFI is defined as an occurrence of 1% to 10%, an uncommon AEFI is defined as an occurrence in 0.1 to 0.99%, and rare or very rare events is defined as an occurrence in less than 0.1%. [34] Pharmacovigilance is typically conducted during post-marketing surveillance, which can consist of passive surveillance, active surveillance, or a combination of both methods.

Post-marketing surveillance can be used: 1) to detect potential safety signals following influenza vaccination, 2) to communicate findings, and 3) to respond to urgent situations systematically and efficiently. [34, 44] In Canada, it is mandatory for vaccine manufacturers with approved seasonal influenza vaccine products to report any serious AE to the Canada Vigilance Program. [34] However, most post-marketing AEFI reporting in Canada is conducted through the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS).

1.5.1 Canadian Vaccine Vigilance Working Group

The Canadian Vaccine Vigilance Working Group (VVWG) was created in 2004 in response to the 2003 National Immunization Report to improve vaccine safety monitoring in Canada. The VVWG aims to achieve three objectives:

1. To develop national guidelines and procedures for monitoring, reporting, and managing AEFI.
2. To share best practices for identifying, sharing, and promoting vaccine safety.
3. To provide a national network to detect and respond to emerging vaccine safety issues quickly.

The VVWG includes representatives from the federal, provincial, and territorial (F/P/T) levels who participate in weekly calls. The VVWG was pivotal in providing enhanced surveillance during the 2009 H1N1 pandemic that provided a platform for rapid communication regarding issues related to vaccine safety. Since then, the VVWG continues to have weekly calls at the start of the seasonal influenza campaign each year to share and evaluate vaccine safety data. [44]

1.5.2 Passive Surveillance

Passive surveillance is the most common method to systematically collect and monitor AE following receipt of the seasonal influenza vaccine. [45] The robustness and quality of the data are often dependent on the funding and resources available. Challenges associated with passive surveillance typically include under-reporting of AEFI cases, missing or incomplete information, and slow detection of AEFIs. The design of passive surveillance does not include an unvaccinated (control) group; therefore, it is not possible to compare the rate of AE in a vaccinated group to the background rate of health events.

1.5.2.1 Canadian Adverse Events Following Immunization Surveillance System (CAEFISS).

CAEFISS is Canada's post-marketing surveillance system, and it is managed by the PHAC. It consists of passive surveillance that uses a standardized case report to capture spontaneous AEFIs of marketed vaccines, including seasonal influenza vaccines. [46] Healthcare providers across Canada can forward their completed case reports to their local health authorities, who would then share the information with the provincial and territorial health authorities. [22] CAEFISS receives all completed AEFI case reports from the F/P/T health authorities across Canada. Federal authorities include the RCMP, Indigenous Services Canada, and Correctional Services Canada. Data are aggregated, and any potential safety signals that PHAC identifies are shared with the Marketed Health Products Directorate and the Canada Vigilance Program to determine future regulatory steps (if necessary). [46] CAEFISS includes passive surveillance, but also active surveillance.

1.5.3 Active Surveillance of AE Following Influenza Vaccination in Canada

Active surveillance requires active recruitment and follow-up with participants for pre-specified AEFI, which often complement passive surveillance systems. It consists of rapid data collection and more complete AEFI reports compared to passive surveillance. [45] However, active surveillance systems will often require significant resources. Therefore, it is not always feasible to implement. [47] Advances in technology in the last decade have demonstrated different methods for reporting and collecting data regarding AE following seasonal influenza vaccination. This has been observed using automated online surveys or text messages sent directly to the participant's email address or phone number. Electronic methods can successfully recruit large cohorts and reduce administrative costs.

1.5.3.1 Canadian Immunization Monitoring Program ACTive (IMPACT)

The Canadian Immunization Monitoring Program ACTive (IMPACT) is an active hospital-based surveillance system within CAEFISS, that monitors severe AEFIs specifically in children. It was established in 1991, and it now consists of 12 pediatric tertiary care hospitals across Canada (representing approximately 90% of pediatric tertiary care beds). It works in collaboration with the Canadian Pediatric Society and the PHAC. It aims to detect potential AEFI using standard case definitions that results in hospitalization, and it aims to monitor changes in AE rates or signals of concern. AEFIs that are captured through IMPACT reflect a temporal association, which means that the event of interest occurred after vaccination and might not be a direct cause of the vaccine. [48]

1.5.3.2 Canadian National Vaccine Safety (CANVAS) Network

The Canadian National Vaccine Safety (CANVAS) network also provides active vaccine safety surveillance in Canada. The CANVAS network was established in 2009, which initially aimed to monitor AE following receipt of the influenza vaccine in healthcare workers during the 2009 influenza pandemic. The CANVAS network then transitioned to monitoring the safety profile of seasonal influenza vaccines. In 2012, infants and children aged 6 months to 17 years old were eligible to participate in the CANVAS network. From 2013/2014 to 2019/2020, it collected and reported on seasonal influenza vaccine safety data from 5 provinces across Canada.

At the beginning of the seasonal influenza vaccine campaigns, the CANVAS network recruits participants to provide vaccine safety information to public health authorities before peak uptake during that year's vaccination season. Data about the participant's health in the

week following vaccination are collected using an online survey that is sent to the participant's email address. Data are collected again 11 months later using an online survey to determine the background rate of health events in an unvaccinated group for the following year's analysis. This enables researchers to calculate the incidence rates of AE comparing a vaccinated group to an unvaccinated group. The primary outcome of the CANVAS network are severe health events defined as having prevented daily activities, resulted in absenteeism from work or school, or required a medical consultation. [49] The CANVAS network also collects participant hospitalization data; however, more emphasis is directed towards less serious health events that are not typically captured in the passive surveillance systems.

1.6 Adverse Events Following Seasonal Influenza Vaccination

1.6.1 Adverse Events Reported Following Seasonal Influenza Vaccination in Infants and Children

A comprehensive review published by Halsey et al. in 2015 found seasonal influenza vaccines administered to children to be safe, and AE following influenza vaccination was typically mild. The most commonly reported AE using IM IIV were local reactions and mild systemic reactions. IIVs with adjuvants were also associated with local reactions, fever, and other systemic events. The most common AE following receipt of the LAIV was coryza (i.e., inflammation and irritation in the nose). The review did not observe significantly higher rates of wheezing in children following receipt of the LAIV. Most AE were similar following receipt of the LAIV4 and the LAIV3. Allergic reactions were associated with the IIV and LAIV; however, they were also mild. Other observed mild allergic reactions included urticaria (i.e., hives) and respiratory symptoms. [50] To date, the CANVAS network has published a few studies that have examined AE following receipt of the seasonal influenza vaccine in Canada.

In 2012, the CANVAS network conducted a pilot study to compare the safety profile of LAIV3 to IIV3. The sample consisted of 1,070 child participants aged 6 months to 17 years old with completed surveys. There were 403 child participants who received IIV3 and 816 who received LAIV3. A total of 26 (6.5%) AEs were recorded following influenza vaccination in the IIV3 group, and 73 (8.9%) AEs were recorded in the LAIV3 group. The most common symptoms in the IIV3 group were respiratory symptoms (3%), fever only (2.5%), fever/chills (2.5%), and anorexia (2.5). In the LAIV3 group, the most common AEs were respiratory symptoms (5.8%), fever/chills (4.5%), gastrointestinal symptoms (3.7%), and anorexia (3.1%). There was no difference in wheezing-related AE between the vaccine groups.

In 2020, the CANVAS network examined the rate of AE following receipt of the seasonal influenza vaccine during the 2017/2018 and 2018/2019 influenza seasons. Data were not restricted to children; however, it included 1,453 participants aged 6 months to 14 years old with completed surveys. The rates of health events in vaccinated and unvaccinated children were not significantly different in both years. The percentage of children who reported having missed school or daily activities and sought medical care was higher in the vaccinated group compared to an unvaccinated group in the 2018/2019 season. However, the percentage who sought medical care only were similar in both seasons. The 2017/2018 season observed a significant risk of AE associated with fevers in children 5-to-14 years old, but not with other signs or symptoms. This was also observed in the 2018/2019 analysis, but the risk of fever-associated AE extended to children ages 6 months to 14 years old. No other signs or symptoms were statistically significant in the 2018/2019 analysis. [51]

This thesis will expand on these two previously conducted studies by investigating AE following receipt of the seasonal influenza vaccine specifically in children during a longer time interval (2013/2014 to 2019/2020).

1.6.2 Adverse Events Reported Following Seasonal Influenza Vaccination in Pregnant People

Influenza vaccination during pregnancy is considered safe, yet limited studies have focused solely on the safety profile of the seasonal influenza vaccine (but rather of the 2009 monovalent influenza vaccine). To date, there have been no studies from the CANVAS network that have investigated the association between vaccination status and severe health events in pregnant people. Limited studies have explored AE following receipt of the seasonal influenza vaccine in pregnant people in Canada.

A study conducted by Dodds et al. examined the relationship between seasonal influenza vaccination during pregnancy and adverse neonatal outcomes in Nova Scotia, Canada, from 2006 to 2009 (before the 2009 influenza pandemic). Their sample included 1,925 vaccinated pregnant women and 7,722 unvaccinated pregnant women. It was observed that vaccinated pregnant women had a lower odds ratio (OR) of small for gestational age and low birth weight than unvaccinated pregnant women. No statistically significant associations were observed for term low birth weight, preterm birth, and a composite outcome[3]. [52]

A follow-up study conducted by Legge et al. explored the relationship between seasonal influenza vaccination in pregnancy and neonatal outcomes in Nova Scotia, Canada, from 2010 to 2012 (after the 2009 influenza pandemic). The study included 1,958 vaccinated pregnant women

[3] Composite neonatal morbidity variable was based on a diagnosis of any of the following: low 5-minute Apgar score (≤ 3), sepsis (positive blood culture, septicaemia, or systemic infection), asphyxia, respiratory distress syndrome (moderate or severe), intraventricular hemorrhage (grade 3 or 4), or acute necrotizing enterocolitis.

and 10,265 unvaccinated pregnant women. Unadjusted analysis observed that vaccinated mothers had lower odds of preterm birth and low birth weight than unvaccinated mothers. Still, there were no differences in other neonatal outcomes (i.e., low birth weight at term, small for gestational age, composite neonatal morbidity variable). No associations were observed after adjusting for confounding variables and interaction terms that included maternal obesity, infant sex, and month of delivery with vaccine receipt. [53]

In 2016, Chambers et al. conducted a study that examined seasonal influenza vaccine safety in Canada and the United States across 4 seasonal influenza seasons (2010-2014). This study used data from the Vaccines and Medications in Pregnancy Surveillance System, that evaluated vaccines administered during pregnancy. It compared data from 1,263 vaccinated pregnant women and 467 unvaccinated pregnant women during any stage of pregnancy. A combined analysis of all influenza seasons did not observe a difference in spontaneous abortion, preterm delivery, small for gestational age, or significant defects between groups. [54]

This thesis aims to contribute to the existing literature by using recent data from the CANVAS network to examine the relationship between vaccination status and severe health outcomes in pregnant people in Canada.

1.7 Agreement Between Methods of Self-Reported Adverse Events Following Immunization

There has been increased utility of using online data collection methods to rapidly identify AE during immunization campaigns in recent years. [55] The accuracy of reported AEFIs is a critical component of vaccine pharmacovigilance; therefore, clear definitions regarding the outcome of interest are essential in influenza vaccine safety surveillance.

A study conducted by Lapphra et al. assessed the feasibility, acceptability, and response rate of web-based self-reported for AEFI compared to telephone respondents from the pandemic and seasonal influenza season in 2009 among healthcare workers and hospital staff using data from the CANVAS network. It observed that there was no difference between online and telephone reporting in participant answers for age, symptoms, and severity of AEFI. Although the research objective was not primarily designed to examine the reliability between online and telephone responses, it reported that the frequency and type of internet self-reported AEs following influenza vaccination were similar to those found in clinical trials. This indicates that internet reporting might be considered reliable and valid assessments in this population. [56]

Currently, there is a lack of available data regarding the agreement of self-reported AE following receipt of the seasonal influenza vaccine in children using Internet-based and telephone data collection methods.

1.8 Research Objectives

1.8.1 Study Objective 1

A. To describe and calculate the rate of severe health events and most severe symptoms following receipt of the **inactivated influenza vaccines** in children (≥6 months) compared to unvaccinated children, using self-report data from 2013/2014 to 2019/2020.

B. To describe and calculate the rate of severe health events and most severe symptoms following receipt of the **live attenuated influenza vaccine** in children (≥2 years old) compared to unvaccinated children, using self-report data from 2013/2014 to 2019/2020.

Hypothesis:

Children who received the inactivated influenza vaccine (≥6 months), or the live attenuated influenza vaccine (≥2 years old) did not report an increased rate of severe health events, compared to an unvaccinated group, using self-report data from 2013/2014 to 2019/2020.

1.8.2 Study Objective 2

To determine the agreement of self-report responses for most severe symptoms using an online survey and telephone follow-up report, child data from 2016/2017 to 2019/2020.

Hypothesis:

It is hypothesized that self-reported most severe symptoms following influenza vaccination demonstrates high concordance (≥80%) between an online survey and telephone report in the child population.

1.8.3 Study Objective 3

To describe and calculate the rate of severe health events and most severe symptoms following receipt of the **inactivated influenza vaccines** in pregnant people **(**15-to-49 years old) compared to unvaccinated pregnant people, using self-report data from 2016/2017 to 2019/2020.

Hypothesis:

Pregnant people who received the inactivated influenza vaccine (15-to-49 years old) did not report an increased rate of severe health events, compared to an unvaccinated group, using self-report data from 2016/2017 to 2019/2020.

Chapter 2: Methodology of All Study Objectives

2.1 Study Design

This research study used a cross-sectional design to analyze influenza vaccine safety data from 2013/2014 to 2019/2020. It compared self-reported health events and symptoms between vaccinated and unvaccinated children and pregnant people. Participant data in the vaccinated and unvaccinated groups were uncorrelated between years.

2.2 Study Setting

Data for this project were obtained from the Canadian National Vaccine Safety (CANVAS) network. [51] Recruitment sites were located in 1) Vancouver, BC; 2) Calgary, AB; 3) Toronto, ON; 4) Ottawa, ON; 5) Quebec City, QC; 6) Sherbrooke, QC; and 7) Halifax, NS. Research ethics approval was obtained at the primary coordination centre, at the Children's & Women's Health Centre of British Columbia[4], and each participating research site across Canada.

2.3 Survey Instrument

The CANVAS network used the SimpleSurvey software, developed by OutSideSoft Solutions Inc (Saint-Jean-sur-Richelieu, Quebec), to collect vaccine safety data from 2013/2014 to 2015/2016. It provided the CANVAS network with tools to create and manage surveys using a secure web application with encryption, firewalls, frequent back-ups, and a recovery plan. Research personnel had access to the participant's email address and phone numbers. In 2016/2017, the CANVAS network switched to REDCap (Research Electronic Data Capture) to

[4] REB #: H10-02274

create and manage survey data. REDCap was developed by Vanderbilt University to provide research teams with a secure platform to collect, store and share research data [57]. The project was created and managed by the BC Children's Hospital Research Institute in Vancouver, Canada. After each year of data collection, data from SimpleSurvey and REDCap were stored offline at the Vaccine Evaluation Center, BC Children's Hospital Institute in Vancouver, Canada.

2.4 Study Procedures

Study participants were invited to complete two online surveys to assess influenza vaccine safety in Canada. The surveys were available in English and French. They were accessible using a computer or mobile device and took approximately five minutes to complete. The first survey was sent to participants' email addresses 8 days after receipt of their seasonal influenza vaccine. The second survey was emailed 11 months later, before the next season's influenza vaccine campaign. Figure 1 describes the study procedures of the CANVAS network for monitoring seasonal influenza vaccine safety. Participants were eligible to participate each year; however, their responses were not linked between years.

2.4.1 Participant Recruitment

Research staff recruited adults and parents of children vaccinated against seasonal influenza to the CANVAS network study at select immunization clinics across Canada during October and November of the 2013/2014 to 2019/2020 influenza seasons. Vaccinated individuals were provided with information about the study procedures and were then invited to participate in the research study by completing a registration form. The paper-based registration form

collected information regarding their vaccination date, first name, location of vaccine clinic, name of influenza vaccine product received, and contact information. This information was then manually entered into SimpleSurvey and REDCap to create a new participant record in the database. The influenza vaccine safety survey was programmed to send directly to the participant's email address that was linked to their record in SimpleSurvey or REDCap. During the 2016/2017 influenza season onwards, participants at select sites were also able to self-register using an online registration web page specific to their research site. There were no incentives provided to participants who enrolled into the study.

2.4.2 Survey Procedures

2.4.2.1 Survey Procedures in the Vaccinated Group

Eight days after receiving the seasonal influenza vaccine, vaccinated participants received an automated email with an embedded link to the influenza vaccine safety survey. Participant consent was obtained at the start of the survey. Participants with an incomplete influenza vaccine safety survey received a reminder email 72 hours after the initial email was sent. Participant recruitment at each site lasted approximately 3 weeks.

2.4.2.2 Survey Procedures in the Unvaccinated Group

Approximately 11 months later, before the next influenza vaccine campaign, the vaccinated participants received an email with an embedded link to the second online survey. Participants who completed the second online survey were part of the unvaccinated group, which aimed to determine the background rate of health events before the upcoming influenza vaccination campaign. All participants with an incomplete survey received a reminder email 72

hours after the initial email was sent. The second online survey closed at least 24 hours before the start of any influenza vaccination campaign for the upcoming year to avoid participants being enrolled in the unvaccinated and the vaccinated group at the same time. Participants who served in the unvaccinated group were eligible to participate in the study again as a vaccinated participant for the upcoming influenza vaccine campaign but needed to re-enroll.

2.4.2.3 Survey Questions in the Vaccinated and Unvaccinated Groups

The survey for the vaccinated group included questions about the participant's demographics, the severity of their health event (if applicable), symptoms (if applicable), type of medical consultation sought (if applicable), and past influenza vaccine history (in the vaccinated group only). In the 2013/2014 survey, all participants were asked to indicate any symptoms they experienced within the first 24 hours and within 7 days of receiving the seasonal influenza vaccine, followed by a series of questions about the severity of their health event. Participants were not asked to indicate their most severe symptom. In the 2014/2015 to 2019/2020 surveys, participants were instead asked if they had experienced a new health problem in the last 7 days, followed by the severity of their health event (if applicable) and symptoms (if applicable). Participants who did not report a new health problem in the last 7 days were directed to the end of the survey. Symptoms were indicated using checkboxes on a predefined list and an open-text field was provided to describe other symptoms not listed in the survey. Participants who reported more than one symptom in the 2014/2015 to 2019/2020 surveys were asked to indicate their most severe symptom.

2.4.3 Telephone Follow-Up Report

Participants who reported a health event that required a medical consultation, as indicated on their completed online survey, were followed up by a research staff member within 48-72 hours via telephone. A research staff member tried up to 5 times to contact eligible participants. The research staff member obtained a detailed history of the participant's AE following influenza vaccination during the telephone call. If the AE met the criteria for reporting an AEFI in the participant's jurisdiction, a research staff would submit a case report form to the participant's respective local health authority.

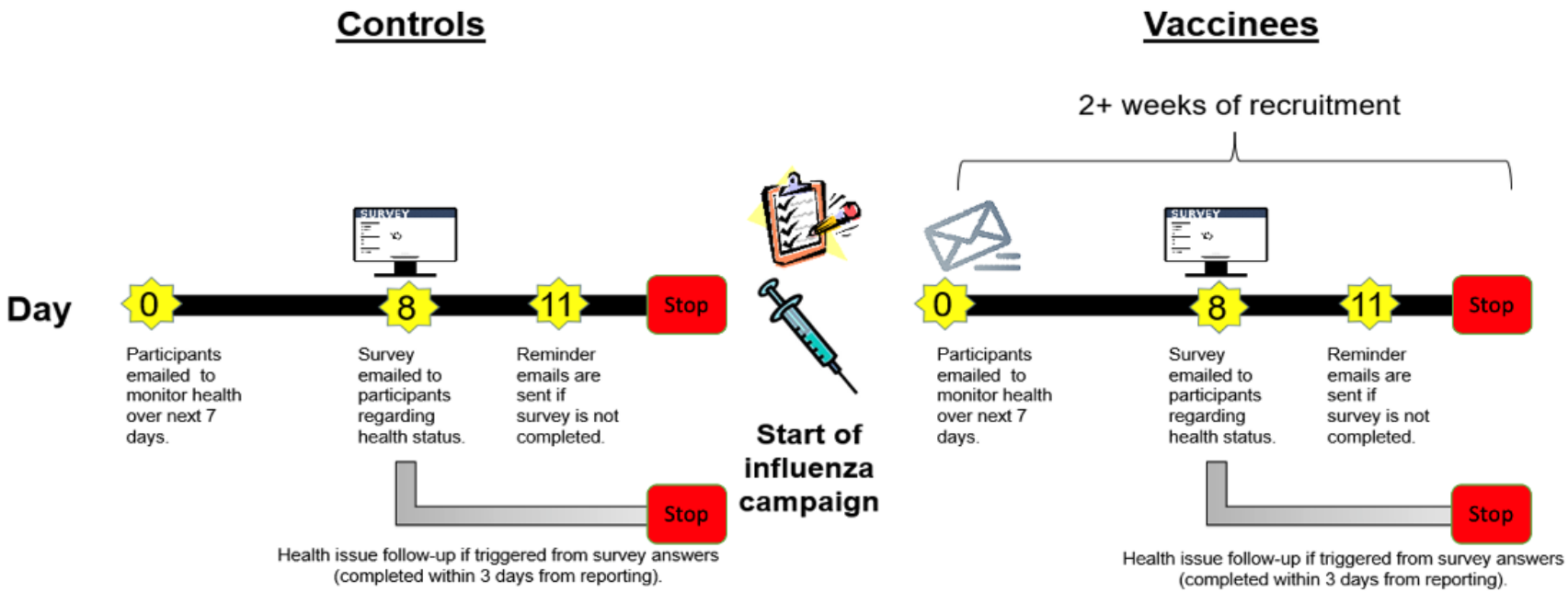


Figure 1. Study Procedures of the Canadian National Vaccine Safety (CANVAS) Network research study from 2013/2014 to 2019/2020.

2.5 Objective 1: Analytical Plan for Child Analysis

2.5.1 Objective 1: Study Variables for Child Analysis

2.5.1.1 Primary Explanatory Variable for Child Analysis

The primary explanatory variable was vaccination status based on the vaccine type. Objective 1A compared child participants who received the IIV to an unvaccinated group from 2013/2014 to 2019/2020. The IIV group consisted of child participants who received Agriflu®, Fluad®, Flulaval®, Fluviral®, Fluzone®, Influvac®, and Vaxigrip®. Objective 1B compared child participants who received the LAIV to an unvaccinated group from 2013/2014 to 2018/2019. The LAIV group consisted of child participants who received FluMist®. Data during 2019/2020 was excluded because FluMist® was unavailable for use in Canada due to supply shortages. Vaccines were only grouped by manufacturer's brand name (and not vaccine composition) due to incomplete data. The reference category was the unvaccinated group.

2.5.1.2 Primary Outcome Variable for Child Analysis

The primary outcome is the occurrence of a severe health event defined as having stopped or prevented daily activities, missed school, or requiring medical consultation. The severe health event must have started within 7 days of receiving the seasonal influenza vaccine for the vaccinated group, but reporting was obtained 7 days after receipt of the vaccine. In the unvaccinated group, the onset of the severe health event must have started in the previous 7 days prior to completing the online survey. A severe health event was categorized as a binary variable.

2.5.1.3 Secondary Outcome Variable for Child Analysis

The secondary outcome was the most severe symptom reported on the online survey in the vaccinated and unvaccinated groups, from 2014/2015 to 2019/2020. This variable was added to the questionnaire during the 2014/2015 influenza season; therefore, data from 2013/2014 was excluded in the secondary analysis.

Child participants who met the criteria for a severe health event (primary outcome) were solicited for symptoms they might have experienced in the last 7 days. A list of predefined symptoms was provided to the participants on the online survey, which is summarized in Appendix A. Participants were able to select as many symptoms using checkboxes. If a symptom was not listed on the survey, an option to indicate "other" symptom was provided, which then opened a text-box field. Croup and urinary symptoms were new symptoms created post-data collection. They were created into their own categories from the "other" variable field due to multiple responses.

Child participants were then asked to identify their most severe symptom based on their previously indicated symptoms. Participants who experienced more than one symptom in the last 7 days were asked to indicate their most severe symptom using an open text-box field and participants with only one symptom present did not need to complete this section. It was assumed that participants with one symptom would have that symptom be listed as their main symptom. Responses for most severe symptom that were included from the "other" open text-box field were reviewed and recoded if they belonged to another symptom provided in the predefined list. Responses for most severe symptom in the open text-box field were reviewed and manually recoded to match a single symptom. Child participants that indicated multiple

symptoms but did not identify their most severe symptom or had unclear responses for their most severe symptom were excluded from the secondary analysis.

2.5.1.4 Additional Variables of Interests for Child Analysis

2.5.1.4.1 Sex

Participant sex was collected and categorized as male or female. Participants with missing responses for sex were excluded from the final analytical sample. Male was set as the reference category.

2.5.1.4.2 Age Category

Participant age was collected based on the pre-defined age categories listed in the survey. The age categories for children were 6-to-23 months, 2-to-4 years old, 5-to-9 years old, 10-to-16 years old (in the 2013/2014 dataset), and 10-to-14 years old (in the 2014/2015 to 2019/2020 datasets). The oldest age category in the 2013/2014 survey and 2014/2015 to 2019/2020 surveys were combined into a single age category and was used as the reference category.

2.5.1.4.3 Year of Enrolment

The year of enrolment represented each influenza season during the study period, from 2013/2014 to 2019/2020. The 2019/2020 influenza season was the reference category for the IIV analyses, and the 2018/2019 influenza season was the reference category for the LAIV analyses since they had the highest proportion of child participants for their respective groups. The LAIV was not distributed in Canada during the 2019/2020 influenza season.

2.5.1.4.4 Enrolment Site

The enrolment site described where the participants were recruited and submitted their online survey. It included 7 locations across Canada, which were located in Vancouver, Calgary, Toronto, Ottawa, Quebec City, Sherbrooke, and Halifax. The eligibility criteria for all sites were the same. The reference category was Calgary since it had the highest proportion of child respondents.

2.5.1.4.5 Immunization History

Participants in the vaccinated group were asked to report the number of seasonal influenza vaccines received in the last 2 years. This was categorized as none, 1 vaccine, or 2 vaccines. The group of participants who received two seasonal influenza vaccines was set as the reference category since it had the highest proportion of child respondents.

2.5.1.4.6 Onset of Severe Health Event

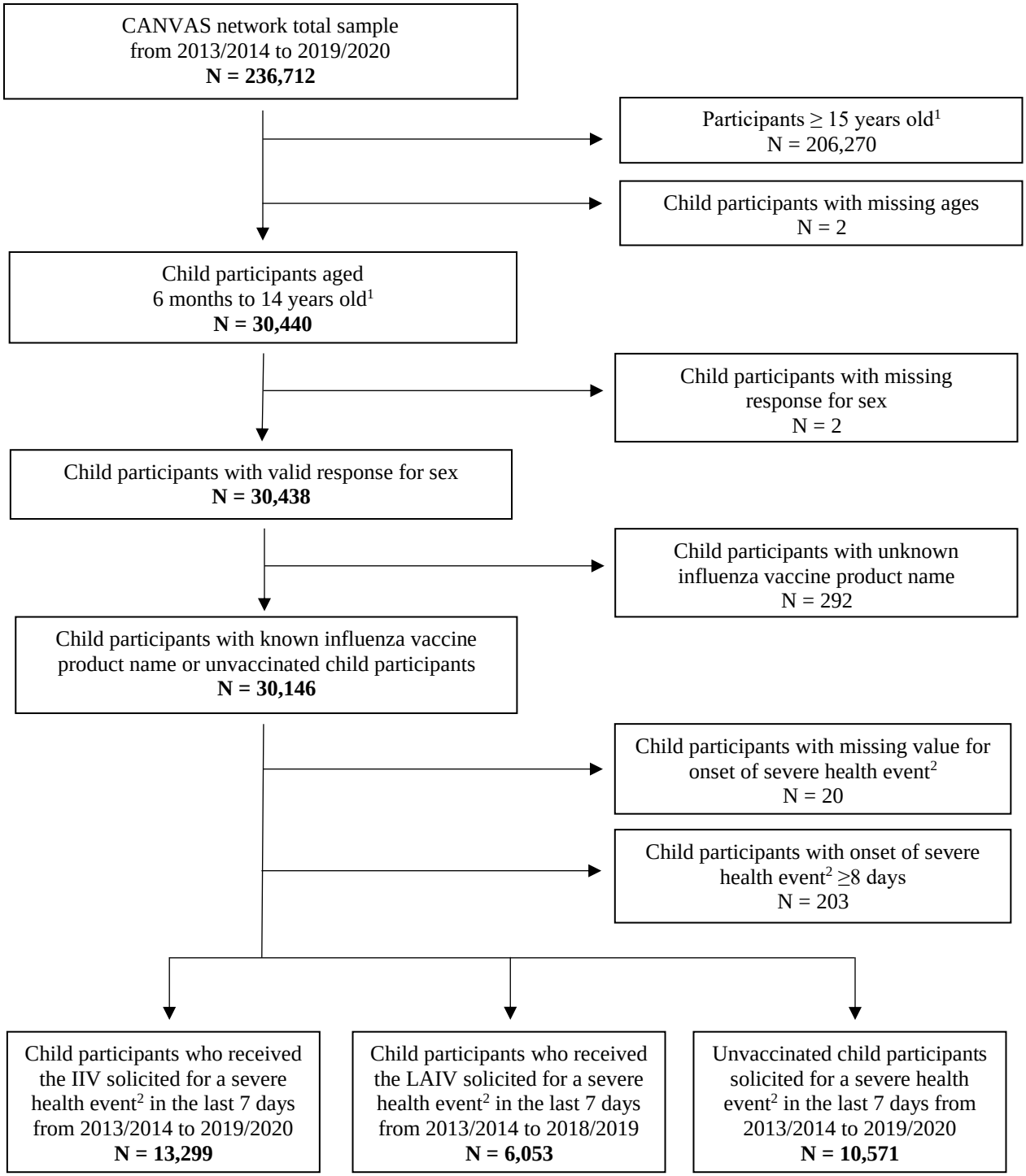
Child participants who met the criteria for a severe health event (primary outcome) were asked to indicate the onset of their severe health event. The onset of their severe health event was categorized as having occurred within 24 hours, within 1-to-3 days, within 4-to-5 days, or within 6-to-7 days of vaccine receipt or commencement of the observation period in the control group. Child participants were excluded if the onset of their severe health event started more than 7 days after vaccination or more than 7 days prior to completing the survey in the unvaccinated group.

2.5.1.4.7 Duration of Severe Health Event

The duration of a severe health event was captured according to predefined categories in the online survey. Child participants were able to select a duration of fewer than 60 minutes, less than 10 hours, less than 24 hours, 1-to-3 days, 4-to-5 days, 6 days or longer, or still present.

2.5.2 Objective 1: Child Analytical Sample

The final analytical sample included eligible child participants with a completed survey during the 2013/2014 to 2019/2020 influenza seasons. Age was restricted from 6 months to 16 years old in the 2013/2014 survey and 6 months to 14 years old in the 2014/2015 to 2019/2020 surveys. Child participants with a missing response for age category, sex, or influenza vaccine product name were excluded from the analyses. All eligible vaccinated and unvaccinated child participants were solicited for a severe health event. If the onset of a severe health event was missing or greater than 8 days, the child participant was excluded. The final study sample for child participants solicited for a severe health event in the vaccinated and unvaccinated groups was 29,923, as described in Figure 2. Child participants with a severe health event were asked for their symptoms. Those with more than 1 symptom were asked to describe the most severe symptom in a text field. The final study sample for child participants solicited for their most severe symptom with a valid response in the vaccinated and unvaccinated groups was 1,526, as described in Figure 3.



IIV: Inactivated influenza vaccine
LAIV: Live attenuated influenza vaccine

[1] Children aged months to 16 years old in 2013/2014
[2] Severe health event: Prevented/stopped activities or missed school or saw healthcare provider

Figure 2. Child analytical sample for severe health event, Canadian National Vaccine Safety (CANVAS) Network data from 2013/2014 to 2019/2020.

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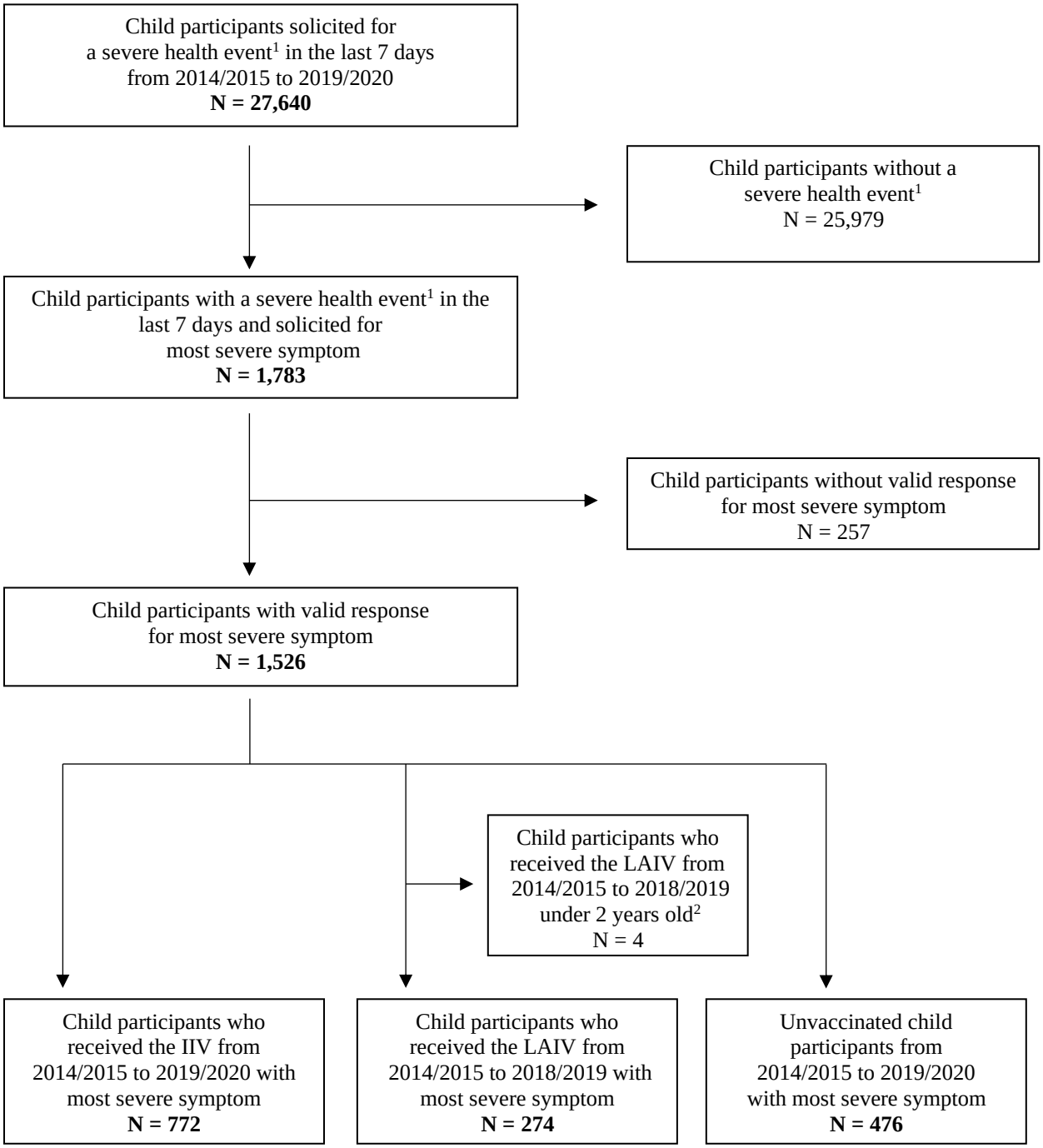


IIV: Inactivated Influenza Vaccine
LAIV: Live Attenuated Influenza Vaccine

[1] Severe health event: Prevented/stopped activities or missed school or saw healthcare provider
[2] Child participants were given FluMist® off label and therefore were excluded from the analysis

Figure 3. Child analytical sample for most severe symptom, Canadian National Vaccine Safety (CANVAS) Network data from 2014/2015 to 2019/2020.

2.5.3 Objective 1: Child Analysis from 2013/2014 to 2019/2020

2.5.3.1 Descriptive Analyses

Descriptive analyses were conducted to summarize responses in the child sample during the 2013/2014 to 2019/2020 influenza seasons. This included variables for vaccination status, vaccine type, sex, age category, year of enrolment, enrolment site, immunization history, and vaccine product name. A summary table for the proportion of severe health events (primary outcome variable) was described by vaccination status and vaccine product name. Additional summary statistics were calculated for the onset and duration of the severe health event based on the vaccine type.

2.5.3.2 Inferential Analyses of Severe Health Events and Most Severe Symptom

The incidence rate ratio (IRR) for severe health events was calculated by vaccine type and for vaccine products that were administered to more than 1000 child participants throughout the study period.

Univariate analyses were conducted to model severe health events (primary outcome variable) with vaccination status for the main analyses, and additional covariates of interest. The covariates included sex, age category, year of enrolment, enrolment site, and immunization history (vaccinated group only). The output from the univariate logistic regressions was used to build a main effect multivariable logistic regression model, using model-building strategies defined by Hosmer et al. [58]

Variables with a p-value of less than 0.25, obtained from the likelihood ratio test (LRT) in the univariate analyses, were included to create a full multivariable logistic regression model. Variables included in the full model with a p-value greater than 0.05 were then removed one by

one to examine changes to the model coefficients and the AIC values for model fit between the full and reduced multivariable logistic regression models. Study variables initially excluded from the full model (with a p-value greater than 0.25 in the univariate analysis) were incorporated into the reduced model to confirm no statistical significance and model fit. Interaction terms were then examined between the primary explanatory variable (vaccination status) and the remaining covariates in the reduced model for statistical significance. The AIC value was also reviewed for model fit. The primary explanatory variable (vaccination status) remained in the multivariable logistic regression model regardless of its statistical significance. Summary tables were provided for the coefficient estimate, standard error, unadjusted OR, and adjusted OR with the 95% CI for each predictor variable.

The IRR was also calculated for most severe symptom by vaccine type from 2014/2015 to 2019/2020.

2.6 Objective 2: Analytical Plan for Agreement Analysis between Reporting Methods

2.6.1 Objective 2: Study Variables for Agreement Analysis between Reporting Methods

2.6.1.1 Online Survey: Most Severe Symptom

Child participants who met the criteria for a severe health event were solicited for their most severe symptom from 2016/2017 to 2019/2020. A list of predefined symptoms was provided to the child participants on the online survey, summarized in Appendix A. If a symptom was not listed on the survey, an option to indicate "other" was provided, which opened a text-box field. New variables for croup and urinary symptoms were created post-data collection. Child participants with multiple symptoms were asked to indicate their most severe symptom. If they had stated only one symptom, that was considered their most severe symptom.

2.6.1.2 Online Survey: Diagnosis and Treatment

Child participants who sought care from a healthcare provider were asked to indicate if they received a diagnosis or treatment on their online survey. Survey responses for both variables were categorized as a binary outcome. Additional details regarding the type of diagnosis and treatment were collected using open text fields, but they were not analyzed due to considerable heterogeneity in the responses.

2.6.1.3 Telephone Follow-Up Report: Most Severe Symptom

Child participants who indicated that their most severe symptom developed within 7 days after receipt of the vaccine, and they sought medical care were then followed up by a research staff member via telephone. The telephone call with the research staff aimed to confirm and

obtain more information about the most severe symptom that led the child to see a healthcare provider.

2.6.1.4 Telephone Follow-Up Report: Diagnosis and Treatment

The child participants were asked to confirm if they received a diagnosis or treatment from a healthcare professional during the telephone follow-up report. Telephone responses for both variables (diagnosis and treatment) were each categorized as a binary outcome. Details describing the type of diagnosis and treatment were also collected in the telephone report, but they were not analyzed due to heterogeneity in the responses.

2.6.2 Objective 2: Child Sample for Agreement Analysis Between Reporting Methods

The final analytical sample for the agreement analysis included child participants aged 6 months to 14 years old with a completed online survey and follow-up telephone report during the 2016/2017 to 2019/2020 influenza seasons. Participants with missing or invalid responses for most severe symptom were excluded from the analysis. Participants were excluded if the symptom onset occurred more than 7 days after receiving the seasonal influenza vaccine or more than 7 days before completing the unvaccinated group's online survey. The final analytical sample included 152 child participants who reported their most severe symptom in the online (vaccinated or unvaccinated) surveys and participated in the telephone follow-up report, as described in Figure 4.

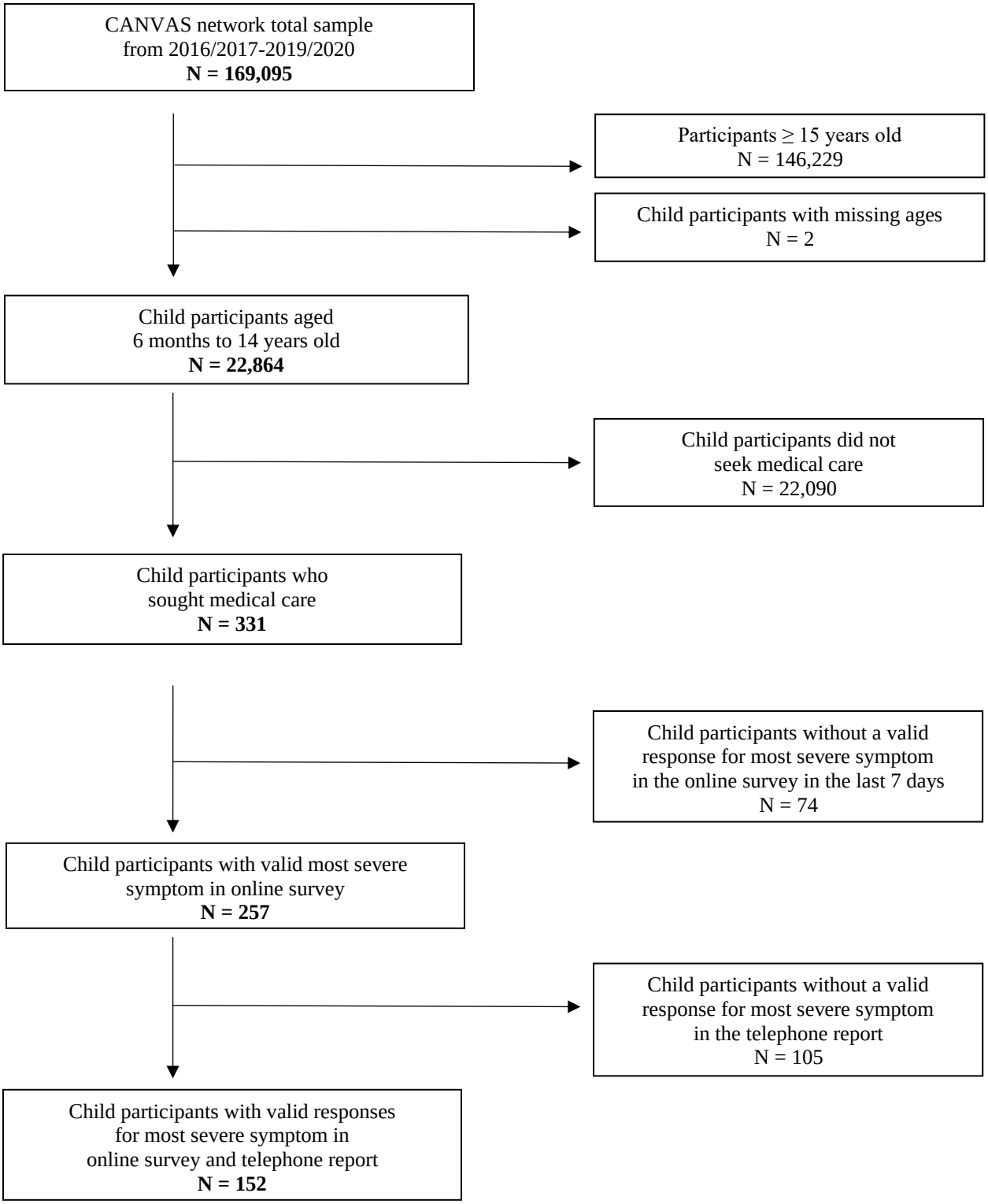


Figure 4. Child analytical sample for agreement of most severe symptom, Canadian National Vaccine Safety (CANVAS) Network data from 2016/2017 to 2019/2020.

2.6.3 Objective 2: Agreement Analysis of Self-Reported Adverse Events between an Online Survey and Telephone Follow-up Report from 2016/2017 to 2019/2020

Descriptive analyses summarized the most severe symptom reported in the online surveys and telephone follow-up reports. Frequency tables were tabulated based on how many participants reported the same response for their most severe symptoms in the online survey and telephone report. The sensitivity, specificity, and kappa statistic were calculated for symptoms with a minimum sample of 10 respondents in the online survey and telephone report. The kappa statistic was also calculated by vaccination status for the most frequently reported severe symptoms. Additional analyses examined the sensitivity, specificity, and the kappa statistic for reporting diagnosis and treatment in the online survey and telephone report.

2.7 Objective 3: Analytical Plan for Pregnancy Analysis

2.7.1 Objective 3: Study Variables for Pregnancy Analysis

2.7.1.1 Primary Explanatory Variable for Pregnancy Analysis

The primary explanatory variable was vaccination status, which compared vaccinated to unvaccinated pregnant participants from 2016/2017 to 2019/2020. The vaccinated group consisted of pregnant participants who received Agriflu®, Fluad®, Flulaval®, Fluviral®, Fluzone®, Influvac®, or Vaxigrip®. The seasonal influenza vaccines were grouped by the manufacturer's brand name and not by the vaccine product's composition since this was not routinely collected. The reference category was the unvaccinated group.

2.7.1.2 Primary Outcome Variable for Pregnancy Analysis

The primary outcome is the occurrence of a severe health event defined as a health event that stopped or prevented daily activities, missed work, or required a medical consultation. The onset of the severe health event must be within 7 days of receiving the seasonal influenza vaccine for the vaccinated group or within the previous 7 days since receipt of the online survey for the unvaccinated group. A severe health event was categorized as a binary variable.

2.7.1.3 Secondary Outcome Variable for Pregnancy Analysis

The secondary outcome is the most severe symptom reported on the online survey in the vaccinated and unvaccinated groups, from 2016/2017 to 2019/2020. Pregnant participants who met the criteria for a severe health event (primary outcome) were solicited for any symptom they experienced in the last 7 days. A list of predefined symptoms was provided on the online survey, summarized in Appendix A. Participants were able to select as many symptoms using

checkboxes. If a symptom was not listed on the survey, an option to indicate "other" non-pregnancy or "other" pregnancy-related symptoms was provided, which opened a text-box field. Responses in the "other" open text-box fields were reviewed and recoded if they belonged to another symptom provided in the predefined list. New variables for croup and urinary symptoms were created post-data collection from the "other" category.

Pregnant participants were then asked to identify their most severe symptom based on the symptoms they had provided. Participants who experienced more than one symptom in the last 7 days were asked to indicate their most severe symptom using an open text-box field and participants with only one symptom present did not need to complete this section. It was assumed that participants with one symptom would have that symptom be listed as their main symptom. Responses for the most severe symptom in the "other" open text-box field were reviewed and recoded if they belonged to another symptom provided in the predefined list. Responses for most severe symptom in the text-box field were reviewed and manually recoded to match a specific symptom. Pregnant participants that indicated multiple symptoms but did not identify their most severe symptom or had unclear responses for their most severe symptom were excluded from the secondary analysis.

2.7.1.4 Additional Variables of Interest

2.7.1.4.1 Trimester

The trimester of the pregnancy was collected in the 2017/2018 to 2019/2020 surveys. This variable was added to the questionnaire during the 2017/2018 influenza season; therefore, it was missing in 2016/2017. The first trimester was set as the reference category.

2.7.1.4.2 Age Category

Participant age was collected based on the predefined age categories listed in the survey. Pregnant people's age categories were later grouped as 15-to-29 years old, 30-to-39 years old, and 40-to-49 years old. The 30-to-39 years old and the 40-to-49 years old age categories were combined into a single category for the regression analysis since both groups had a low sample of reported severe health events. The reference category was set as the age category 30-to-49 years since it had the highest proportion of respondents.

2.7.1.4.3 Year of Enrolment

The year of enrolment represented each influenza season during the study period, from 2016/2017 to 2019/2020. The 2019/2020 influenza season was the reference category since it had the highest proportion of participant respondents.

2.7.1.4.4 Enrolment Site

The enrolment site described where the participants submitted their online survey. It included 7 locations across Canada, located in Vancouver, Calgary, Toronto, Ottawa, Quebec City, Sherbrooke, and Halifax. The eligibility criteria for all sites were the same. The reference category was Calgary since it had the highest proportion of participant respondents.

2.7.1.5 Immunization History

Participants in the vaccinated group were asked to report the number of seasonal influenza vaccines received in the last 2 years. This was categorized as none, 1 vaccine, or 2

vaccines. The group of participants who received 2 seasonal influenza vaccines was set as the reference category, since it had the highest proportion of respondents for pregnant participants.

2.7.1.6 Onset of Health Event

Pregnant participants who met the criteria for a severe health event (primary outcome) were asked to indicate the onset of their health event. The onset of their severe health event was categorized (post-data collection) as having occurred within 24 hours, within 1-to-3 days, within 4-to-5 days, or within 6-to-7 days. Pregnant participants were excluded if the onset of their severe health event was missing or if it started more than 7 days after vaccination or more than 7 days before receiving the survey in the unvaccinated group.

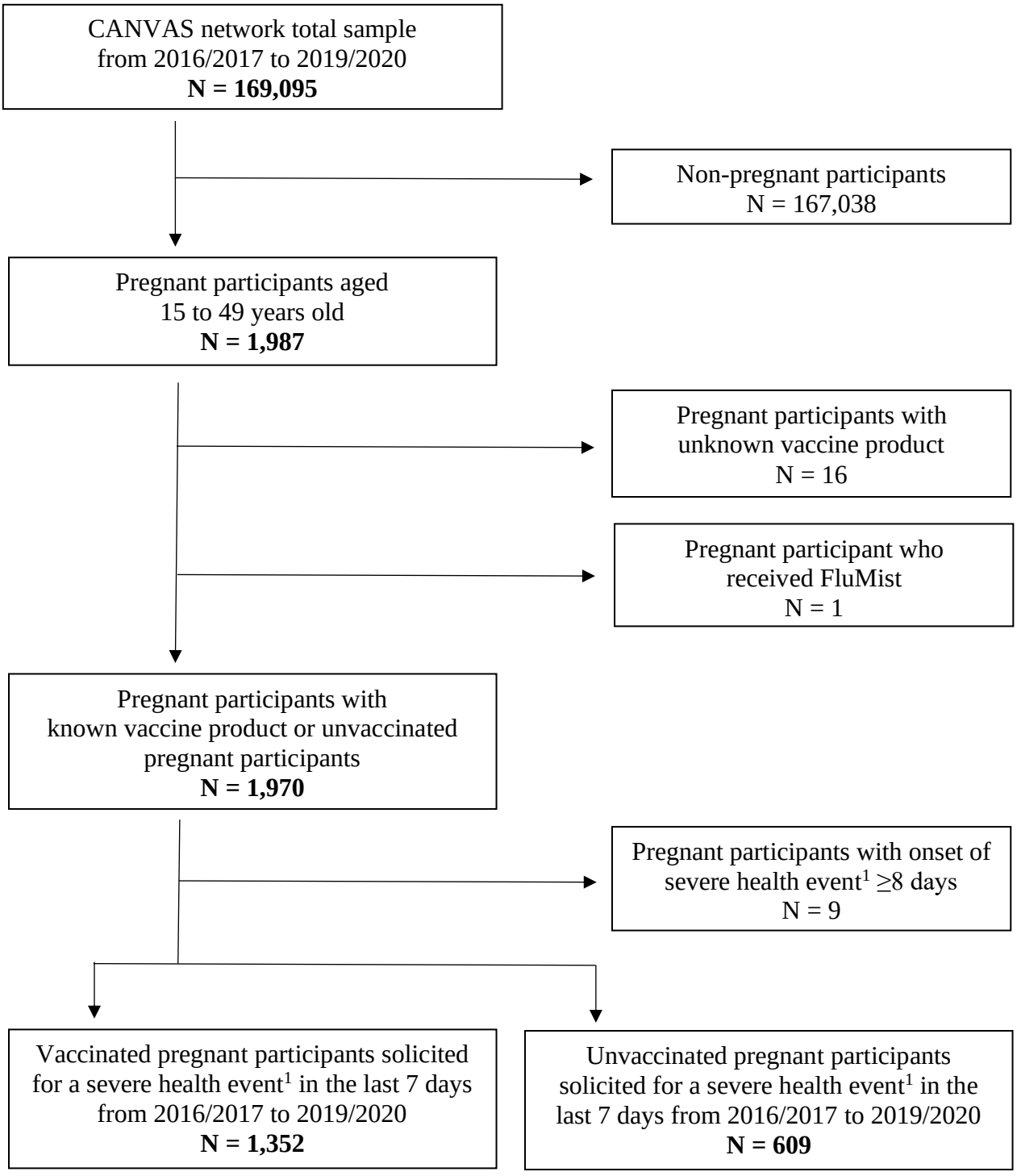
2.7.1.7 Duration of Health Event

The duration of a severe health event was captured according to predefined categories in the online survey. Pregnant participants were able to select a duration of fewer than 24 hours, 1-to-3 days, 4-to-5 days, 6 days or longer, or still present.

2.7.2 Objective 3: Pregnancy Sample

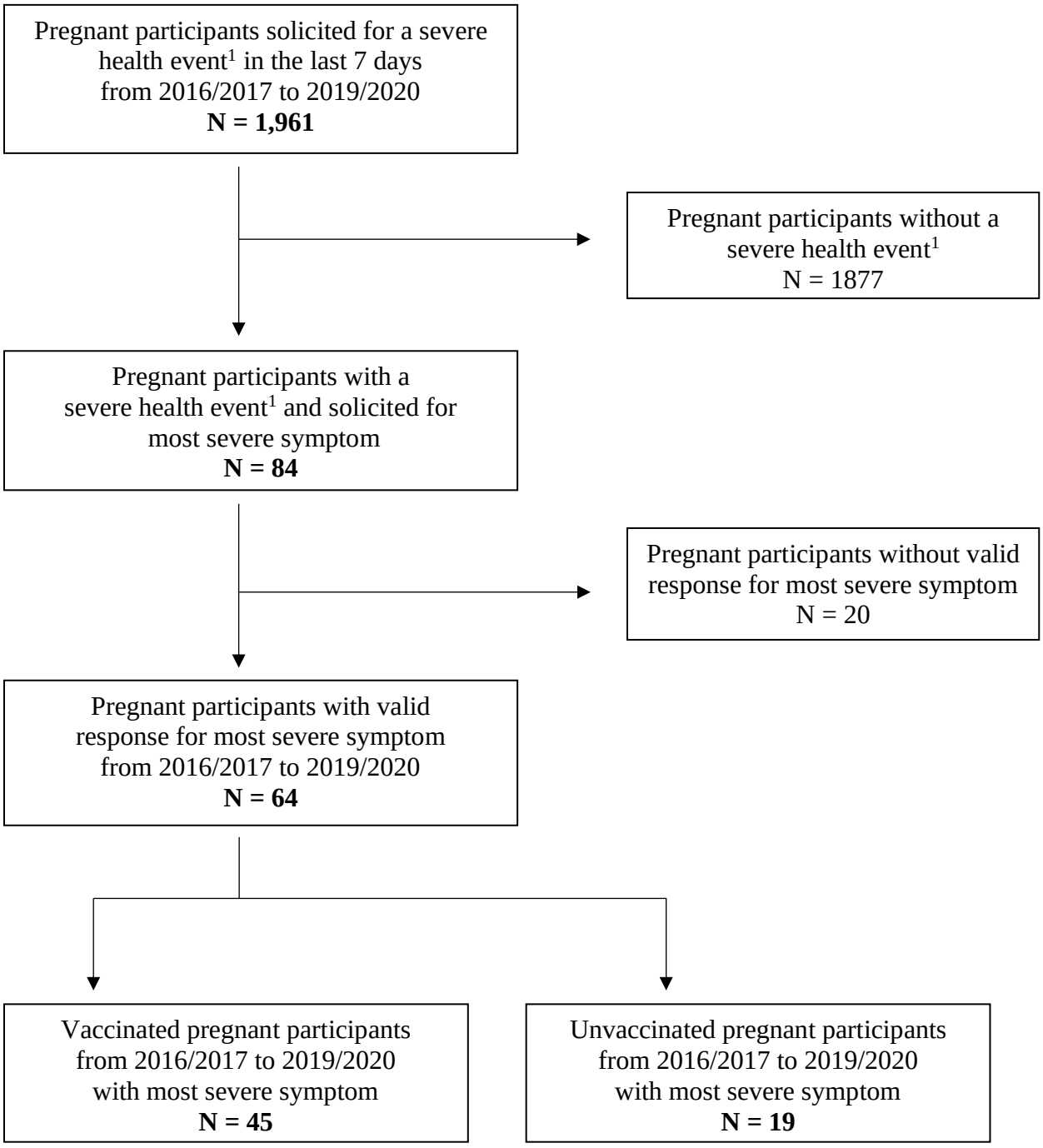
The final analytical sample included eligible pregnant participants with a completed survey during the 2016/2017 to 2019/2020 influenza seasons. Age was restricted from 15-to-49 years old. Pregnant participants with a missing response for influenza vaccine product names were excluded from the analyses. Participants who received FluMist® were also excluded from the analyses since it was not recommended for pregnant people during the study period. [25, 26] All eligible vaccinated, and unvaccinated pregnant participants were solicited for a severe health

event. Pregnant participants were excluded if the onset of their severe health event was missing or greater than 8 days. The final study sample for pregnant participants solicited for a severe health event in the vaccinated and unvaccinated groups was 1,961, as described in Figure 5. Pregnant participants with a severe health event were then solicited for their most severe symptom. The final study sample for pregnant participants solicited for their most severe symptom in the vaccinated and unvaccinated groups was 64, as described in Figure 6.



[1] Severe health event: Prevented/stopped activities or missed school or saw healthcare provider

Figure 5. Pregnancy analytical sample for severe health event, Canadian National Vaccine Safety (CANVAS) Network data from 2016/2017 to 2019/2020.



[1] Severe health event: Prevented/stopped activities or missed school or saw healthcare provider

Figure 6. Pregnancy analytical sample for most severe symptom, Canadian National Vaccine Safety (CANVAS) Network data from 2016/2017 to 2019/2020.

2.7.3 Objective 3: Pregnancy Analysis from 2016/2017 to 2019/2020

2.7.3.1 Descriptive Analysis

Descriptive analyses were conducted to summarize responses in the pregnancy sample during the 2016/2017 to 2019/2020 influenza seasons. This included variables for vaccination status, trimester of pregnancy, age category, year of enrolment, enrolment site, immunization history, and vaccine product name. A summary table for the proportion of severe health events (primary outcome variable) was described by vaccination status and vaccine product name. Additional summary statistics were calculated for the onset and duration of the severe health event based on the vaccination status.

2.7.3.2 Inferential Analyses of Severe Health Events and Most Severe Symptom

The IRR for severe health events was calculated by vaccine type and for vaccine products administered to more than 100 pregnant participants throughout the study period.

Univariate analyses were conducted to model severe health events (primary outcome variable) with vaccination status and additional covariates of interest. The covariates were trimester, age category, year of enrolment, enrolment site, and immunization history (vaccinated group only). The output from the univariate logistic regressions was used to build a main effect multivariable logistic regression model. The multivariable logistic regression models were built using model-building strategies defined by Hosmer et al. [58]

Variables with a p-value of less than 0.25, obtained from the likelihood ratio test (LRT) in the univariates analyses, were included to create a full multivariable logistic regression model. Variables included in the full model with a p-value greater than 0.05 were then removed one by one to examine changes to the model coefficients. The AIC values for model fit between the full

and reduced multivariable logistic regression models were also reviewed. Study variables initially excluded from the full model (with a p-value greater than 0.25 in the univariate analysis) were re-incorporated into the reduced model to confirm no statistical significance and model fit. Interaction terms were then examined between the primary explanatory variable (vaccination status) and the remaining covariates in the reduced model for statistical significance and the AIC value for model fit. The primary explanatory variable remained in the multivariable logistic regression model regardless of its statistical significance. Summary tables were provided for the coefficient estimate, standard error, unadjusted OR, and adjusted OR with the 95% CI for each predictor variable.

The IRR for most severe symptom was also calculated from 2016/2017 to 2019/2020.

2.8 Statistical analyses

All statistical analyses were conducted using SAS version 9.4.

Chapter 3: Safety of Seasonal Influenza Vaccine in Canadian Children from 2013/2014 to 2019/2020

3.1 Study Sample

The final analytical sample consisted of 29,923 child participants with a completed online survey during the 2013/2014 to 2019/2020 influenza seasons. Table 3 summarizes the number of child participants who completed the online survey, stratified by vaccine status. The proportion of child participants with completed surveys increased each year from 2,283 (7.6%) in 2013/2014 to 6,860 (22.9%) in 2019/2020. The final analytical sample had a higher proportion of male participants than female participants, as described in Table 4; however, the proportion of male and females was mostly similar. Most child participants were 5-to-9 years old (38.4%) followed by 2-to-4 years old (30.0%). Table 5 describes the proportion of child participants who completed the online survey by age group and vaccination status. The sample consisted of 59.4% of child participants from Calgary, and 21.5% from Sherbrooke, with the remainder from the other sites described in Table 6.

Table 3. Vaccination status by year, child data from 2013/2014 to 2019/2020.

Year	IIV n (%)[1]	LAIV n (%)[1]	Unvaccinated n (%)[1]	Total n (%)[1]
2013/2014	563 (1.88)	878 (2.93)	842 (2.81)	2,283 (7.63)
2014/2015	552 (1.84)	1,195 (3.99)	834 (2.79)	2,581 (8.63)
2015/2016	476 (1.59)	1,018 (3.40)	1,120 (3.74)	2,614 (8.74)
2016/2017	901 (3.01)	1,194 (3.99)	1,027 (3.43)	3,122 (10.43)
2017/2018	3,440 (11.50)	908 (3.03)	1,421 (4.75)	5,769 (19.28)
2018/2019	2,770 (9.26)	860 (2.87)	3,064 (10.24)	6,694 (22.37)
2019/2020	4,597 (15.36)	0 (0.00)[2]	2,263 (7.56)	6,860 (22.93)
Total	**13,299 (44.44)**	**6,053 (20.23)**	**10,571 (35.33)**	**29,923 (100.00)**

IIV: Inactivated Influenza Vaccine
LAIV: Live Attenuated Influenza Vaccine
[1] Percentages are calculated based on the total sample (n=29,923)
[2] LAIV was recommended for use but not available in Canada

Table 4. Sex by year and vaccination status, child data from 2013/2014 to 2019/2020.

Year	Male n (%)[1]	Female n (%)[1]	Total n (%)[1]
2013/2014	**1,147 (3.83)**	**1,136 (3.80)**	**2,283 (7.63)**
IIV	283 (0.95)	280 (0.94)	563 (1.88)
LAIV	437 (1.46)	441 (1.47)	878 (2.93)
Unvaccinated	427 (1.43)	415 (1.39)	842 (2.81)
2014/2015	**1,366 (4.57)**	**1,215 (4.06)**	**2,581 (8.63)**
IIV	294 (0.98)	258 (0.86)	552 (1.84)
LAIV	640 (2.14)	555 (1.85)	1,195 (3.99)
Unvaccinated	432 (1.44)	402 (1.34)	837 (2.80)
2015/2016	**1,366 (4.57)**	**1,248 (4.17)**	**2,614 (8.74)**
IIV	258 (0.86)	218 (0.73)	476 (1.59)
LAIV	512 (1.71)	506 (1.69)	1,018 (3.40)
Unvaccinated	596 (1.99)	524 (1.75)	1,120 (3.74)
2016/2017	**1,651 (5.52)**	**1,471 (4.92)**	**3,122 (10.43)**
IIV	463 (1.55)	438 (1.46)	901 (3.01)
LAIV	629 (2.10)	565 (1.89)	1,194 (3.99)
Unvaccinated	559 (1.87)	468 (1.56)	1,027 (3.43)
2017/2018	**2,981 (9.96)**	**2,788 (9.32)**	**5,769 (19.28)**
IIV	1,766 (5.90)	1,674 (5.59)	3,440 (11.50)
LAIV	466 (1.56)	442 (1.48)	908 (3.03)
Unvaccinated	749 (2.50)	672 (2.25)	1,421 (4.75)
2018/2019	**3,411 (11.40)**	**3,283 (10.97)**	**6,694 (22.37)**
IIV	1,395 (4.66)	1,375 (4.60)	2,770 (9.26)
LAIV	453 (1.51)	407 (1.36)	860 (2.87)
Unvaccinated	1,563 (5.22)	1,501 (5.02)	3,064 (10.24)
2019/2020	**3,499 (11.69)**	**3,361 (11.23)**	**6,860 (22.93)**
IIV	2,316 (7.74)	2,281 (7.62)	4,597 (15.36)
LAIV[2]	N/A	N/A	N/A
Unvaccinated	1,183 (3.95)	1,080 (3.61)	2,263 (7.56)
Total	**15,421 (51.54)**	**14,502 (48.46)**	**29,923 (100.00)**
IIV	6,775 (22.64)	6,524 (21.80)	13,299 (44.44)
LAIV	3,137 (10.48)	2,916 (9.75)	6,053 (20.23)
Unvaccinated	5,509 (18.41)	5,062 (16.92)	10,571 (35.33)

IIV: Inactivated Influenza Vaccine

LAIV: Live Attenuated Influenza Vaccine

[1] Percentages are calculated based on the total sample (n=29,923)

[2] LAIV was recommended for use but not available in Canada

Table 5. Age categories by year and vaccination status, child data from 2013/2014 to 2019/2020.

Year	6-to-23 months n (%)[1]	2-to-4 years old n (%)[1]	5-to-9 years old n (%)[1]	10-to-14 years old n (%)[1]	Total n (%)[1]
2013/2014	**243 (0.81)**	**526 (1.76)**	**908 (3.03)**	**606 (2.03)[2]**	**2,283 (7.63)**
IIV	193 (0.64)	82 (0.27)	133 (0.44)	155 (0.52)	563 (1.88)
LAIV	7 (0.02)	271 (0.91)	410 (1.37)	190 (0.63)	878 (2.93)
Unvaccinated	43 (0.14)	173 (0.58)	365 (1.22)	261 (0.87)	842 (2.81)
2014/2015	**293 (0.98)**	**725 (2.42)**	**1,051 (3.51)**	**512 (1.71)**	**2,581 (8.63)**
IIV	210 (0.70)	117 (0.39)	135 (0.45)	90 (0.30)	552 (1.84)
LAIV	13 (0.04)	386 (1.29)	589 (1.97)	207 (0.69)	1,195 (3.99)
Unvaccinated	70 (0.23)	222 (0.74)	327 (1.09)	215 (0.72)	834 (2.79)
2015/2016	**263 (0.88)**	**706 (2.36)**	**1,093 (3.65)**	**552 (1.84)**	**2,614 (8.74)**
IIV	180 (0.60)	89 (0.30)	118 (0.39)	89 (0.30)	476 (1.59)
LAIV	21 (0.07)	313 (1.05)	483 (1.61)	201 (0.67)	1,018 (3.40)
Unvaccinated	62 (0.21)	304 (1.02)	492 (1.64)	262 (0.88)	1,120 (3.74)
2016/2017	**336 (1.12)**	**856 (2.86)**	**1,271 (4.25)**	**659 (2.20)**	**3,122 (10.43)**
IIV	271 (0.91)	208 (0.70)	241 (0.81)	181 (0.60)	901 (3.01)
LAIV	11 (0.04)	403 (1.35)	554 (1.85)	226 (0.76)	1,194 (3.99)
Unvaccinated	54 (0.18)	245 (0.82)	476 (1.59)	252 (0.84)	1,027 (3.43)
2017/2018	**675 (2.26)**	**1,642 (5.49)**	**2,325 (7.77)**	**1,127 (3.77)**	**5,769 (19.28)**
IIV	582 (1.94)	952 (3.18)	1323 (4.42)	583 (1.95)	3,440 (11.50)
LAIV	7 (0.02)	305 (1.02)	406 (1.36)	190 (0.63)	908 (3.03)
Unvaccinated	86 (0.29)	385 (1.29)	596 (1.99)	354 (1.18)	1,421 (4.75)
2018/2019	**685 (2.29)**	**2,120 (7.08)**	**2,540 (8.49)**	**1,349 (4.51)**	**6,694 (22.37)**
IIV	528 (1.76)	987 (3.30)	835 (2.79)	420 (1.40)	2,770 (9.26)
LAIV	10 (0.03)	227 (0.76)	366 (1.22)	257 (0.86)	860 (2.87)
Unvaccinated	147 (0.49)	906 (3.03)	1,339 (4.47)	672 (2.25)	3,064 (10.24)
2019/2020	**897 (3.00)**	**2,410 (8.05)**	**2,288 (7.65)**	**1,265 (4.23)**	**6,860 (22.93)**
IIV	768 (2.57)	1,646 (5.50)	1,429 (4.78)	754 (2.52)	4,597 (15.36)
LAIV[3]	N/A	N/A	N/A	N/A	N/A
Unvaccinated	129 (0.43)	764 (2.55)	859 (2.87)	511 (1.71)	2,263 (7.56)
Total	**3,392 (11.34)**	**8,985 (30.03)**	**11,476 (38.35)**	**6,070 (20.29)**	**29,923 (100.00)**
IIV	2,732 (9.13)	4,081 (13.64)	4,214 (14.08)	2,272 (7.59)	13,299 (44.44)
LAIV	69 (0.23)	1,905 (6.37)	2,808 (9.38)	1,271 (4.25)	6,053 (20.23)
Unvaccinated	591 (1.98)	2,999 (10.02)	4,454 (14.88)	2,527 (8.45)	10,571 (35.33)

IIV: Inactivated Influenza Vaccine

LAIV: Live Attenuated Influenza Vaccine

[1] Percentages are calculated based on the total sample (n=29,923)

[2] Children aged 10-to-16 years old

[3] LAIV was recommended for use but not available in Canada

Table 6. Enrolment site by year and vaccination status, child data from 2013/2014 to 2019/2020.

Year	Calgary n (%)[1]	Vancouver n (%)[1]	Toronto n (%)[1]	Ottawa n (%)[1]	Quebec City n (%)[1]	Sherbrooke n (%)[1]	Halifax n (%)[1]	Total n (%)[1]
2013/2014	**1,701 (5.68)**	**128 (0.42)**	**75 (0.25)**	**9 (0.03)**	**8 (0.03)**	**334 (1.12)**	**28 (0.09)**	**2,283 (7.63)**
IIV	278 (0.93)	41 (0.14)	70 (0.23)	6 (0.02)	3 (0.01)	155 (0.52)	10 (0.03)	563 (1.88)
LAIV	629 (2.10)	72 (0.24)	0 (0.00)	0 (0.00)	0 (0.00)	177 (0.59)	0 (0.00)	878 (2.93)
Unvaccinated	794 (2.65)	15 (0.05)	5 (0.02)	3 (0.01)	5 (0.02)	2 (0.01)	18 (0.06)	842 (2.81)
2014/2015	**1,423 (4.76)**	**199 (0.67)**	**96 (0.32)**	**6 (0.02)**	**4 (0.01)**	**832 (2.78)**	**21 (0.07)**	**2,581 (8.63)**
IIV	224 (0.75)	47 (0.16)	62 (0.21)	1 (0.00)	0 (0.00)	218 (0.73)	0 (0.00)	552 (1.84)
LAIV	677 (2.26)	87 (0.29)	0 (0.00)	0 (0.00)	0 (0.00)	431 (1.44)	0 (0.00)	1,195 (3.99)
Unvaccinated	522 (1.74)	65 (0.22)	34 (0.11)	5 (0.02)	4 (0.01)	183 (0.61)	21 (0.07)	834 (2.79)
2015/2016	**1,195 (3.99)**	**178 (0.59)**	**110 (0.37)**	**41 (0.14)**	**7 (0.02)**	**1,071 (3.58)**	**12 (0.04)**	**2,614 (8.74)**
IIV	148 (0.49)	34 (0.11)	52 (0.17)	38 (0.13)	0 (0.00)	197 (0.66)	7 (0.02)	476 (1.59)
LAIV	485 (1.62)	40 (0.13)	11 (0.04)	0 (0.00)	0 (0.00)	482 (1.61)	0 (0.00)	1,018 (3.40)
Unvaccinated	562 (1.88)	104 (0.35)	47 (0.16)	3 (0.01)	7 (0.02)	392 (1.31)	5 (0.02)	1,120 (3.74)
2016/2017	**1,282 (4.28)**	**251 (0.84)**	**126 (0.42)**	**38 (0.13)**	**230 (0.77)**	**1,168 (3.90)**	**27 (0.09)**	**3,122 (10.43)**
IIV	397 (1.33)	111 (0.37)	81 (0.27)	12 (0.04)	86 (0.29)	202 (0.68)	12 (0.04)	901 (3.01)
LAIV	494 (1.65)	77 (0.26)	8 (0.03)	0 (0.00)	139 (0.46)	476 (1.59)	0 (0.00)	1,194 (3.99)
Unvaccinated	391 (1.31)	63 (0.21)	37 (0.12)	26 (0.09)	5 (0.02)	490 (1.64)	15 (0.05)	1,027 (3.43)
2017/2018	**3,333 (11.14)**	**259 (0.87)**	**88 (0.29)**	**6 (0.02)**	**868 (2.90)**	**1,189 (3.97)**	**26 (0.09)**	**5,769 (19.28)**
IIV	2,713 (9.07)	139 (0.46)	19 (0.06)	1 (0.00)	326 (1.09)	241 (0.81)	1 (0.00)	3,440 (11.50)
LAIV	0 (0.00)	5 (0.02)	2 (0.01)	0 (0.00)	416 (1.39)	480 (1.60)	5 (0.02)	908 (3.03)
Unvaccinated	620 (2.07)	115 (0.38)	67 (0.22)	5 (0.02)	126 (0.42)	468 (1.56)	20 (0.07)	1,421 (4.75)
2018/2019	**4,278 (14.30)**	**220 (0.74)**	**45 (0.15)**	**5 (0.02)**	**1,181 (3.95)**	**943 (3.15)**	**22 (0.07)**	**6,694 (22.37)**
IIV	2,355 (7.87)	67 (0.22)	16 (0.05)	0 (0.00)	199 (0.67)	130 (0.43)	3 (0.01)	2,770 (9.26)
LAIV	0 (0.00)	51 (0.17)	9 (0.03)	0 (0.00)	456 (1.52)	344 (1.15)	0 (0.00)	860 (2.87)
Unvaccinated	1,923 (6.43)	102 (0.34)	20 (0.07)	5 (0.02)	526 (1.76)	469 (1.57)	19 (0.06)	3,064 (10.24)
2019/2020	**4,575 (15.29)**	**221 (0.74)**	**107 (0.36)**	**92 (0.31)**	**955 (3.19)**	**894 (2.99)**	**16 (0.05)**	**6,860 (22.93)**
IIV	2,964 (9.91)	151 (0.50)	82 (0.27)	92 (0.31)	667 (2.23)	629 (2.10)	12 (0.04)	4,597 (15.36)
LAIV[2]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Unvaccinated	1,611 (5.38)	70 (0.23)	25 (0.08)	0 (0.00)	288 (0.96)	265 (0.89)	4 (0.01)	2,263 (7.56)
Total	**17,787 (59.44)**	**1,456 (4.87)**	**647 (2.16)**	**197 (0.66)**	**3,253 (10.87)**	**6,431 (21.49)**	**152 (0.51)**	**29,923 (100.00)**
IIV	9,079 (30.34)	590 (1.97)	382 (1.28)	150 (0.50)	1,281 (4.28)	1,772 (5.92)	45 (0.15)	13,299 (44.44)
LAIV	2,285 (7.64)	332 (1.11)	30 (0.10)	0 (0.00)	1,011 (3.38)	2,390 (7.99)	5 (0.02)	6,053 (20.23)
Unvaccinated	6,423 (21.47)	534 (1.78)	235 (0.79)	47 (0.16)	961 (3.21)	2,269 (7.58)	102 (0.34)	10,571 (35.33)

IIV: Inactivated Influenza Vaccine

LAIV: Live Attenuated Influenza Vaccine

[1] Percentages are calculated based on the total sample (n=29,923)

[2] LAIV was recommended for use but not available in Canada

3.2 Descriptive Statistics

3.2.1 Seasonal Influenza Vaccines Administered to Children from 2013/2014 to 2019/2020

During the 2013/2014 to 2019/2020 influenza seasons, a higher proportion of child participants received the IIV than the LAIV. However, the LAIV was not available in Canada during the 2019/2020 influenza season. From 2013/2014 to 2019/2020 a total of 13,299 (68.7%) child participants received IIV and 6,053 (31.3%) child participants received LAIV. IIV Fluzone® (39.5%), LAIV FluMist® (31.3%), and IIV Flulaval® (19.4%) were the most frequently administered seasonal influenza vaccine products during the study period. There were 69 children aged 6-to-23 months who received FluMist®. This was considered off-label since it was not recommended for use in this age group due to increased risk of wheezing compared to injectable influenza vaccines. [24-26]. These 69 participants were excluded from inferential analyses. Table 7 describes the proportion of each seasonal influenza vaccine product by age category.

Table 7. Seasonal influenza vaccine product name and vaccine type by age category, child data from 2013/2014 to 2019/2020.

Vaccine Product	6 to 23 months n (%)[2]	2-to-4 years old n (%)[2]	5-to-9 years old n (%)[2]	10 to 14 years old[1] n (%)[2]	Total n (%)[2]
IIV	**2,732 (14.12)**	**4,081 (21.09)**	**4,214 (21.78)**	**2,272 (11.74)**	**13,299 (68.72)**
Agriflu®	50 (0.26)	36 (0.19)	33 (0.17)	41 (0.21)	160 (0.83)
Fluad®	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.01)	1 (0.01)
Flulaval®	775 (4.00)	1,238 (6.40)	1,106 (5.72)	625 (3.23)	3,744 (19.35)
Fluviral®	472 (2.44)	267 (1.38)	375 (1.94)	318 (1.64)	1,432 (7.40)
Fluzone®	1,344 (6.95)	2,477 (12.80)	2,618 (13.53)	1,211 (6.26)	7,650 (39.53)
Influvac®	9 (0.05)	10 (0.05)	16 (0.08)	20 (0.10)	55 (0.28)
Vaxigrip®	82 (0.42)	53 (0.27)	66 (0.34)	56 (0.29)	257 (1.33)
LAIV	**69 (0.36)[3]**	**1,905 (9.84)**	**2,808 (14.51)**	**1,271 (6.57)**	**6,053 (31.28)**
FluMist®	69 (0.36)[3]	1,905 (9.84)	2,808 (14.51)	1,271 (6.57)	6,053 (31.28)
Total	**2,801 (14.47)**	**5,986 (30.93)**	**7,022 (36.29)**	**3,543 (18.31)**	**19,352 (100.00)**

IIV: Inactivated Influenza Vaccine
LAIV: Live Attenuated Influenza Vaccine
[1] The age group for this category was 10-16 years of age in the 2013/2014 survey
[2] Percentages are calculated based on the total sample (n=19,352)
[3] Children aged 6 to 23 months who received FluMist® were excluded from inferential analyses since it was not recommended for this age group during the study period

Of the 19,352 seasonal influenza vaccine products administered to child participants, Calgary had the highest proportion of the IIV administered; meanwhile, Sherbrooke had the highest proportion of the LAIV administered, as described in Table 8. It was observed that only 3 seasonal influenza vaccine products were administered to child participants at all 7 sites. Similarly, Fluviral® was the only seasonal influenza vaccine product administered each year (from 2013/2014 to 2019/2020) in this sample, as described in Table 9. There were 14,864 (76.8%) child participants who had been vaccinated each year for the past two years and 2,901 (15.0%) who had been vaccinated once in the past two years. There were 1,587 (8.2%) child participants who had not been vaccinated with a seasonal influenza vaccine in the previous 2 years. Appendix B describes the number of seasonal influenza vaccines received in the past 2 years from 2013/2014 to 2019/2020, stratified by vaccine type.

Table 8. Seasonal influenza vaccine product name and vaccine type by site, child data from 2013/2014 to 2019/2020.

Vaccine Product	Calgary n (%)[1]	Vancouver n (%)[1]	Toronto n (%)[1]	Ottawa n (%)[1]	Quebec City n (%)[1]	Sherbrooke n (%)[1]	Halifax n (%)[1]	Total n (%)[1]
IIV	**9,079 (46.92)**	**590 (3.05)**	**382 (1.97)**	**150 (0.78)**	**1,281 (6.62)**	**1,772 (9.16)**	**45 (0.23)**	**13,299 (68.72)**
Agriflu®	16 (0.08)	70 (0.36)	18 (0.09)	7 (0.04)	17 (0.09)	32 (0.17)	0 (0.00)	160 (0.83)
Fluad®	0 (0.00)	1 (0.01)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.01)
Flulaval®	2,318 (11.98)	234 (1.21)	76 (0.39)	19 (0.10)	355 (1,83)	729 (3.77)	13 (0.07)	3,744 (19.35)
Fluviral®	535 (2.76)	64 (0.33)	23 (0.12)	20 (0.10)	81 (0.42)	698 (3.61)	11 (0.06)	1,432 (7.40)
Fluzone®	6,206 (32.07)	221 (1.14)	137 (0.71)	97 (0.50)	804 (4.15)	164 (0.85)	21 (0.11)	7,650 (39.53)
Influvac®	3 (0.02)	0 (0.00)	19 (0.10)	7 (0.04)	24 (0.12)	2 (0.01)	0 (0.00)	55 (0.28)
Vaxigrip®	1 (0.01)	0 (0.00)	109 (0.56)	0 (0.00)	0 (0.00)	147 (0.76)	0 (0.00)	257 (1.33)
LAIV	**2,285 (11.81)**	**332 (1.72)**	**30 (0.16)**	**0 (0.00)**	**1,011 (5.22)**	**2,390 (12.35)**	**5 (0.03)**	**6,053 (31.28)**
FluMist®	2,285 (11.81)	332 (1.72)	30 (0.16)	0 (0.00)	1,011 (5.22)	2,390 (12.35)	5 (0.03)	6,053 (31.28)
Total	**11,364 (58.72)**	**922 (4.76)**	**412 (2.13)**	**150 (0.78)**	**2,292 (11.84)**	**4,162 (21.51)**	**50 (0.26)**	**19,352 (100.00)**

IIV: Inactivated Influenza Vaccine

LAIV: Live Attenuated Influenza Vaccine

[1] Percentages are calculated based on the total sample (n=19,352)

Table 9. Seasonal influenza vaccine product name and vaccine type by year, child data from 2013/2014 to 2019/2020.

Vaccine Product	2013/2014 n (%)[1]	2014/2015 n (%)[1]	2015/2016 n (%)[1]	2016/2017 n (%)[1]	2017/2018 n (%)[1]	2018/2019 n (%)[1]	2019/2020 n (%)[1]	Total n (%)[1]
IIV	**563 (2.91)**	**552 (2.85)**	**476 (2.46)**	**901 (4.66)**	**3,440 (17.78)**	**2,770 (14.31)**	**4,597 (23.75)**	**13,299 (68.72)**
Agriflu®	34 (0.18)	37 (0.19)	33 (0.17)	17 (0.09)	35 (0.18)	0 (0.00)	4 (0.02)	160 (0.83)
Fluad®	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.01)	0 (0.00)	0 (0.00)	1 (0.01)
Flulaval®	0 (0.00)	0 (0.00)	0 (0.00)	131 (0.68)	393 (2.03)	726 (3.75)	2,494 (12.89)	3,744 (19.35)
Fluviral®	452 (2.34)	332 (1.72)	236 (1.22)	168 (0.87)	147 (0.76)	93 (0.48)	4 (0.02)	1,432 (7.40)
Fluzone®	3 (0.02)	0 (0.00)	198 (1.02)	553 (2.86)	2,850 (14.73)	1,951 (10.08)	2,095 (10.83)	7,650 (39.53)
Influvac®	0 (0.00)	0 (0.00)	9 (0.05)	32 (0.17)	14 (0.07)	0 (0.00)	0 (0.00)	55 (0.28)
Vaxigrip®	74 (0.38)	183 (0.95)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	257 (1.33)
LAIV	**878 (4.54)**	**1,195 (6.18)**	**1,018 (5.26)**	**1,194 (6.17)**	**908 (4.69)**	**860 (4.44)**	**0 (0.00)**	**6,053 (31.28)**
FluMist®	878 (4.54)	1,195 (6.18)	1,018 (5.26)	1,194 (6.17)	908 (4.69)	860 (4.44)	0 (0.00)[2]	6,053 (31.28)
Total	**1,441 (7.45)**	**1,747 (9.03)**	**1,494 (7.72)**	**2,095 (10.83)**	**4,348 (22.47)**	**3,630 (18.76)**	**4,597 (23.75)**	**19,352 (100.00)**

IIV: Inactivated Influenza Vaccine

LAIV: Live Attenuated Influenza Vaccine

[1] Percentages are calculated based on the total sample (n=19,352)

[2] LAIV was recommended for use but not available in Canada

3.2.2 Self-Reported Severe Health Events in Children from 2013/2014 to 2019/2020

Table 10 describes the proportion of severe health events reported in the vaccinated and unvaccinated groups and the IRRs from 2013/2014 to 2019/2020. There were 944 (7.10%) child participants that reported a severe health event among all children vaccinated with the IIV from 2013/2014 to 2019/2020. In the corresponding unvaccinated group, 617 (5.84%) child participants reported a severe health event. In contrast, 336 (5.61%) child participants reported a severe health event among all children vaccinated with the LAIV from 2013/2014 to 2018/2019. In the corresponding unvaccinated group, 419 (5.34%) child participants aged 2-to-14 years old reported a severe health event.

The unadjusted IRR for a severe health event was 1.22 with a 95% CI of 1.10 and 1.34 in children vaccinated with the IIV compared to unvaccinated children. However, after adjusting for year of enrolment, the rate was statistically significant in the 2014/2015 (IIR: 1.98; 95% CI: 1.27, 3.10), 2016/2017 (IRR: 1.86; 95% CI: 1.32, 2.63), and 2018/2019 (IRR: 1.32; 95% CI: 1.08, 1.62) influenza seasons. In contrast, the unadjusted IRR for a severe health event was not statistically significant in children vaccinated with the LAIV compared to unvaccinated children. However, it was statistically significant in 2014/2015 (IIR: 1.62; 95% CI: 1.05, 2.48), 2016/2017 (IIR: 1.50; 95% CI: 1.05, 2.14), and 2017/2018 (IRR: 0.67; 95% CI: 0.46, 0.97) when stratified by year. The unadjusted IRRs for Flulaval and Fluzone were each statistically significant during the study period, as described in Table 11. Although both products were not administered to participants every year.

The proportion of severe health events reported by immunization history is described in Appendix C for child participants who received the IIV, and Appendix D for child participants

who received the LAIV. Participants who were vaccinated in each of the last two year reported the lowest proportion of severe health events for both the IIV and the LAIV.

Table 12 describes the onset and duration of severe health events in child participants by IIV status from 2013/2014 to 2019/2020. Among the 944 vaccinated child participants with a severe health event, 39.30% reported the onset of their severe health event within 24 hours after vaccination. In contrast, there were 617 unvaccinated participants with a severe health event and only 58 (9.40%) reported an onset within 24 hours of the monitoring period. The highest proportion (40.52%) of severe health events reported in the unvaccinated group was captured in the 6-to-7 days before the monitoring period. In the IIV group, 26.80% of severe health events had a duration of 1-to-3 days compared to 20.26% in the unvaccinated group. In addition, 25.85% and 42.95% of severe health events were still ongoing at the time of survey completion in the IIV group and unvaccinated group, respectively. There was a total of 33 (2.11%) child participants who did not report the duration of their severe health event in both groups combined. This included 6 child participants with missing values in the IIV group and 27 child participants with missing values in the unvaccinated group.

Table 13 describes the onset and duration of severe health events in child participants by LAIV status from 2013/2014 to 2018/2019. Of the 336 vaccinated child participants with a severe health event, 38.69% reported the onset of their severe health event within 1-to-3 days after vaccination. In contrast, 23.63% of unvaccinated child participants reported their severe health event onset within 1-to-3 days of the monitoring period. There were 38.66% of unvaccinated child participants who reported the onset of their severe health event in the 6-to-7 days before the monitoring period compared to 13.10% in the vaccinated group. There were 27.98% and 38.42% of severe health events still present at the time of survey completion in the

vaccinated and unvaccinated groups, respectively. A total of 39 (5.17%) of child participants did not report the duration of their severe health event in the vaccinated and unvaccinated groups combined. This included 13 child participants in the group vaccinated with the LAIV and 26 in the unvaccinated group.

Table 10. Incidence rate ratio for severe health events[1] by vaccine type (IIV and LAIV) and year, child data from 2013/2014 to 2019/2020.

Year	Severe Health Event[1]					
	IIV Cases/Total (%)	Unvaccinated Cases/Total (%)	IRR (95% CI)	LAIV Cases/Total (%)	Unvaccinated Cases/Total (%)	IRR (95% CI)
2013/2014	26/563[2] (4.62)	52/842[2] (6.18)	0.75[2] (0.47, 1.18)	42/871[3] (4.82)	49/799[3] (6.13)	0.79[3] (0.53, 1.17)
2014/2015	42/552 (7.61)	32/834 (3.84)	**1.98 (1.27, 3.10)**	70/1182 (5.92)	28/764 (3.66)	**1.62 (1.05, 2.48)**
2015/2016	39/476 (8.19)	65/1120 (5.80)	1.41 (0.96, 2.07)	62/997 (6.22)	59/1058 (5.58)	1.12 (0.79, 1.58)
2016/2017	80/901 (8.88)	49/1027 (4.77)	**1.86 (1.32, 2.63)**	80/1183 (6.76)	44/973 (4.52)	**1.50 (1.05, 2.14)**
2017/2018	257/3440 (7.47)	88/1421 (6.19)	1.21 (0.95, 1.52)	38/901 (4.22)	84/1335 (6.29)	**0.67 (0.46, 0.97)**
2018/2019	195/2770 (7.04)	163/3064 (5.32)	**1.32 (1.08, 1.62)**	44/850 (5.18)	155/2917 (5.31)	0.97 (0.70, 1.35)
2019/2020	305/4597 (6.63)	168/2263 (7.42)	0.89 (0.75, 1.07)	N/A[4]	N/A	N/A
Total	944/13299 (7.10)	617/10571 (5.84)	**1.22 (1.10, 1.34)**	336/5984 (5.61)	419/7846 (5.34)	1.05 (0.91, 1.21)

IIV: Inactivated Influenza Vaccine
LAIV: Live Attenuated Influenza Vaccine
IRR: Incidence Rate Ratio
CI: Confidence Interval
[1] Severe health event: Prevented/stopped activities or missed school or saw healthcare provider
[2] Children 6 months-16 years of age in 2014/2014
[3] Children 2-16 years of age in 2013/2014
[4] LAIV was recommended for use but not available in Canada

Table 11. Incidence rate ratio for severe health events[1] between vaccinated and unvaccinated participants for the most frequently used vaccine products, child data from 2013/2014 to 2019/2020.

	Severe Health Event[1]							
	IIV[2]						LAIV	
	Flulaval®		Fluviral®		Fluzone®		FluMist®*	
Year	Cases/Total (%)	IRR (95% CI)	Cases/Total (%)	IRR (95% CI)	Cases/Total (%)	IRR (95% CI)	Cases/Total (%)	IRR (95% CI)
2013/2014	0/0[3] (0.00)	N/A[3]	22/452[3] (4.87)	0.79[3] (0.49,1.28)	0/3[3] (0.00)	N/A[3]	42/871[4] (4.82)	0.79[4] (0.53, 1.17)
2014/2015	0/0 (0.00)	N/A	31/332 (9.34)	**2.43 (1.51, 3.92)**	0/0 (0.00)	N/A	70/1182 (5.92)	**1.62 (1.05, 2.48)**
2015/2016	0/0 (0.00)	N/A	19/236 (8.05)	1.39 (0.85, 2.27)	13/198 (6.57)	1.13 (0.64, 2.01)	62/997 (6.22)	1.12 (0.79, 1.58)
2016/2017	8/131 (6.11)	1.28 (0.62, 2.64)	13/168 (7.74)	1.62 (0.90, 2.92)	56/553 (10.13)	**2.12 (1.47, 3.07)**	80/1183 (6.76)	**1.50 (1.05, 2.14)**
2017/2018	28/393 (7.12)	1.15 (0.76, 1.73)	6/147 (4.08)	0.66 (0.29, 1.48)	218/2850 (7.65)	1.24 (0.97, 1.57)	38/901 (4.22)	**0.67 (0.46, 0.97)**
2018/2019	52/726 (7.16)	1.35 (1.00, 1.82)	7/93 (7.53)	1.41 (0.68, 2.93)	136/1951 (6.97)	**1.31 (1.05, 1.63)**	44/850 (5.18)	0.97 (0.70, 1.35)
2019/2020	184/2494 (7.38)	0.99 (0.81, 1.22)	0/4 (0.00)	N/A	121/2095 (5.78)	**0.78 (0.62, 0.98)**	N/A[5]	N/A[5]
Total	272/3744 (7.26)	**1.24 (1.08, 1.43)**	98/1432 (6.84)	1.17 (0.95, 1.44)	544/7650 (7.11)	**1.22 (1.09, 1.36)**	336/5984 (5.61)	1.05 (0.91, 1.21)

IIV: Inactivated Influenza Vaccine
LAIV: Live Attenuated Influenza Vaccine
IRR: Incidence Rate Ratio
CI: Confidence Interval
[1] Severe health event: Prevented/stopped activities or missed school or saw healthcare provider
[2] Excluded Agriflu, Fluad, Influvac and Vaxigrip from inferential analyses due to low sample size within each group.
[3] Children aged 6 months-16 years old
[4] Children aged 2-16 years old
[5] LAIV was recommended for use but not available in Canada

Table 12. Onset and duration of severe health event[1] by IIV status, child data from 2013/2014 to 2019/2020.

Onset of Severe Health Event	Duration of Severe Health Event	Severe Health Event[1] IIV Group n (%)[2]	Unvaccinated Group n (%)[3]	Total n (%)
Within 24 hours		**371 (39.30)**	**58 (9.40)**	**429 (27.48)**
	<60 minutes	2 (0.21)	0 (0.00)	2 (0.13)
	<10 hours	30 (3.18)	7 (1.13)	37 (2.37)
	<24 hours	81 (8.58)	4 (0.65)	85 (5.45)
	2-3 days	114 (12.08)	5 (0.81)	119 (7.62)
	4-5 days	59 (6.25)	1 (0.16)	60 (3.84)
	6+ days	32 (3.39)	0 (0.00)	32 (2.05)
	Still Present	50 (5.30)	40 (6.48)	90 (5.77)
	Missing	3 (0.32)	1 (0.16)	4 (0.26)
Within 1-3 days		**283 (29.98)**	**140 (22.69)**	**423 (27.10)**
	<60 minutes	1 (0.11)	0 (0.00)	1 (0.06)
	<10 hours	7 (0.74)	7 (1.13)	14 (0.90)
	<24 hours	38 (4.03)	9 (1.46)	47 (3.01)
	1-3 days	78 (8.26)	28 (4.54)	106 (6.79)
	4-5 days	56 (5.93)	5 (0.81)	61 (3.91)
	6+ days	32 (3.39)	1 (0.16)	33 (2.11)
	Still Present	71 (7.52)	73 (11.83)	144 (9.22)
	Missing	0 (0.00)	17 (2.76)	17 (1.09)
Within 4-5 days		**171 (18.11)**	**169 (27.39)**	**340 (21.78)**
	<60 minutes	0 (0.00)	0 (0.00)	0 (0.00)
	<10 hours	8 (0.85)	2 (0.32)	10 (0.64)
	<24 hours	23 (2.44)	8 (1.30)	31 (1.99)
	1-3 days	35 (3.71)	48 (7.78)	83 (5.32)
	4-5 days	26 (2.75)	30 (4.86)	56 (3.59)
	6+ days	6 (0.64)	3 (0.49)	9 (0.58)
	Still Present	71 (7.52)	73 (11.83)	144 (9.22)
	Missing	2 (0.21)	5 (0.81)	7 (0.45)
Within 6-7 days		**119 (12.61)**	**250 (40.52)**	**369 (23.64)**
	<60 minutes	0 (0.00)	0 (0.00)	0 (0.00)
	<10 hours	3 (0.32)	6 (0.97)	9 (0.58)
	<24 hours	15(1.59)	12 (1.94)	27 (1.73)
	1-3 days	26 (2.75)	44 (7.13)	70 (4.48)
	4-5 days	12 (1.27)	65 (10.53)	77 (4.93)
	6+ days	10 (1.06)	40 (6.48)	50 (3.20)
	Still Present	52 (5.51)	79 (12.80)	131 (8.39)
	Missing	1 (0.11)	4 (0.65)	5 (0.32)
Total		**944 (100.00)**	**617 (100.00)**	**1,561 (100.00)**
	<60 minutes	3 (0.32)	0 (0.00)	3 (0.19)
	<10 hours	48 (5.08)	22 (3.57)	70 (4.48)
	<24 hours	157(16.63)	33 (5.35)	190 (12.17)
	1-3 days	253 (26.80)	125 (20.26)	378 (24.22)
	4-5 days	153 (16.21)	101 (16.37)	254 (16.27)
	6+ days	80 (8.47)	44 (7.13)	124 (7.94)
	Still Present	244 (25.85)	265 (42.95)	509 (32.61)
	Missing	6 (0.64)	27 (4.38)	33 (2.11)

IIV: Inactivated Influenza Vaccine

[1] Severe health event: prevented/stopped activities or missed school or saw healthcare provider

[2] Time period since vaccination (n=944)

[3] Time period from start of monitoring period (n=617)

Table 13. Onset and duration of severe health event[1] by LAIV status, child data from 2013/2014 to 2018/2019.

Onset of Severe Health Event	Duration of Severe Health Event	Severe Health Event[1] LAIV Group n (%)[2]	Unvaccinated Group n (%)[3]	Total n (%)
Within 24 hours		**85 (25.30)**	**34 (8.11)**	**119 (15.76)**
	<60 minutes	0 (0.00)	0 (0.00)	0 (0.00)
	<10 hours	5 (1.49)	7 (1.67)	12 (1.59)
	<24 hours	12 (3.57)	2 (0.48)	14 (1.85)
	2-3 days	17 (5.06)	2 (0.48)	19 (2.52)
	4-5 days	21(6.25)	0 (0.00)	21 (2.78)
	6+ days	12 (3.57)	0 (0.00)	12 (1.59)
	Still Present	17 (5.06)	22 (5.25)	39 (5.17)
	Missing	1 (0.30)	1 (0.24)	2 (0.26)
Within 1-3 days		**130 (38.69)**	**99 (23.63)**	**229 (30.33)**
	<60 minutes	0 (0.00)	0 (0.00)	0 (0.00)
	<10 hours	4 (1.19)	3 (0.72)	7 (0.93)
	<24 hours	22 (6.55)	6 (1.43)	28 (3.71)
	1-3 days	33 (9.82)	21 (5.01)	54 (7.15)
	4-5 days	24 (7.14)	5 (1.19)	29 (3.84)
	6+ days	11 (3.27)	1 (0.24)	12 (1.59)
	Still Present	30 (8.93)	47 (11.22)	77 (10.20)
	Missing	6 (1.79)	16 (3.82)	22 (2.91)
Within 4-5 days		**77 (22.92)**	**124 (29.59)**	**201 (26.62)**
	<60 minutes	0 (0.00)	0 (0.00)	0 (0.00)
	<10 hours	2 (0.60)	2 (0.48)	4 (0.53)
	<24 hours	6 (1.79)	7 (1.67)	13 (1.72)
	1-3 days	28 (8.33)	34 (8.11)	62 (8.21)
	4-5 days	5 (1.49)	26 (6.21)	31 (4.11)
	6+ days	4 (1.19)	0 (0.00)	4 (0.53)
	Still Present	30 (8.93)	50 (11.93)	80 (10.60)
	Missing	2 (0.60)	5 (1.19)	7 (0.93)
Within 6-7 days		**44 (13.10)**	**162 (38.66)**	**206 (27.28)**
	<60 minutes	0 (0.00)	0 (0.00)	0 (0.00)
	<10 hours	0 (0.00)	6 (1.43)	6 (0.79)
	<24 hours	7 (2.08)	6 (1.43)	13 (1.72)
	1-3 days	12 (3.57)	34 (8.11)	46 (6.09)
	4-5 days	3 (0.89)	42 (10.02)	45 (5.96)
	6+ days	1 (0.30)	28 (6.68)	29 (3.84)
	Still Present	17 (5.06)	42 (10.02)	59 (7.81)
	Missing	4 (1.19)	4 (0.95)	8 (1.06)
Total		**336 (100.00)**	**419 (100.00)**	**755 (100.00)**
	<60 minutes	0 (0.00)	0 (0.00)	0 (0.00)
	<10 hours	11 (3.27)	18 (4.30)	29 (3.84)
	<24 hours	47 (13.99)	21 (5.01)	68 (9.01)
	1-3 days	90 (26.79)	91 (21.72)	181 (23.97)
	4-5 days	53 (15.77)	73 (17.42)	126 (16.69)
	6+ days	28 (8.33)	29 (6.92)	57 (7.55)
	Still Present	94 (27.98)	161 (38.42)	255 (33.77)
	Missing	13 (3.87)	26 (6.21)	39 (5.17)

LAIV: Live Attenuated Influenza Vaccine

[1] Severe health event: prevented/stopped activities or missed school or saw healthcare provider

[2] Time period since vaccination (n=336)

[3] Time period from start of monitoring period (n=419)

3.3 Inferential Statistics

3.3.1 Logistic Regressions Modelling Severe Health Events by IIV Status in Children from 2013/2014 to 2019/2020

Univariate logistic regressions were conducted to model severe health event in children by IIV status and the following covariates of interest: sex, age category, year of enrolment, enrolment site, and previous influenza immunization history. The unadjusted OR and 95% CI for severe health event modeled by the primary explanatory variable, IIV status, was 1.23 (1.11, 1.37). There were no statistically significant differences for severe health events modeled by sex and immunization history. Variables for age category and enrolment site were statistically significant with a p-value less than 0.01. Year of enrolment had a p-value of 0.08. Child participants aged 6-to-23 months and 2-to-4 years had an unadjusted OR and 95% CI of 1.79 (1.49, 2.14) and 1.67 (1.43, 1.96), respectively, when compared to the reference category (10-to-14 years old). However, there were no statistical differences in severe health event in the 5-to-9 years age group compared to the reference category. The 2014/2015 influenza season was the only year with a statistically significant unadjusted OR for severe health events when compared to the reference group (2019/2020 influenza season). No statistical differences in severe health event were observed in the other years compared to the reference category. The unadjusted OR for severe health events at enrolment sites located in Toronto, Quebec City, and Sherbrooke were statistically significant compared to the reference group (Calgary). Appendix E summarizes the unadjusted logistic regression models for severe health events as the primary outcome and each covariate of interest by vaccination status for the IIV.

A multivariable logistic regression modeled severe health event by IIV status. Covariates with a p-value of less than 0.05 (age category and enrolment site) were included in the model. Year of enrolment was then incorporated into the multivariable logistic regression model to

examine if it improved the model fit and whether it was statistically significant (with a p-value less than 0.05). It was not, and therefore, it was excluded from the final model. The full multivariable logistic regression model did not include immunization history since it was asked only to vaccinated participants.

Interaction terms examined IIV status and all statistically significant covariates. Interaction terms between IIV status and year of age category was not found to be statistically significant, but IIV status and enrolment site was found to have a statistically significant association (with a p-value less than 0.05). However, the difference in AIC values for the full model with interaction terms (11413.36) was negligible compared to the full model without interaction terms (11428.72). Therefore, the parsimonious model with IIV status, age category, and enrolment site (without the interaction terms) was considered the final multivariable logistic regression model, as described in Table 14.

3.3.2 Logistic Regressions Modelling Severe Health Events by LAIV Status in Children from 2013/2014 to 2018/2019

Univariate logistic regression models were conducted to model severe health event in children by LAIV status. Covariates of interest included the following: sex, age category, year of enrolment, enrolment site, and immunization history. Enrolment sites located in Ottawa and Halifax were removed from inferential analyses since they did not have sufficient child participants with severe health events to provide an estimate. There was no statistical difference in severe health event modeled by LAIV status, sex, year of enrolment, or immunization history. Age category and enrolment site were statistically significant with a p-value less than 0.01 when modeled for severe health event in univariate analysis. Child participants 2-to-4 years of age had an unadjusted OR and 95% CI of 1.94 (1.57, 2.40) compared to the reference group (10-to-14

years old). However, there was no statistical difference in severe health event observed in the 5-to-9 years age group compared to the reference group. The unadjusted OR for severe health event at the enrolment site located in Quebec City was statistically significant when compared to the reference group (Calgary). Appendix F summarizes the unadjusted logistic regression models for severe health events as the primary outcome and each covariate of interest by vaccination status for the LAIV.

A multivariable logistic regression modelled severe health events by LAIV status. Covariates with a p-value less than 0.05 (age category and enrolment site) were incorporated into the final model. Excluded variables (sex and year of enrolment) were then re-incorporated into the multivariable logistic regression model to examine if it improved the model fit and whether it was statistically significant (with a p-value less than 0.05). Since neither variable improved the model fit, they were excluded from the final model. Immunization history was not included in the full multivariable logistic regression model since vaccinated participants were only asked. There were no statistically significant interaction terms between 1) LAIV status and age category, and 2) LAIV status and year of enrolment. The final multivariable logistic regression model included LAIV status, age category, and enrolment site, which is described in Table 15 with the adjusted OR and 95% CI for all explanatory variables.

Table 14. Univariate and multivariable logistic regressions modelling severe health events[1] with IIV status and significant covariates[±] as explanatory variables, data from 2013/2014 to 2019/2020.

Variables	Severe Health Events[1]			
	Estimate	Standard Error	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio[±3] (95% CI)
Vaccination Status				
Unvaccinated	-	-	Reference	Reference
IIV	0.2092	0.0535	1.23 (1.11, 1.37)	1.11 (1.00, 1.25)
Sex				
Male	-	-	Reference	N/A
Female	-0.0623	0.0524	0.94 (0.85, 1.04)	
Age Categories				
10-14 years old	-	-	Reference	Reference
5-9 years old	0.1407	0.0816	1.15 (0.98, 1.35)	1.11 (0.95, 1.31)
2-4 years old	0.5136	0.0801	1.67 (1.43, 1.96)	1.59 (1.35, 1.86)
6-23 months	0.5806	0.0915	1.79 (1.49, 2.14)	1.73 (1.44, 2.07)
Year				
2019/2020	-	-	Reference	
2018/2019	-0.1247	0.0724	0.88 (0.77, 1.02)	
2017/2018	0.0311	0.0734	1.03 (0.89, 1.19)	
2016/2017	-0.0311	0.1029	0.97 (0.79, 1.19)	N/A
2015/2016	-0.0606	0.1121	0.94 (0.76, 1.17)	
2014/2015	-0.2722	0.1286	0.76 (0.59, 0.98)	
2013/2014	-0.2310	0.1259	0.79 (0.62, 1.02)	
Enrolment Site				
Calgary	-	-	Reference	Reference
Vancouver	0.1945	0.1117	1.22 (0.98, 1.51)	1.21 (0.97, 1.50)
Toronto	-0.7205	0.2194	0.49 (0.32, 0.75)	0.55 (0.35, 0.84)
Ottawa	0.0810	0.2705	1.08 (0.64, 1.84)	1.07 (0.63, 1.82)
Quebec City	-0.3779	0.1023	0.69 (0.56, 0.84)	0.68 (0.56, 0.83)
Sherbrooke	-0.3318	0.0776	0.72 (0.62, 0.84)	0.72 (0.62, 0.84)
Halifax	0.3257	0.2827	1.39 (0.80, 2.41)	1.43 (0.82, 2.49)
Immunization History (Last 2 Years)[2]				
2	-	-	Reference	
1	0.1568	0.0891	1.17 (0.98, 1.39)	N/A
0	0.1488	0.1116	1.16 (0.93, 1.44)	

CI: Confidence Interval

IIV: Inactivated Influenza Vaccine

[±] Adjusted for age category, year, and enrolment site

[1] Severe health event: prevented/stopped activities or missed school or saw healthcare provider

[2] Not considered for multivariable logistic regression since it was asked to vaccinated participants only

[3] Interaction terms between: 1) IIV status and year, and 2) IIV status and enrolment site, were found to have statistically significant associations (p-value < 0.05) but were not included in the final model because they did not improve the model fit

Table 15. Univariate and multivariable logistic regressions modelling severe health events[1] with LAIV status and significant covariates[±] as explanatory variables, data from 2013/2014 to 2018/2019.

Variables	Severe Health Events[1]			
	Estimate	Standard Error	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio[±] (95% CI)
Vaccination Status				
Unvaccinated	-	-	Reference	Reference
LAIV	0.0723	0.0759	1.08 (0.93, 1.25)	1.11 (0.95, 1.29)
Sex				
Male	-	-	Reference	N/A
Female	0.0849	0.0755	1.09 (0.94, 1.26)	
Age				
10-14 years old	-	-	Reference	Reference
5-9 years old	0.2094	0.1072	1.23 (1.00, 1.52)	1.23 (0.99, 1.52)
2-4 years old	0.6630	0.1078	1.94 (1.57, 2.40)	1.95 (1.58, 2.41)
Year				
2018/2019	-	-	Reference	
2017/2018	0.0157	0.1196	1.02 (0.80, 1.28)	
2016/2017	0.0868	0.1188	1.09 (0.86, 1.38)	N/A
2015/2016	0.1047	0.1195	1.11 (0.88, 1.40)	
2014/2015	-0.0552	0.1278	0.95 (0.74, 1.22)	
2013/2014	0.0339	0.1308	1.03 (0.80, 1.34)	
Site				
Calgary	-	-	Reference	Reference
Vancouver	0.5361	0.1368	1.71 (1.31, 2.24)	1.61 (1.23, 2.11)
Toronto	-0.0806	0.3010	0.92 (0.51, 1.66)	1.03 (0.57, 1.85)
Quebec City	-0.2835	0.1346	0.75 (0.58, 0.98)	0.70 (0.53, 0.91)
Sherbrooke	-0.1055	0.0882	0.90 (0.76, 1.07)	0.84 (0.70, 1.00)
Immunization History[2]				
2	-	-	Reference	
1	0.5348	0.1485	1.71 (1.28, 2.28)	N/A
0	0.4099	0.2359	1.51 (0.95, 2.39)	

CI: Confidence Interval

IIV: Inactivated Influenza Vaccine

[±] Adjusted for age category, and enrolment site

[1] Severe health event: prevented/stopped activities or missed school or saw healthcare provider

[2] Not considered for multivariable logistic regression since it was asked to vaccinated participants only

Table 16. Incidence rate ratios for most severe symptoms[1] by inactivated influenza and live attenuated influenza vaccine, child data from 2014/2015 to 2019/2020.

Most Severe Symptom[1]	Inactivated Influenza Vaccine				Live Attenuated Influenza Vaccine[2]			
	N	Total in Vaccinated Group N=12598 Cases (%)	Total in Unvaccinated Group N=9640 Cases (%)	Incidence Rate Ratio (95% CI)	N	Total in Vaccinated Group N=5096 Cases (%)	Total in Unvaccinated Group N=6990 Cases (%)	Incidence Rate Ratio (95% CI)
Fever	250	177 (1.40)	73 (0.76)	**1.86 (1.41, 2.43)**	115	69 (1.35)	46 (0.66)	**2.06 (1.42, 2.98)**
Gastrointestinal	214	140 (1.11)	74 (0.77)	**1.45 (1.09, 1.92)**	92	43 (0.84)	49 (0.70)	1.20 (0.80, 1.81)
Cough	191	111 (0.88)	80 (0.83)	1.06 (0.80, 1.41)	85	38 (0.75)	47 (0.67)	1.11 (0.72, 1.70)
Congestion	84	28 (0.22)	56 (0.58)	0.38 (0.24, 0.60)	58	20 (0.39)	38 (0.54)	0.72 (0.42, 1.24)
Unwell	68	55 (0.44)	13 (0.13)	**3.24 (1.77, 5.92)**	17	10 (0.20)	7 (0.10)	1.96 (0.75, 5.14)
Sore Throat	66	19 (0.15)	47 (0.49)	0.31 (0.18, 0.53)	43	17 (0.33)	39 (0.56)	0.60 (0.34, 1.06)
Runny Nose	60	21 (0.17)	39 (0.40)	0.41 (0.24, 0.70)	43	18 (0.35)	25 (0.36)	0.99 (0.54, 1.81)
Multiple Symptoms[3]	59	44 (0.35)	15 (0.16)	**2.24 (1.25, 4.03)**	28	20 (0.39)	8 (0.11)	**3.43 (1.51, 7.78)**
Headache	39	29 (0.23)	10 (0.10)	**2.22 (1.08, 4.55)**	16	9 (0.18)	7 (0.10)	1.76 (0.66, 4.73)
Injection Site Reaction	35	35 (0.28)	N/A	N/A	0	N/A	N/A	N/A
Hives	24	20 (0.16)	4 (0.04)	**3.83 (1.31, 11.19)**	10	6 (0.12)	4 (0.06)	2.06 (0.58, 7.29)
Breathing Difficulty	23	18 (0.14)	5 (0.05)	**2.75 (1.02, 7.42)**	3	0 (0.00)	3 (0.04)	N/A
Ear Symptoms	22	8 (0.06)	14 (0.15)	0.44 (0.18, 1.04)	16	7 (0.14)	9 (0.13)	1.07 (0.40, 2.86)
Wheezing	18	9 (0.07)	9 (0.09)	0.77 (0.30, 1.93)	9	2 (0.04)	7 (0.10)	0.39 (0.08, 1.89)
Croup	12	8 (0.06)	4 (0.04)	1.53 (0.46, 5.08)	4	1 (0.02)	3 (0.04)	0.46 (0.05, 4.39)
Difficulty Eating	10	7 (0.06)	3 (0.03)	1.79 (0.46, 6.90)	3	2 (0.04)	1 (0.01)	2.74 (0.25, 30.25)
Red Eyes	9	6 (0.05)	3 (0.03)	1.53 (0.38, 6.12)	3	1 (0.02)	2 (0.03)	0.69 (0.06, 7.56)
Eye Tears	7	6 (0.05)	1 (0.01)	4.59 (0.55, 38.13)	2	1 (0.02)	1 (0.01)	1.37 (0.09, 21.92)
Urinary Symptoms	6	3 (0.02)	3 (0.03)	0.77 (0.15, 3.79)	3	0 (0.00)	3 (0.04)	N/A
Hoarseness	4	3 (0.02)	1 (0.01)	2.30 (0.24, 22.07)	0	0 (0.00)	0 (0.00)	N/A
Throat Swelling	3	3 (0.02)	0 (0.00)	N/A	0	0 (0.00)	0 (0.00)	N/A
Face Swelling	3	2 (0.02)	1 (0.01)	1.53 (0.14, 16.88)	0	0 (0.00)	0 (0.00)	N/A
Eye Swelling	2	2 (0.02)	0 (0.00)	N/A	0	0 (0.00)	0 (0.00)	N/A
Palpitations	2	1 (0.01)	1 (0.01)	0.77 (0.05, 12.23)	1	0 (0.00)	1 (0.01)	N/A
Chest Tightness	1	1 (0.01)	0 (0.00)	N/A	1	1 (0.02)	0 (0.00)	N/A
Seizure	1	1 (0.01)	0 (0.00)	N/A	1	1 (0.02)	0 (0.00)	N/A
Low Blood Pressure	1	1 (0.01)	0 (0.00)	N/A	0	0 (0.00)	0 (0.00)	N/A
Febrile Seizure	1	1 (0.01)	0 (0.00)	N/A	0	0 (0.00)	0 (0.00)	N/A
Persistent Crying	1	1 (0.01)	0 (0.00)	N/A	0	0 (0.00)	0 (0.00)	N/A
Fainting	1	0 (0.00)	1 (0.01)	N/A	1	0 (0.00)	1 (0.01)	N/A
Itchy Eyes	0	0 (0.00)	0 (0.00)	N/A	1	1 (0.02)	0 (0.00)	N/A
Total	1248	772 (6.13)	476 (4.94)	**1.24 (1.11, 1.39)**	588	274 (5.38)	314 (4.49)	**1.20 (1.02, 1.40)**

CI: Confidence Interval

[1] Most severe symptom was asked to participants who indicated a severe health event only

[2] Children aged 2-14 years old

[3] Participants who indicated more than one symptom for most severe

3.3.3 Secondary Analysis: Self-Reported Most Severe Symptoms in Children from 2014/2015 to 2019/2020

3.3.3.1 Most Severe Symptoms in Children with IIV

A total of 772 vaccinated and 476 unvaccinated child participants aged 6 months to 14 years old with a severe event reported a most severe symptom in the 2014/2015 to 2019/2020 surveys. The most frequently reported most severe symptoms in the vaccinated and unvaccinated groups were fever, gastrointestinal symptoms, and cough, as described in Table 16. It was observed that fever, gastrointestinal symptoms, feeling unwell, headaches, hives, breathing difficulty, and multiple symptoms had a statistically significant IRR in child participants who received IIV compared to unvaccinated child participants. Appendix G summarizes all "other" most severe symptoms reported in the open-text field by vaccine status. Vaccinated child participants that reported multiple severe symptoms for their most severe symptom had their responses summarized in Appendix H for participants with the IIV and Appendix J for unvaccinated participants.

Of the 772 vaccinated child participants with a self-reported most severe symptom, 227 (29.4%) reported having sought medical consultation, and 157 (20.3%) reported having obtained a diagnosis. In the unvaccinated group, 132 (27.7%) reported seeking medical consultation, and 108 (22.7%) reported receiving a diagnosis, as described in Table 17.

3.3.3.2 Most Severe Symptoms in Children with LAIV

A total of 274 vaccinated and 314 unvaccinated child participants with a severe event 2 to-14 years of age reported a most severe symptom from 2014/2015 to 2018/2019. The most frequently reported severe symptoms were fever, gastrointestinal symptoms, and coughing, as described in Table 16. It was also observed that fever had a statistically significant IRR in child

participants who received LAIV compared to the unvaccinated group. No statistical differences were observed in the IRR for congestion, runny nose, or wheezing. Appendix G summarizes all "other" most severe symptoms reported in the open-text field by vaccine status. Vaccinated child participants that reported multiple severe symptoms had their responses summarized in Appendix I for participants with the LAIV, and Appendix J for unvaccinated participants.

Of the 274 vaccinated child participants with a self-reported most severe symptom, 77 (28.0%) reported having sought medical consultation, and 58 (21.2%) reported having obtained a diagnosis. In the unvaccinated group, 88 (28.0%) reported seeking medical consultation, and 70 (22.3%) reported receiving a diagnosis, as described in Table 18.

Table 17. Medical consultation and diagnosis for most severe symptom following receipt of IIV status, child data from 2014/2015 to 2019/2020.

Most Severe Symptom	IIV Group			Unvaccinated Group		
	N	Healthcare Visit / Consultation` (%)[1]	Obtained Diagnosis[2] (%)[1]	N	Healthcare Visit / Consultation (%)[1]	Obtained Diagnosis[2] (%)[1]
Fever	177	35 (19.77)	21 (11.86)	73	24 (32.88)	20 (27.40)
Gastrointestinal	140	22 (15.71)	11 (0.71)	74	13 (17.57)	9 (12.16)
Cough	111	38 (34.23)	25 (22.52)	80	19 (23.75)	14 (17.50)
Unwell	55	5 (9.09)	2 (3.64)	13	2 (15.38)	2 (15.38)
Multiple Symptoms	44	12 (27.27)	11 (25.00)	15	4 (26.67)	3 (20.00)
Injection Site Reaction	35	17 (38.57)	13 (37.14)	0	N/A	N/A
Headache	29	5 (17.24)	2 (6.90)	10	0 (0.00)	0 (0.00)
Congestion	28	4 (14.29)	2 (7.14)	56	4 (7.14)	2 (3.57)
Runny Nose	21	1 (4.76)	1 (4.76)	39	2 (5.13)	2 (5.13)
Hives	20	16 (80.00)	10 (50.00)	4	3 (75.00)	3 (75.00)
Sore Throat	19	7 (36.84)	5 (26.32)	47	12 (25.53)	11 (23.40)
Breathing Difficulty	18	14 (77.78)	11 (61.11)	5	4 (80.00)	3 (60.00)
Other Symptoms	12	11 (91.67)	8 (66.67)	19	17 (89.47)	15 (15.79)
Wheezing	9	6 (66.67)	5 (55.56)	9	5 (55.56)	5 (55.56)
Ear Symptoms	8	8 (100.00)	8 (100.00)	14	11 (78.57)	11 (78.57)
Croup	8	8 (100.00)	8 (100.00)	4	4 (100.00)	4 (100.00)
Difficulty Eating	7	1 (14.29)	0 (0.00)	3	1 (33.33)	0 (0.00)
Red Eyes	6	5 (83.33)	5 (83.33)	3	2 (66.67)	2 (66.67)
Eye Tears	6	2 (33.33)	2 (33.33)	1	1 (100.00)	1 (100.00)
Hoarseness	3	1 (33.33)	1 (33.33)	1	0 (0.00)	0 (0.00)
Throat Swelling	3	3 (100.00)	2 (66.67)	0	N/A	N/A
Urinary Symptoms	3	3 (100.00)	2 (66.67)	3	2 (66.67)	0 (0.00)
Face Swelling	2	1 (50.00)	1 (50.00)	1	1 (100.00)	1 (100.00)
Eye Swelling	2	0 (0.00)	0 (0.00)	0	N/A	N/A
Chest Tightness	1	0 (0.00)	0 (0.00)	0	N/A	N/A
Palpitations	1	0 (0.00)	0 (0.00)	1	1 (100.00)	0 (0.00)
Low Blood Pressure	1	0 (0.00)	0 (0.00)	0	N/A	N/A
Seizure	1	1 (100.00)	0 (0.00)	0	N/A	N/A
Febrile Seizure	1	1 (100.00)	1 (100.00)	0	N/A	N/A
Persistent Crying	1	0 (0.00)	0 (0.00)	0	N/A	N/A
Fainting	0	N/A	N/A	1	0 (0.00)	0 (0.00)
Total	**772**	**227 (29.40)**	**157 (20.34)**	**476**	**132 (27.73)**	**108 (22.69)**

IIV: Inactivated Influenza Vaccine

[1] Denominator is the total sample of the specified most severe symptom

[2] Diagnosis might not match with the most severe symptom that was reported

Table 18. Outcome of self-report of most severe symptom following receipt of LAIV status, child data from 2014/2015 to 2019/2020.

Most Severe Symptom	LAIV Group			Unvaccinated Group		
	N	Healthcare Visit / Consultation` (%)[1]	Obtained Diagnosis[2] (%)[1]	N	Healthcare Visit / Consultation (%)[1]	Obtained Diagnosis[2] (%)[1]
Fever	69	15 (21.74)	12 (17.39)	46	15 (32.61)	12 (26.09)
Gastrointestinal	43	4 (9.30)	4 (9.30)	49	10 (20.41)	8 (16.33)
Cough	38	16 (42.11)	12 (31.58)	47	9 (19.15)	5 (10.64)
Congestion	20	4 (20.00)	3 (15.0)	38	2 (5.26)	1 (2.63)
Multiple Symptoms	20	6 (30.00)	4 (20.00)	8	2 (25.00)	1 (12.50)
Runny Nose	18	3 (16.67)	1 (5.56)	25	2 (8.00)	2 (8.00)
Sore Throat	17	4(23.53)	2 (11.76)	39	9 (23.08)	8 (20.51)
Unwell	10	0 (0.00)	0 (0.00)	7	2 (28.57)	2 (28.57)
Headache	9	2 (22.22)	1 (11.11)	7	0 (0.00)	0 (0.00)
Ear Symptoms	7	7 (100.00)	7 (100.00)	9	7 (77.78)	7 (77.78)
Other Symptoms	7	5 (71.43)	5 (71.43)	13	12 (92.31)	10 (76.92)
Hives	6	4 (66.67)	2 (33.33)	4	3 (75.00)	3 (75.00)
Wheezing	2	2 (100.00)	1 (50.00)	7	4 (57.14)	4 (57.14)
Difficulty Eating	2	0 (0.00)	0 (0.00)	1	0 (0.00)	0 (0.00)
Chest Tightness	1	1 (100.00)	0 (0.00)	0	0 (0.00)	0 (0.00)
Red Eyes	1	1 (100.00)	1 (100.00)	2	1 (50.00)	1 (50.00)
Itchy Eyes	1	1 (100.00)	1 (100.00)	0	0 (0.00)	0 (0.00)
Eye Tears	1	0 (0.00)	0 (0.00)	1	1 (100.00)	1 (100.00)
Seizure	1	1 (100.00)	1 (100.00)	0	0 (0.00)	0 (0.00)
Croup	1	1 (100.00)	1 (100.00)	3	3 (100.00)	3 (100.00)
Breathing Difficulty	0	N/A	N/A	3	3 (100.00)	2 (66.67)
Urinary Symptoms	0	N/A	N/A	3	2 (66.67)	0 (0.00)
Hoarseness	0	N/A	N/A	0	0 (0.00)	0 (0.00)
Face Swelling	0	N/A	N/A	0	0 (0.00)	0 (0.00)
Palpitations	0	N/A	N/A	1	1 (100.00)	0 (0.00)
Fainting	0	N/A	N/A	1	0 (0.00)	0 (0.00)
Total	**274**	**77 (28.00)**	**58 (21.17)**	**314**	**88 (28.03)**	**70 (22.29)**

LAIV: Live Attenuated Influenza Vaccine

[1] Denominator is the total sample of the specified most severe symptom

[2] Diagnosis might not match with the most severe symptom that was reported

Chapter 4: Agreement of Self-Reported Most Severe Symptom between the Online Survey and the Telephone Report

4.1 Study Sample and Descriptive Statistics

There were 152 (45.9%) out of 331 eligible child participants with a valid response for self-reported most severe symptom in their online survey and a telephone follow-up report from 2016/2017 to 2019/2020. This included vaccinated and unvaccinated child participants. Table 19 describes the most frequently reported most severe symptom in the online survey and telephone report: fever, gastrointestinal symptoms, injection site reactions (vaccinated group only), ear-related symptoms, coughing, and hives. Appendix K describes the corresponding responses in the telephone report for each most severe symptom that was reported from 2016/2017 to 2019/2020.

Table 19. Frequency of most severe symptoms reported in online survey and in telephone follow-up reports, child data from 2016/2017 to 2019/2020.

Most Severe Symptom	Online Survey n (%)	Telephone Report n (%)
Fever	31 (20.39)	33 (21.71)
Gastrointestinal	22 (14.47)	22 (14.47)
Injection Site Reaction[1]	17 (11.18)	21 (13.82)
Ear Symptoms	16 (10.53)	20 (13.16)
Cough	15 (9.87)	12 (7.89)
Hives	13 (8.55)	14 (9.21)
Unwell	5 (3.29)	2 (1.32)
Sore Throat	4 (2.63)	3 (1.97)
Breathing Difficulty	4 (2.63)	5 (3.29)
Croup	4 (2.63)	4 (2.63)
Headache	3 (1.97)	2 (1.32)
Wheezing	3 (1.97)	3 (1.97)
Runny Nose	3 (1.97)	N/A
Red Eye	3 (1.97)	5 (3.29)
Face Swelling	2 (1.32)	1 (0.66)
Urinary Symptoms	2 (1.32)	1 (0.66)
Congestion	1 (0.66)	1 (0.66)
Itchy Eyes	1 (0.66)	N/A
Eye Tears	1 (0.66)	N/A
Seizure	1 (0.66)	1 (0.66)
Difficulty Eating	1 (0.66)	1 (0.66)
Shingles	N/A	1 (0.66)
Total	**152 (100.00)**	**152 (100.00)**

[1] Asked to vaccinated participants only.

Note: different symptoms may be reported by the same individual in their online and telephone report

4.2 Inferential Statistic

4.2.1 Most Severe Symptom in the Online Survey and Telephone Report

The most frequently reported most severe symptom (with a minimum sample of 10 responses in the online survey and the telephone report) were included for inferential analysis to determine the sensitivity, specificity, and agreement between reporting methods, as described in Table 20. The sensitivity between the online survey and telephone report was moderate to high for ear-related symptoms (60.0%), fever (72.7%), coughing (75.0%), injection site reactions (81.0%), hives (85.7%), and gastrointestinal symptoms (86.4%). The specificity between the online survey and the telephone report was very high for all symptoms, ranging from 85.5% to 100.0%. The symptom agreement between the two reporting methods was as follows: hives (Kappa: 0.88), injection site reaction (Kappa: 0.87), and gastrointestinal symptoms (Kappa: 0.84) fever (Kappa: 0.68), coughing (Kappa: 0.63), and ear-related symptoms (Kappa: 0.62) (Table 20). Symptom agreement was similar when analysis was restricted to the vaccinated group only, while symptom agreement varied considerably when restricted to the unvaccinated group.

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Table 20. Sensitivity, specificity, and agreement of frequently reported most severe symptoms in online survey and telephone follow-up, child data from 2016/2017 to 2019/2020.

Hives (Survey Response)	Hives (Telephone Follow-Up)			Sensitivity	Specificity	Kappa Estimate (95% CI)	Vaccinated N=116 Kappa Estimate (95% CI)	Unvaccinated N=36 Kappa Estimate (95% CI)
	Yes	No	Total					
Yes	12	1	13			0.88	0.91	0.65
No	2	137	139	85.71%	99.28%	(0.74, 1.00)	(0.78, 1.00)	(0.03, 1.00)
Total	14	138	152					
Injection Site Reaction[1] (Survey Response)	Injection Site Reaction[1] (Telephone Follow-Up)			Sensitivity	Specificity	Kappa Estimate (95% CI)	Vaccinated N=116 Kappa Estimate (95% CI)	Unvaccinated N=36 Kappa Estimate (95% CI)
	Yes	No	Total					
Yes	17	0	17			0.87	0.87	
No	4	95	99	80.95%	100.00%	(0.75, 0.99)	(0.75, 0.99)	N/A
Total	21	95	116					
Gastrointestinal (Survey Response)	Gastrointestinal (Telephone Follow-Up)			Sensitivity	Specificity	Kappa Estimate (95% CI)	Vaccinated N=116 Kappa Estimate (95% CI)	Unvaccinated N=36 Kappa Estimate (95% CI)
	Yes	No	Total					
Yes	19	3	22			0.84	0.81	0.91
No	3	127	130	86.36%	85.53%	(0.72, 0.96)	(0.66, 0.97)	(0.73, 1.00)
Total	22	130	152					
Fever (Survey Response)	Fever (Telephone Follow-Up)			Sensitivity	Specificity	Kappa Estimate (95% CI)	Vaccinated N=116 Kappa Estimate (95% CI)	Unvaccinated N=36 Kappa Estimate (95% CI)
	Yes	No	Total					
Yes	24	7	31			0.68	0.75	0.47
No	9	112	121	72.73%	94.12%	(0.54, 0.83)	(0.60, 0.89)	(0.10, 0.83)
Total	33	119	152					
Cough (Survey Response)	Cough (Telephone Follow-Up)			Sensitivity	Specificity	Kappa Estimate (95% CI)	Vaccinated N=116 Kappa Estimate (95% CI)	Unvaccinated N=36 Kappa Estimate (95% CI)
	Yes	No	Yes					
Yes	9	6	15			0.63	0.60	0.79
No	3	134	137	75.00%	95.71%	(0.42, 0.85)	(0.35, 0.85)	(0.38, 1.00)
Total	12	140	152					
Ear Symptoms (Survey Response)	Ear Symptoms (Telephone Follow-Up)			Sensitivity	Specificity	Kappa Estimate (95% CI)	Vaccinated N=116 Kappa Estimate (95% CI)	Unvaccinated N=36 Kappa Estimate (95% CI)
	Yes	No	Yes					
Yes	12	4	16			0.62	0.74	0.41
No	8	128	136	60.00%	96.97%	(0.43, 0.82)	(0.52, 0.96)	(0.05, 0.77)
Total	20	132	152					

[1] Asked to vaccinated participants only.

4.2.2 Diagnosis and Treatment in the Online Survey and Telephone Report

Of the 152 child participants who reported having sought medical care in their online survey and were eligible for telephone follow-up, 146 (96.1%) reported a diagnosis. The sensitivity and specificity for diagnosis comparing between the online survey and telephone report were 92.1% and 77.8%, respectively. The overall agreement for both groups combined was substantial (kappa 0.71), but slightly better in the vaccinated group (kappa 0.73), and moderate in the unvaccinated group (kappa 0.53), as described in Table 21. Of the participants who sought medical care, 125 (82.2%) participants received treatment during their medical consultation. The sensitivity and specificity of whether someone received treatment between the online survey and telephone report were 86.4% and 91.9%, respectively. The kappa estimate was 0.73, but in the vaccinated group it increased to 0.79, and in the unvaccinated group, it decreased to 0.05, as described in Table 22.

Table 21. Sensitivity, specificity, and agreement of reported diagnosis between online surveys and telephone follow-up, child data from 2016/2017 to 2019/2020.

Diagnosis (Survey Response)	Diagnosis (Telephone Follow-Up)			Sensitivity	Specificity	Kappa Estimate (95% CI)	Vaccinated N=116 Kappa Estimate (95% CI)	Unvaccinated N=30 Kappa Estimate (95% CI)
	Yes	No	Total					
Yes	93	10	103			0.71	0.73	0.53
No	8	35	43	92.08%	77.78%	(0.58, 0.83)	(0.60, 0.86)	(0.16, 0.91)
Total	101	45	146					

Table 22. Sensitivity, specificity, and agreement of reported treatment between online surveys and telephone follow-up, child data from 2016/2017 to 2019/2020.

Treatment (Survey Response)	Treatment (Telephone Follow-Up)			Sensitivity	Specificity	Kappa Estimate (95% CI)	Vaccinated N= 116 Kappa Estimate (95% CI)	Unvaccinated N=9 Kappa Estimate (95% CI)
	Yes	No	Total					
Yes	76	3	79			0.73	0.79	0.05
No	12	34	46	86.36%	91.89%	(0.61, 0.86)	(0.67, 0.91)	(-0.53, 0.63)
Total	88	37	125					

Chapter 5: Safety of Seasonal Influenza Vaccine in Canadian Pregnant People from 2016/2017 to 2019/2020

5.1 Study Sample

The final analytical sample consisted of 1,961 pregnant participants solicited for severe health events during the 2016/2017 to 2019/2020 influenza seasons. There was a total of 1,352 (68.9%) vaccinated pregnant participants compared to 609 (31.1%) unvaccinated pregnant participants, as described in Table 23. The sample consisted of 419 (21.4%) participants in the 1st trimester, 646 (32.9%) participants in the 2nd trimester, 503 (25.6%) participants in the 3rd trimester and 393 (20.0%) participants with a missing trimester, as summarized in Table 24. There were 439 (22.4%) pregnant participants aged 15-to-29 years old, 1,427 (72.8%) pregnant participants aged 30-to-39 years old, and 95 (4.8%) pregnant participants aged 40-to-49 years old. Table 25 summarizes the proportion of pregnant participants by year of enrolment and age category. The majority of pregnant participants were enrolled from Calgary (25.8%), Quebec City (21.7%), and Sherbrooke (18.2%), as described in Table 26.

Table 23. Vaccination status in pregnant participants from 2016/2017 to 2019/2020.

Year	Vaccinated n (%)[1]	Unvaccinated n (%)[1]	Total n (%)[1]
2016/2017	236 (12.03)	156 (7.96)	392 (19.99)
2017/2018	351 (17.90)	133 (6.78)	484 (24.68)
2018/2019	339 (17.29)	177 (9.03)	516 (26.31)
2019/2020	426 (21.72)	143 (7.29)	569 (29.02)
Total	**1,352 (68.94)**	**609 (31.06)**	**1,961 (100.00)**

[1] Percentages are calculated based on the total sample (n=1961)

Table 24. Trimester[1] by year and vaccination status in pregnant participants from 2016/2017 to 2019/2020.

Year	1st Trimester n (%)[1]	2nd Trimester n (%)[1]	3rd Trimester n (%)[1]	Missing n (%)[1]	Total n (%)[1]
2016/2017	**0 (0.00)**	**0 (0.00)**	**0 (0.00)**	**392 (19.99)**	**392 (19.99)**
Vaccinated	0 (0.00)	0 (0.00)	0 (0.00)	236 (12.03)	236 (12.03)
Unvaccinated	0 (0.00)	0 (0.00)	0 (0.00)	156 (7.96)	156 (7.96)
2017/2018	**134 (6.83)**	**210 (10.71)**	**140 (7.14)**	**0 (0.00)**	**484 (24.68)**
Vaccinated	91 (4.64)	153 (7.80)	107 (5.46)	0 (0.00)	351 (17.90)
Unvaccinated	43 (2.19)	57 (2.91)	33 (1.68)	0 (0.00)	133 (6.78)
2018/2019	**144 (7.34)**	**201 (10.25)**	**171 (8.72)**	**0 (0.00)**	**516 (26.31)**
Vaccinated	83 (4.23)	137 (6.99)	119 (6.07)	0 (0.00)	339 (17.29)
Unvaccinated	61 (3.11)	64 (3.26)	52 (2.65)	0 (0.00)	177 (9.03)
2019/2020	**141 (7.19)**	**235 (11.98)**	**192 (9.79)**	**1 (0.05)**	**569 (29.02)**
Vaccinated	97 (4.95)	174 (8.87)	155 (7.90)	0 (0.00)	426 (21.72)
Unvaccinated	44 (2.24)	61 (3.11)	37 (1.89)	1 (0.05)	143 (7.29)
Total	**419 (21.37)**	**646 (32.94)**	**502 (25.60)**	**393 (20.04)**	**1,961 (100.00)**
Vaccinated	271 (13.82)	464 (23.66)	381 (19.43)	236 (12.03)	1,352 (68.94)
Unvaccinated	148 (7.55)	182 (9.28)	122 (6.22)	157 (8.01)	609 (31.06)

[1] Percentages are calculated based on the total sample (n=1961)

Table 25. Age category by year and vaccination status in pregnant participants from 2016/2017 to 2019/2020.

Year	15 to 29 years old n (%)[1]	30 to 39 years old n (%)[1]	40 to 49 years old n (%)[1]	Total n (%)[1]
2016/2017	**98 (5.00)**	**262 (13.36)**	**32 (1.63)**	**392 (19.99)**
Vaccinated	57 (2.91)	166 (8.47)	13 (0.66)	236 (12.03)
Unvaccinated	41 (2.09)	96 (4.90)	19 (0.97)	156 (7.96)
2017/2018	**97 (4.95)**	**366 (18.66)**	**21 (1.07)**	**484 (24.68)**
Vaccinated	76 (3.88)	260 (13.26)	15 (0.76)	351 (17.90)
Unvaccinated	21 (1.07)	106 (5.41)	6 (0.31)	133 (6.78)
2018/2019	**110 (5.61)**	**380 (19.38)**	**26 (1.33)**	**516 (26.31)**
Vaccinated	73 (3.72)	249 (12.70)	17 (0.87)	339 (17.29)
Unvaccinated	37 (1.89)	131 (6.68)	9 (0.46)	177 (9.03)
2019/2020	**134 (6.83)**	**419 (21.37)**	**16 (0.82)**	**569 (29.02)**
Vaccinated	107 (5.46)	308 (15.71)	11 (0.56)	426 (21.72)
Unvaccinated	27 (1.38)	111 (5.66)	5 (0.25)	143 (7.29)
Total	**439 (22.39)**	**1,427 (72.77)**	**95 (4.84)**	**1,961 (100.00)**
Vaccinated	313 (15.96)	983 (50.13)	56 (2.86)	1,352 (68.94)
Unvaccinated	126 (6.43)	444 (22.64)	39 (1.99)	609 (31.06)

[1] Percentages are calculated based on the total sample (n=1961)

5.2 Descriptive Statistics

5.2.1 Seasonal Influenza Vaccines Administered to Pregnant People from 2016/2017 to 2019/2020

There were 7 seasonal influenza products administered to pregnant people from 2016/2017 to 2019/2020. Table 27 and 28 summarizes the most frequently administered vaccines by enrolment site and year, respectively. They were Fluzone® (40.0%), Fluviral® (25.9%), and Flulaval® (17.1%). Table 29 summarizes the proportion of seasonal influenza vaccine products administered by trimester from 2017/2018 to 2019/2020, and Table 30 describes the proportion of seasonal influenza vaccine products administered by age category from 2016/2017 to 2019/2020.

There were 971 (71.8%) vaccinated pregnant participants who previously received the seasonal influenza in each of the previous 2 years, and 211 (15.6%) vaccinated pregnant participants who previously received at least one dose of the seasonal influenza vaccine in the previous 2 years. There were 170 (12.6%) pregnant participants who reported not receiving any seasonal influenza vaccine in the previous 2 years. Appendix L describes the number of seasonal influenza vaccines received in the previous 2 years in pregnant people, from 2016/2017 to 2019/2020.

Table 26. Enrolment site by year and vaccination status in pregnant participants from 2016/2017 to 2019/2020.

Year	Calgary n (%)[1]	Vancouver n (%)[1]	Toronto n (%)[1]	Ottawa n (%)[1]	Quebec City n (%)[1]	Sherbrooke n (%)[1]	Halifax n (%)[1]	Total n (%)[1]
2016/2017	**79 (4.03)**	**42 (2.14)**	**32 (1.63)**	**34 (1.73)**	**91 (4.64)**	**88 (4.49)**	**26 (1.33)**	**392 (19.99)**
Vaccinated	61 (3.11)	26 (1.33)	24 (1.22)	20 (1.02)	42 (2.14)	48 (2.45)	15 (0.76)	236 (12.03)
Unvaccinated	18 (0.92)	16 (0.82)	8 (0.41)	14 (0.71)	49 (2.50)	40 (2.04)	11 (0.56)	156 (7.96)
2017/2018	**140 (7.14)**	**37 (1.89)**	**67 (3.42)**	**19 (0.97)**	**95 (4.84)**	**91 (4.64)**	**35 (1.78)**	**484 (24.68)**
Vaccinated	116 (5.92)	22 (1.12)	45 (2.29)	13 (0.66)	70 (3.57)	63 (3.21)	22 (1.12)	351 (17.90)
Unvaccinated	24 (1.22)	15 (0.76)	22 (1.12)	6 (0.31)	25 (1.27)	28 (1.43)	13 (0.66)	133 (6.78)
2018/2019	**151 (7.70)**	**42 (2.14)**	**49 (2.50)**	**30 (1.53)**	**122 (6.22)**	**71 (3.62)**	**51 (2.60)**	**516 (26.31)**
Vaccinated	102 (5.20)	28 (1.43)	32 (1.63)	17 (0.87)	85 (4.33)	39 (1.99)	36 (1.84)	339 (17.29)
Unvaccinated	49 (2.50)	14 (0.71)	17 (0.87)	13 (0.66)	37 (1.89)	32 (1.63)	15 (0.76)	117 (5.97)
2019/2020	**135 (6.88)**	**74 (3.77)**	**53 (2.70)**	**40 (2.04)**	**118 (6.02)**	**106 (5.41)**	**43 (2.19)**	**569 (29.02)**
Vaccinated	90 (4.59)	56 (2.86)	33 (1.68)	27 (1.38)	107 (5.46)	91 (4.64)	22 (1.12)	426 (21.72)
Unvaccinated	45 (2.29)	18 (0.92)	20 (1.02)	13 (0.66)	11 (0.56)	15 (0.76)	21 (1.07)	143 (7.29)
Total	**505 (25.75)**	**195 (9.94)**	**201 (10.25)**	**123 (6.27)**	**426 (21.72)**	**356 (18.15)**	**155 (7.90)**	**1,961 (100.00)**
Vaccinated	369 (18.82)	132 (6.73)	134 (6.83)	77 (3.93)	304 (15.50)	241 (12.29)	95 (4.84)	1352 (68.94)
Unvaccinated	136 (6.94)	63 (3.21)	67 (3.42)	46 (2.35)	122 (6.22)	115 (5.86)	60 (3.06)	609 (31.06)

[1] Percentages are calculated based on the total sample (n=1961)

Table 27. Seasonal influenza product by enrolment site in vaccinated pregnant participants from 2016/2017 to 2019/2020.

Year	Calgary n (%)[1]	Vancouver n (%)[1]	Toronto n (%)[1]	Ottawa n (%)[1]	Quebec City n (%)[1]	Sherbrooke n (%)[1]	Halifax n (%)[1]	Total n (%)[1]
Afluria®	0 (0.00)	4 (0.30)	0 (0.00)	0 (0.00)	0 (0.00)	4 (0.30)	0 (0.00)	8 (0.59)
Agriflu®	0 (0.00)	46 (3.40)	0 (0.00)	0 (0.00)	21 (1.55)	21 (1.55)	0 (0.00)	88 (6.51)
Fluad®	1 (0.07)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.07)
Flulaval®	72 (5.33)	4 (0.30)	2 (0.15)	14 (1.04)	18 (1.33)	62 (4.59)	59 (4.36)	231 (17.09)
Fluviral®	0 (0.00)	70 (5.18)	45 (3.33)	0 (0.00)	120 (8.88)	115 (8.51)	0 (0.00)	350 (25.89)
Fluzone®	296 (21.89)	1 (0.07)	63 (4.66)	30 (2.22)	90 (6.66)	25 (1.85)	36 (2.66)	541 (40.01)
Influvac®	0 (0.00)	7 (0.52)	24 (1.78)	33 (2.44)	55 (4.07)	14 (1.04)	0 (0.00)	133 (9.84)
Total	**369 (27.29)**	**132 (9.76)**	**134 (9.91)**	**77 (5.70)**	**304 (22.49)**	**241 (17.83)**	**95 (7.03)**	**1,352 (100.00)**

[1] Percentages are calculated based on the total vaccinated sample (n=1352)

Table 28. Seasonal influenza product by year in vaccinated pregnant participants from 2016/2017 to 2019/2020.

Vaccine Product	2016/2017 n (%)[1]	2017/2018 n (%)[1]	2018/2019 n (%)[1]	2019/2020 n (%)[1]	Total n (%)[1]
Afluria®	0 (0.00)	0 (0.00)	0 (0.00)	8 (0.59)	8 (0.59)
Agriflu®	11 (0.81)	52 (3.85)	0 (0.00)	25 (1.85)	88 (6.51)
Fluad®	1 (0.07)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.07)
Flulaval®	2 (0.15)	2 (0.15)	80 (5.92)	147 (10.87)	231 (17.09)
Fluviral®	104 (7.69)	103 (7.62)	117 (8.65)	26 (1.92)	350 (25.89)
Fluzone®	74 (5.47)	138 (10.21)	110 (8.14)	219 (16.20)	541 (40.01)
Influvac®	44 (3.25)	56 (4.14)	32 (2.37)	1 (0.07)	133 (9.84)
Total	**236 (17.46)**	**351 (25.96)**	**339 (25.07)**	**426 (31.51)**	**1,352 (100.00)**

[1] Percentages are calculated based on the total vaccinated sample (n=1,352)

Table 29. Seasonal influenza product by trimester in vaccinated pregnant participants from 2016/2017 to 2019/2020.

Vaccine Product	1st Trimester n (%)[1]	2nd Trimester n (%)[1]	3rd Trimester n (%)[1]	Missing n (%)[1]	Total n (%)[1]
Afluria®	3 (0.22)	4 (0.30)	1 (0.07)	0 (0.00)	8 (0.59)
Agriflu®	20 (1.48)	37 (2.74)	20 (1.48)	11 (0.81)	88 (6.51)
Fluad®	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.07)	1 (0.07)
Flulaval®	59 (4.36)	81 (5.99)	89 (6.58)	2 (0.15)	231 (17.09)
Fluviral®	50 (3.70)	114 (8.43)	82 (6.07)	104 (7.69)	350 (25.89)
Fluzone®	123 (9.10)	186 (13.76)	158 (11.69)	74 (5.47)	541 (40.01)
Influvac®	16 (1.18)	42 (3.11)	31 (2.29)	44 (3.25)	133 (9.84)
Total	**271 (20.04)**	**464 (34.32)**	**381 (28.18)**	**236 (17.46)**	**1,352 (100.00)**

[1] Percentages are calculated based on the total vaccinated sample (n=1352)

Table 30. Seasonal influenza product by age category in vaccinated pregnant participants from 2016/2017 to 2019/2020.

Vaccine Product	15 to 29 years old n (%)[1]	30 to 39 years old n (%)[1]	40 to 49 years old n (%)[1]	Total n (%)[1]
Afluria®	0 (0.00)	8 (0.59)	0 (0.00)	8 (0.59)
Agriflu®	23 (1.70)	63 (4.66)	2 (0.15)	88 (6.51)
Fluad®	0 (0.00)	1 (0.07)	0 (0.00)	1 (0.07)
Flulaval®	63 (4.66)	162 (11.98)	6 (0.44)	231 (17.09)
Fluviral®	85 (6.29)	250 (18.49)	15 (1.11)	350 (25.89)
Fluzone®	106 (7.84)	409 (30.25)	26 (1.92)	541 (40.01)
Influvac®	36 (2.66)	90 (6.66)	7 (0.52)	133 (9.84)
Total	**313 (23.15)**	**983 (72.71)**	**56 (4.14)**	**1,352 (100.00)**

[1] Percentages are calculated based on the total vaccinated sample (n=1352)

5.2.2 Self-Reported Severe Health Event in Pregnant People from 2016/2017 to 2019/2020

There was a total of 58 (4.3%) vaccinated pregnant participants that reported a severe health event compared to 26 (4.3%) in the unvaccinated group from 2016/2017 to 2019/2020. There was no statistical difference in the IRR for severe health events between vaccinated and unvaccinated pregnant people. Table 31 describes the proportion of severe health events reported in the vaccinated and unvaccinated groups and the IRRs from 2016/2017 to 2019/2020. Table 32 summarizes the IRR for severe health events by Flulaval®, Fluviral®, Fluzone®, and Influvac®. The proportion of severe health events reported by immunization history is described in Appendix M for vaccinated pregnant participants.

Table 33 describes the onset and duration of severe health events in vaccinated pregnant participants from 2016/2017 to 2019/2020. Of the 84 pregnant participants, 39.66% of those who were vaccinated reported the onset of their severe health event within 24 hours after vaccination. In contrast, 7.69% of unvaccinated participants reported the onset within the first 24 hours of the monitoring period. However, 38.46% of unvaccinated participants reported the onset of their severe health event in the 6-to-7 days before the monitoring period. Of the total sample, 36.21% and 65.38% of severe health events were still ongoing in the vaccinated and unvaccinated groups, respectively.

Table 31. Frequency, proportion, and incidence rate ratio for severe health events by vaccination status and year, pregnancy data from 2016/2017 to 2019/2020.

Year	Severe Health Event[1]		
	Vaccinated Cases/Total (%)	Unvaccinated Cases/Total (%)	IRR (95% CI)
2016/2017	14/236 (5.93)	5/156 (3.21)	1.85 (0.68, 5.04)
2017/2018	12/351 (3.42)	8/133 (6.02)	0.57 (0.24, 1.36)
2018/2019	11/339 (3.24)	5/177 (2.82)	1.15 (0.41, 3.25)
2019/2020	21/426 (4.93)	8/143 (5.59)	0.88 (0.40, 1.95)
Total	58/1352 (4.29)	26/609 (4.27)	1.00 (0.64, 1.58)

IRR: Incidence Rate Ratio
CI: Confidence Interval
[1] Severe health event: Prevented/stopped activities or missed school or saw healthcare provider

Table 32. Frequency, proportion, and incidence rate ratio for severe health events[1] by vaccine product and year, pregnancy data from 2016/2017 to 2019/2020.

Year	Severe Health Event[1]							
	Flulaval®		Fluviral®		Fluzone®		Influvac®	
	Cases/Total (%)	IRR (95% CI)	Cases/Total (%)	IRR (95% CI)	Cases/Total (%)	IRR (95% CI)	Cases/Total (%)	IRR (95% CI)
2016	0/2 (0.00)	N/A	5/104 (4.81)	1.50 (0.45, 5.05)	7/74 (9.46)	2.95 (0.97, 10.30)	1/44 (2.27)	0.71 (0.09, 5.91)
2017	0/2 (0.00)	N/A	1/103 (0.97)	0.16 (0.02, 1.27)	9/138 (6.52)	1.08 (0.43, 2.73)	2/56 (3.57)	0.59 (0.13, 2.71)
2018	5/80 (6.25)	2.21 (0.66, 7.43)	4/117 (3.42)	1.21 (0.33, 4.41)	2/110 (1.82)	0.64 (0.13, 3.26)	0/32 (0.00)	N/A
2019	4/147 (2.72)	0.49 (0.15, 1.58)	1/26 (3.85)	0.69 (0.09, 5.27)	9/219 (4.11)	0.73 (0.29, 1.86)	0/1 (0.00)	N/A
Total	9/231 (3.90)	0.91 (0.43, 1.92)	11/350 (3.14)	0.74 (0.37, 1.47)	27/541 (4.99)	1.17 (0.69, 1.98)	3/609 (2.26)	0.53 (0.16, 1.72)

IRR: Incidence Rate Ratio
CI: Confidence Interval
[1] Severe health event: prevented/stopped activities or missed school or saw healthcare provider

Table 33. Onset and duration of severe health event[1] by vaccination status, pregnancy data from 2016/2017 to 2019/2020.

Onset of Problem	Duration of Problem	Severe Health Event[1]		
		Vaccinated Group n (%)[2]	Unvaccinated Group n (%)[3]	Total n (%)
Within 24 hours		**23 (39.66)**	**2 (7.69)**	**25 (29.76)**
	<24 hours	5 (8.62)	0 (0.00)	5 (5.95)
	2-3 days	8 (13.79)	0 (0.00)	8 (9.52)
	4-5 days	2 (3.45)	0 (0.00)	2 (2.38)
	6+ days	2 (3.45)	0 (0.00)	2 (2.38)
	Still Present	6 (10.34)	2 (7.69)	8 (9.52)
Within 1-3 days		**15 (25.86)**	**8 (30.77)**	**23 (27.38)**
	<24 hours	4 (6.90)	1 (3.85)	5 (5.95)
	1-3 days	2 (3.45)	1 (3.85)	3 (3.57)
	4-5 days	2 (3.45)	0 (0.00)	2 (2.38)
	6+ days	0 (0.00)	0 (0.00)	0 (0.00)
	Still Present	7 (12.07)	6 (23.08)	13 (15.48)
Within 4-5 days		**9 (15.52)**	**6 (23.08)**	**15 (17.86)**
	<24 hours	1 (1.72)	0 (0.00)	1 (1.19)
	1-3 days	0 (0.00)	1 (3.85)	1 (1.19)
	4-5 days	2 (3.45)	0 (0.00)	2 (2.38)
	6+ days	1 (1.72)	0 (0.00)	1 (1.19)
	Still Present	5 (8.62)	5 (19.23)	10 (11.90)
Within 6-7 days		**11 (18.97)**	**10 (38.46)**	**21 (25.00)**
	<24 hours	3 (5.17)	0 (0.00)	3 (3.57)
	1-3 days	3 (5.17)	2 (7.69)	5 (5.95)
	4-5 days	1 (1.72)	4 (15.38)	5 (5.95)
	6+ days	1 (1.72)	0 (0.00)	1 (1.19)
	Still Present	3 (5.17)	4 (15.38)	7 (8.33)
Total		**58 (100.00)**	**26 (100.00)**	**84 (100.00)**
	<24 hours	13 (22.41)	1 (3.85)	14 (16.67)
	1-3 days	13 (22.41)	4 (15.38)	17 (20.24)
	4-5 days	7 (12.07)	4 (15.38)	11 (13.10)
	6+ days	4 (6.90)	0 (0.00)	4 (4.76)
	Still Present	21 (36.21)	17 (65.38)	38 (45.24)

[1] Severe health event: prevented/stopped activities or missed school or saw healthcare provider
[2] Time period since vaccination (n=58)
[3] Time period since survey receipt (n=26)

5.3 Inferential Statistics

5.3.1 Logistic Regression Modelling Severe Health Events by Vaccination Status in Pregnant People from 2016/2017 to 2019/2020

Univariate logistic regressions were conducted to model severe health events in pregnant people by vaccination status. Covariates of interest included: trimester, age category, year of enrolment, enrolment site, and immunization history. The enrolment site for Ottawa was removed from inferential analyses since it did not have sufficient participants with severe health events to provide an estimate. The unadjusted OR and 95% CI for severe health events modeled by the primary explanatory variable, vaccination status, was 0.95 (0.59, 1.53). There were no statistical differences for severe health events when modeled by trimester, age category, year of enrolment, or immunization history. The enrolment site was statistically significant with a p-value less than 0.01 when modeled separately for severe health events. The unadjusted OR for severe health events for the study sites in Quebec City and Sherbrooke were statistically significant when compared to the reference group (Calgary). Appendix N summarizes the unadjusted logistic regression models for severe health events as the primary outcome and each covariate of interest by vaccination status.

A multivariable logistic regression modeled severe health events by vaccination status, as described in Table 34. Covariates with a p-value less than 0.25 (trimester, and enrolment site) were included in the multivariable model. Immunization history was not considered in the multivariable logistic regression model since vaccinated participants were only asked. Covariates that were not statistically significant (with a p-value less than 0.05) were removed from the final multivariable model. There were no statistically significant interaction terms between vaccination status and enrolment site. The final multivariable logistic regression model contained

vaccination status and enrolment site, which is described in Table 34 with the adjusted OR and 95% CI.

Table 34. Univariate and multivariable logistic regressions modelling severe health event[1] by vaccination status and significant covariates[±] as explanatory variables, pregnancy data from 2017/2018 to 2019/2020.

Variables	Severe Health Events[1]			
	Estimate	Standard Error	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio[±] (95% CI)
Vaccination Status				
Unvaccinated	-	-	Reference	Reference
Vaccinated	-0.0525	0.2429	0.95 (0.59, 1.53)	0.95 (0.59, 1.53)
Trimester[2]				
1st	-	-	Reference	N/A
2nd	-0.5679	0.3026	0.57 (0.31, 1.03)	
3rd	-0.5691	0.3247	0.57 (0.30, 1.07)	
Age Categories				
30-49 years old	-	-	Reference	N/A
15-29 years old	-0.2853	0.2912	0.75 (0.43, 1.33)	
Year				
2019/2020	-	-	Reference	N/A
2018/2019	-0.5624	0.3263	0.57 (0.30, 1.08)	
2017/2018	-0.2179	0.2999	0.80 (0.45, 1.45)	
2016/2017	0.0028	0.3054	1.00 (0.55, 1.83)	
Enrolment Site				
Calgary	-	-	Reference	Reference
Vancouver	0.2786	0.3185	1.32 (0.71, 2.47)	1.32 (0.71, 2.46)
Toronto	-0.4899	0.4044	0.61 (0.28, 1.35)	0.61 (0.28, 1.35)
Quebec City	-1.3986	0.4226	0.25 (0.11, 0.57)	0.25 (0.11, 0.57)
Sherbrooke	-0.7523	0.3566	0.47 (0.23, 0.95)	0.47 (0.23, 0.95)
Halifax	-0.2176	0.4064	0.80 (0.36, 1.78)	0.80 (0.36, 1.78)
Immunization History (Last 2 Years)[3]				
2	-	-	Reference	N/A
1	0.1420	0.5950	1.15 (0.36, 3.70)	
0	0.5139	0.4796	1.67 (0.65, 4.28)	

CI: Confidence Interval

[±] Adjusted for enrolment site

[1] Severe health event: prevented/stopped activities or missed school or saw healthcare provider

[2] Data from 2017/2018 to 2019/2020 only.

[3] Not considered for multivariable logistic regression since it was asked to vaccinated participants only

5.4 Self-Reported Most Severe Symptoms in Pregnant People from 2016/2017 to 2019/2020

5.4.1 Most Severe Symptoms in Pregnant People

A total of 45 vaccinated and 19 unvaccinated pregnant participants with a severe health event specified their most severe symptom. The most frequently reported most severe symptom among vaccinated pregnant people was feeling unwell. Congestion and headache were the most frequently reported most severe symptoms among unvaccinated pregnant people. Only one pregnancy-related most severe symptom was reported in the unvaccinated group, and none were reported in the vaccinated group. No statistical differences were observed in the IRR for any of the most severe symptoms reported, as described in table 35. Vaccinated pregnant participants who reported multiple symptoms as their most severe symptom had their responses summarized in Appendix O. No pregnant participants reported multiple symptoms as their most severe symptom in the unvaccinated group.

A total of 7 (15.6%) out of the 45 vaccinated pregnant participants reported having sought medical consultation for their most severe symptom, and 6 (13.3%) reported having obtained a diagnosis. A total of 6 (31.6%) out of the 19 unvaccinated pregnant participants reported having sought medical consultation for their most severe symptom, and 5 (26.3%) reported having obtained a diagnosis, as described in Table 36.

Table 35.Frequency, proportion, and incidence rate ratios for most severe symptom by vaccination status, pregnancy data from 2016/2017 to 2019/2020.

Most Severe Symptom	N	Total in Vaccinated Group N=1339 Cases (%)	Total in Unvaccinated Group N=602 Cases (%)	Incidence Rate Ratio (95% CI)
Non-Pregnancy Related				
Unwell	13	12 (0.90)	1 (0.17)	5.40 (0.70, 41.90)
Gastrointestinal	10	8 (0.60)	2 (0.33)	1.80 (0.38, 8.44)
Congestion	10	6 (0.45)	4 (0.66)	0.67 (0.19, 2.38)
Cough	7	5 (0.37)	2 (0.33)	1.12 (0.22, 5.78)
Multiple Symptoms[1]	6	6 (0.45)	0 (0.00)	N/A
Headache	4	0 (0.00)	4 (0.66)	N/A
Injection Site Reaction	2	2 (0.15)	N/A	N/A
Sore Throat	2	2 (0.15)	0 (0.00)	N/A
Runny Nose	2	1 (0.07)	1 (0.17)	0.45 (0.03, 7.18)
Fever	1	1 (0.07)	0 (0.00)	N/A
Hoarseness	1	0 (0.00)	1 (0.17)	N/A
Breathing Difficulty	1	1 (0.07)	0 (0.00)	N/A
Low Blood Pressure	1	0 (0.00)	1 (0.17)	N/A
Dental pain	1	0 (0.00)	1 (0.17)	N/A
Urinary Symptom	1	0 (0.00)	1 (0.17)	N/A
Croup	1	1 (0.07)	0 (0.00)	N/A
Pregnancy Related				
Spotting	1	0 (0.00)	1 (0.17)	N/A
Combined				
Total	64	45 (3.36)	19 (3.16)	1.06 (0.63, 1.80)

CI: Confidence Interval

[1] Participants who indicated more than one symptom for most severe

Table 36. Outcome of self-report of most severe symptom following receipt of seasonal influenza vaccine, pregnancy data from 2016/2017 to 2019/2020.

Most Severe Symptom	Vaccinated Group			Unvaccinated Group		
	N	Healthcare Visit / Consultation` (%)[1]	Obtained Diagnosis[2] (%)[1]	N	Healthcare Visit / Consultation (%)[1]	Obtained Diagnosis[2] (%)[1]
Unwell	12	2 (16.67)	2 (16.67)	1	0 (0.00)	0 (0.00)
Gastrointestinal	8	0 (0.00)	0 (0.00)	2	2 (100.00)	2 (100.00)
Congestion	6	1 (16.67)	1 (16.67)	4	0 (0.00)	0 (0.00)
Multiple Symptoms	6	1 (16.67)	0 (0.00)	0	N/A	N/A
Cough	5	2 (40.00)	2 (16.67)	2	0 (0.00)	0 (0.00)
Injection Site Reaction	2	0 (0.00)	0 (0.00)	0	N/A	N/A
Sore Throat	2	0 (0.00)	0 (0.00)	0	N/A	N/A
Fever	1	1 (100.00)	0 (0.00)	0	N/A	N/A
Breathing Difficulty	1	1 (100.00)	0 (0.00)	0	N/A	N/A
Runny Nose	1	1 (100.00)	0 (0.00)	1	0 (0.00)	0 (0.00)
Croup	1	1 (100.00)	1 (100.00)	0	N/A	N/A
Headache	0	N/A	N/A	4	1 (25.00)	1 (25.00)
Hoarseness	0	N/A	N/A	1	0 (0.00)	0 (0.00)
Low Blood Pressure	0	N/A	N/A	1	0 (0.00)	0 (0.00)
Other	0	N/A	N/A	1	1 (100.00)	1 (100.00)
Urinary Symptom	0	N/A	N/A	1	1 (100.00)	1 (100.00
Spotting	0	N/A	N/A	1	1 (100.00)	0 (0.00)
Total	**45**	**7 (15.56)**	**6 (13.33)**	**19**	**6 (31.58)**	**5 (26.32)**

[1] Denominator is the total sample of the specified most severe symptom
[2] Diagnosis might not match with the most severe symptom that was reported

Chapter 6: Discussion

6.1 Child Analysis

6.1.1 Association Between Seasonal Influenza Vaccination and Severe Health Event

The IIV and the LAIV administered to children from 2013/2014 to 2019/2020 in Canada did not observe a statistically significant association with severe health events. The unadjusted IRR and univariate logistic regression model had a statistically significant association for IIV status and severe health events in children. After adjusting for age category and enrolment site in the multivariate logistic regression, IIV status was not associated with severe health events with an OR of 1.11 and 95% CI of 1.00 and 1.25. In contrast, the unadjusted IRR and univariate logistic regression for severe health events in children who received LAIV were not statistically significant compared to the unvaccinated group. After adjusting for age category and enrolment site, vaccination with the LAIV still did not demonstrate an association with severe health events with an OR of 1.11 and a 95% CI of 0.95 and 1.29. The proportion of severe health events in children vaccinated with IIV (7.1%) and LAIV (5.6%) were both low.

The IIV and the LAIV groups had a higher proportion of participants who reported the onset of their severe health event in the first 1-to-3 days compared to the unvaccinated groups. In the unvaccinated groups, the onset of the severe health event was predominantly captured within 6-to-7 days from the start of the monitoring period. The duration of severe health events in vaccinated and unvaccinated child participants in both vaccinated groups were similar. It was observed that severe health events lasted 1-to-3 days long or were still present when completing the survey. A similar duration for severe health events was observed in the corresponding

unvaccinated groups. This shows that many severe health events could be considered mild since they persisted only for a short period.

There were 772 child participants vaccinated with the IIV and 274 child participants vaccinated with the LAIV who reported their most severe symptom. Fever, gastrointestinal symptoms, feeling unwell, headache, hives, and breathing difficulty were found to be statistically significant in children vaccinated with the IIV compared to the unvaccinated group. In contrast, fever was the only most severe symptom that was statistically significant in children vaccinated with the LAIV compared to the unvaccinated group. Both (IIV and LAIV) groups observed a statistically significant rate of reporting multiple symptoms in the vaccinated groups compared to the unvaccinated group. Since this category was created after data collection (and not provided as an option in the survey), the responses could have varied with any number and combination of symptoms. This is not surprising given that participants reported more symptoms in the vaccinated groups for the IIV and LAIV compared to the unvaccinated groups. Among child participants who reported their most severe symptom, the proportion of child participants who required a healthcare visit or medical consultation in the IIV group (29.4%) and LAIV group (27.7%) was low to moderate. Similarly, the proportion of those diagnosed in the IIV group (20.3%) and the LAIV group (22.7%) was slightly lower. This highlights that a large proportion of participants experienced no symptoms that required a medical consultation.

The LAIV and IIV results from this study are similar to the literature. A study conducted by Haber et al. examined the safety profile of the IIV4 to the IIV3 in children aged 6 months to 16 years old using data from the Vaccine Adverse Event Reporting System (VAERS) in the United States. [59] It found that the AE reported following receipt of the IIV4 was similar to that following receipt of the IIV3. The findings observed that 93% of the reports in the IIV4 group

were non-serious and mild, with fever and injection site reactions being the most commonly reported symptoms in the IIV4 and IIV3 groups. This was similar to the findings from this thesis, which observed similar frequently reported symptoms in the IIV group. The main difference in their study methodology is that data was sourced from the VAERS, which is a passive surveillance system that can include reports from healthcare professionals, vaccine manufacturers, and the general public. [60] Since it does not consist of an unvaccinated control group, their study also differed having used participants vaccinated with the IIV3 as the control group.

A study conducted by Daley et al. examined the safety profile of the LAIV in children and adolescents aged 2-to-17 years old using data from the Vaccine Safety Datalink[5] from 2003/2004 to 2013/2014. [61] It observed that the trivalent composition of the LAIV did not pose any risk to children in 14 pre-specified AE categories. There were 4 AE categories that underwent medical record review and observed that the LAIV was significantly associated with anaphylaxis and syncope; however, the risk of occurrence for these two AE were rare. The findings from this study were similar to this thesis, given that there were very few AEs associated with the LAIV and this thesis observed a statistically significant association with fever only. An important distinction to note is that their study only explored the outcomes associated with the trivalent LAIV. In contrast, the majority LAIV products in this thesis were with the quadrivalent formulation.

A separate study from Belshe et al. explored the safety of the LAIV compared to the IIV in infants in children aged 6-to-59 months of age. [62] Among children who were vaccinated for the first time, it was observed that fever (>37.8^{O}C) occurred in 5.4% of the LAIV group

[5] Collaboration between the Centers for Disease Control and Prevention (CDC) and 9 integrated healthcare organizations in the United States of America.

compared to 2.0% in the IIV within the second day of receiving the first dose of the vaccine ($p<0.001$). However, no differences were observed after receiving the second dose of the vaccine. In addition, there was no increased risk of medically significant wheezing in children between the LAIV and IIV groups; however, an increase in medically significant wheezing was observed in children less than 12 months of age. The findings were partly similar to the child analyses, which saw increased rates of fever reported in the IIV and LAIV groups compared to an unvaccinated group; however, the analyses could not explore differences after first and second doses of the vaccine. In addition, the rate of wheezing did not show a difference in both the IIV and LAIV groups compared to the unvaccinated groups in this thesis.

In a separate study conducted by Caspard et al., they explored the safety profile of child participants aged 2-to-17 years old with an underlying high-risk condition who received the LAIV matched to an IIV group and an unvaccinated group. [63] Based on data collected at 42 days and 6 months, there was no difference in the risk of hospitalization from the LAIV group compared to an unvaccinated group. In addition, hospitalization after receiving the LAIV was lower than the IIV. Since the current CANVAS network does not collect data on pre-existing health conditions, it was reassuring to observe that the LAIV is still considered safe in children with underlying health conditions. However, it is uncertain whether participants with underlying health conditions would report higher rates of severe health events based on the primary outcome of this thesis analysis.

The results in the child analysis found no association between vaccination status (for the IIV and the LAIV groups) and severe health events in children. It adds to the current literature by examining AE following receipt of the seasonal influenza vaccine using 7 years of data from the CANVAS network. The main difference between the findings from the analyses and the

literature is that this thesis includes a control group, which consists of unvaccinated child participants.

6.1.2 Agreement Between Child Responses in the Online Survey and the Telephone Report

The child responses reported in the online survey and the telephone report demonstrated moderate to high concordance for reported most severe symptoms, diagnosis, and treatment. The symptoms for which there was the highest level of agreement in both groups combined were hives (88%), injection site reaction (87%), gastrointestinal symptom (84%), fever (68%), cough (63%), and ear symptom (62%). However, when the analyses were stratified by vaccination status, the Kappa estimates varied. The agreement in the vaccinated group was well measured, having reflected similar values to the overall estimates for each symptom. However, the agreement in the unvaccinated group varied considerably depending on the symptom. It is plausible that vaccinated participants demonstrated better recall than their unvaccinated counterparts since they had been vaccinated and would therefore be more conscious of experiencing an AE. Most severe health events reported in child participants vaccinated with IIV and LAIV had an onset within 3 days. In contrast, the onset of severe health events in the unvaccinated groups varied, with most occurring within 6-to-7 days. The findings show that vaccinated participants could accurately describe their most severe symptoms using an online survey, which was later verified by a research staff over the telephone.

The results from these study mirror findings from an earlier CANVAS network study conducted in 2014 by Bettinger et al., which found high agreement for allergic events (93%), respiratory symptoms/infections (84%), gastrointestinal symptoms (79%), and systemic symptoms (67%) between the online survey and the telephone interview. [64] Although data

from the 2014/2015 influenza season was not included in this analysis, it is reassuring to see continued agreement from an earlier study using the same data collection methods. There are currently no other research studies that have examined the agreement between participants' responses regarding AE following influenza vaccination using an online survey and telephone interview.

There remain limited studies that have examined the agreement of AEFI between reporting methods comparing online and telephone reports. A cross-sectional study conducted by Ackerson et al. examined the concordance between medical records and parent patient reports (obtained from phone interviews and mailed questionnaires) of clinical characteristics and factors related to febrile seizure based on the Brighton Collaboration guidelines. [65] There were 110 children aged 3-to-60 months included in the analyses from January 2002 to December 2005. They observed a high percent total agreement when individual items were grouped into larger domains for predisposing factors (89.1%) and seizure characteristics (66.4%). However, the Kappa statistic for predisposing factors (0.08) and seizure characteristics (0.07) was low, which is expected for rare events. A limitation of this study was that participants were interviewed 2-to-6 years after the event compared to a few days in our study. Therefore, it is likely that the participants might have forgotten the details of the event. The concordance might likely have improved if patient reports were collected closer to the event.

Few studies also explored the concordance between mailed patient reports and their medical record in adults. A previous study conducted by Tisnado et al. examined the concordance between the medical record and patient survey data in adults in ambulatory care, which observed good concordance for percent total agreement and Kappa in domain level analyses for reporting diagnosis (82%, 0.6), clinical services (82%, 0.6) and medication use

(85%, 0.6). [66] Similarly, a study conducted by Fowles et al. examined the sensitivity and specificity of diagnoses reported by adults in a mailed survey and their ambulatory medical record. They observed that specificity was higher than sensitivity for all chronic conditions when they compared the two data collection methods. [67]

Given the rapid rise in technology, there has been a shift towards using electronic methods such as online surveys or SMS for AEFI surveillance given its efficiency; however, few studies have evaluated the reliability in reporting and the validity between alternative reporting methods of AEFIs. It is important that future studies continue to investigate the reliability and validity of self-report AEFI using electronic data capture methods since these platforms provide the opportunity to collect data in real-time with a greater reach to more participants. It is essential that future studies also consider how responses might differ based on participants' characteristics such as age group, education level, or previous medical history.

6.2 Pregnancy Analysis

6.2.1 Association Between Seasonal Influenza Vaccination and Severe Health Event

The main findings from the pregnancy analysis show no association between the seasonal influenza vaccine and severe health events in pregnant people aged 15-to-49 years old for the unadjusted IRR and the unadjusted logistic regression analyses. The multivariate logistic regression analysis only adjusted for enrolment site, which also observed no association with vaccination status. Thus, influenza vaccines were not associated with severe health events by all measures.

Few pregnant participants reported their most severe symptom in the vaccinated and unvaccinated groups. The majority of most severe symptoms were non-pregnancy related, with

spotting being the only pregnancy-related most severe symptom observed in the unvaccinated group. There were no differences in the rate of non-pregnancy-related most severe symptoms for unwell, gastrointestinal symptoms, congestion, cough, and runny nose between the vaccinated and unvaccinated groups; however, the CI for all these symptoms was large.

The product monographs for all 7 seasonal influenza vaccines included in the analyses did not indicate any increased risk in pregnant women after vaccination [30, 68-73]; however, some vaccine product monographs did not report safety data for pregnant women.

In addition to the few Canadian studies that were previously described, there are few studies in the United States that examined the safety of the seasonal influenza vaccine in pregnant women with a control group. In a randomized prospective study conducted by Munoz et al., they examined the safety and immunogenicity of three trivalent seasonal influenza vaccines administered to pregnant women in the 2nd and 3rd trimesters compared to non-pregnant women. Injection site and systemic reactions were most frequently reported in both groups; however, they were typically mild, and most of the symptoms were resolved within 72 hours. The systemic symptoms reported also observed no differences in outcomes between the pregnant and non-pregnant vaccinated groups. Several pregnancy-related events were captured during the follow-up period, but they were not considered to be related to the vaccine. [74] This study illustrates that symptoms between vaccinated pregnant women and non-pregnant women are relatively similar. Although the non-pregnant vaccinated group serves as a good comparator, it is difficult to draw direct comparisons given the physiological differences compared to pregnant women.

In 2013, Nordin et al. examined the risk for medically attended events after receiving the IIV3 compared to unvaccinated pregnant women in the first trimester of pregnancy. Data were

collected during the 2002-2003 to 2008-2009 seasonal influenza seasons. Among 75,906 vaccinated pregnant women and 147,992 unvaccinated pregnant women matched by age, site, and pregnancy start date, it found that IIV3 was not associated with medically attended events within the first 3 days and 42 days after vaccination. In addition, the rates for allergic reactions, cellulitis, fever or malaise, soreness or swelling, rash, seizures, and altered mental status were low between the vaccinated and unvaccinated pregnant women. [75] An overlapping study was also conducted by Nordin et al. in the United States using data from 2004/2005 to 2008/2009 to examine the risk of preterm or small for gestational age birth in pregnant women. The sample consisted of 57,554 propensity scored-matched vaccinated and unvaccinated pregnant women. No associations were observed for small gestational age at birth and preterm birth during the first, or third trimester in pregnant women. [76] More recently, Donahue et al. examined the risk of spontaneous abortion after receiving IIV in pregnant women during the 2012-2013 to 2014-2015 influenza seasons. Among all 1,236 matched pairs, there was no association found between IIV and spontaneous abortion. Further stratification found no association when comparing matched pairs vaccinated in the previous influenza season and those unvaccinated in the previous season. [77] These studies help illustrate the sparse nature of pregnancy-related AE following receipt of the seasonal influenza vaccine. Given that there was only one pregnancy-related most severe symptom captured in this thesis analysis, it is plausible that other pregnancy-related most severe symptoms might have been detected with a larger sample size.

The findings from this analysis adds to the existing literature by demonstrating that pregnant people who receive the seasonal influenza vaccine report low proportions of severe health events and most severe symptoms when compared to unvaccinated pregnant people. Given low number of AEs reported in this sample, the seasonal influenza vaccine does not pose

additional risk toward pregnant people and the vaccine should continue to be administered to this population to prevent serious health outcomes.

6.3 Strengths of the Study

The CANVAS network is an established sentinel surveillance system that collects data on the safety profile of the seasonal influenza vaccine administered to individuals in Canada. This study expands upon previously conducted studies from the CANVAS network [51, 78, 79], by examining the safety profile of the seasonal influenza vaccine using 7 years of data for multi-year cross-sectional analysis.

A primary strength of the study design is it consists of an unvaccinated group that helps determine the background rate of severe health events. Compared to commonly used passive surveillance systems, it was possible to draw inferences regarding the rate of severe health events and symptoms between vaccinated and unvaccinated groups. Passive surveillance systems typically rely on immunization registries for denominator data or may use doses distributed as most influenza vaccine administration is not recorded in immunization registries.

Given that the number of participants who participated in the CANVAS network influenza vaccine safety study increased each year, it allowed an opportunity to examine the association between vaccination and severe health events with a larger sample size and allowed stratification between years. Since many of the study variables were similar between surveys, the number of participants remained high in the final sample, after removing incomplete surveys.

The online delivery of the surveys enabled rapid identification of potential AEFI, which also requires fewer resources. This helped overcome some common pitfalls in passive

surveillance systems such as under-reporting and slow AE detection; however, this is limited to 7-day reporting period only.

6.4 Limitations of the Study

Participants were recruited from select immunization clinics across Canada, mostly from healthcare settings. During the consent process, it was emphasized to the prospective participants that they should still complete the survey even if they did not experience a severe health event. Participants who do not experience a severe health event might be less inclined to respond to the survey, which may lead to over-reporting of the outcome of interest. The response rate was not calculated for the current analyses; however, in a previous CANVAS network study approximately 10% of non-responders were contacted by phone and the rate of severe health events among those who responded using the survey and via telephone was similar. [79]

The CANVAS network relies on self-report data collection from its participants; therefore, the validity of the responses might not be a precise estimate of AEFIs. Although participants are emailed their surveys at the same time (either 8 days after vaccination or a few weeks before the start of the influenza vaccination campaigns), they might not respond to the survey immediately, and therefore some minute details might be forgotten. In addition, vaccinated participants might be more cautious (due to having experienced an intervention); therefore, they might be more inclined to report symptoms even if they are mild. In comparison, participants in the unvaccinated group might not report mild symptoms since they did not receive an intervention or may not remember the correct time for onset and duration. The reminder email sent to the unvaccinated group attempts to minimize this difference between the vaccinated and

unvaccinated group. Since the CANVAS network does not have access to medical records, it is not possible to verify the health outcome of every participant with a severe health event.

Depending on the participant's medical knowledge, their reported symptoms may not be a true reflection of what is occurring. Those who work or study in the medical field might have more knowledge about medical terms and might describe the state of their health more accurately. In addition, even if multiple participants were to describe the same symptom as their most severe, their definitions of the symptom might still differ. Since only participants who reported a severe health event and required a medical consultation were eligible for a telephone call, it was not possible to verify the agreement of all participant responses for their most severe symptom.

The telephone call conducted by a research staff member confirmed details about the participant's most severe symptom. This allowed the participant to respond using two different data collection methods (online survey versus telephone call). In addition, the time period between the reporting methods varied by a few days based on the availability for the phone call. Although the agreement analysis aimed to determine the level of concordance between reported symptoms, diagnosis, and treatment, they were collected at two different time periods and not asked precisely in the same order, which might result in different outcomes.

Due to the study's design, participants were required to enroll in the study each year, even if they had participated in the previous year. This did not allow for repeated measures analyses within participants. In addition, since participant enrolment was not tracked across recruitment years, it was assumed that participants were independent of each other throughout the study period from 2013/2014 to 2019/2020. Future studies should aim to overcome this shortfall and conduct longitudinal studies to track the trends in AEFI in participants who have

received the seasonal influenza vaccine over multiple years. This could be beneficial in determining whether participants who have previously been vaccinated are less likely to experience an AE in later years.

Lastly, the child analysis required a sample size of 22,869 children in each the vaccinated and unvaccinated groups to detect a 10% difference (assuming a proportion of 6.7% AEFI among unvaccinated children) with a power of 80% and an alpha of 0.05. Since the child analysis was separated into vaccine types (IIV and LAIV), the study objective was not sufficiently powered to detect an association. In addition, the pregnancy analysis required a sample size of 57,125 pregnant people in each of the vaccinated and unvaccinated groups to detect a 10% difference (assuming a proportion of 2.8% AEFI among unvaccinated pregnant people) with a power of 80% and an alpha of 0.05. Since the final analytical sample for the pregnancy analysis was low, it was not sufficiently powered to detect an association; therefore, the descriptive analysis was emphasized.

Although it was possible to conduct a multi-year cross-sectional analysis for the safety of the seasonal influenza vaccine, it is plausible that some associations were not observed due to missing variables not collected in the survey. Some variables to consider would be information about the participant's prior medical history and current comorbidities, since these factors might influence how the body responds to vaccination.

6.5 Public Health Relevance

The CANVAS network serves as a platform for annual monitoring of the seasonal influenza vaccine safety profile during the start of immunization campaigns in Canada. The design of the study is unique compared to other studies since it includes an unvaccinated control

group. This is different from most influenza vaccine safety studies, which uses other vaccines as the control group.

Based on data from 2013/2014 to 2019/2020, it was observed that children and pregnant people are not at increased risk of AE following receipt of the seasonal influenza vaccine. Since the composition of the seasonal influenza vaccine changes annually (based on recommendations from the WHO), active surveillance systems, such as CANVAS, should continue to supplement passive surveillance systems to quickly detect unexpected signals of interest. In addition, since the seasonal influenza vaccines are administered to many individuals each year, it is critical that any unexpected signals are detected earlier in the immunization campaigns to prevent potential harm to other recipients.

Due to the rapid rise of electronic data collection tools, it is critical that public health also adapts alongside these changes as we now see increased use of online surveys and text-messaging platforms to capture AEFI. Such methods could be applied more broadly to rural or remote locations in Canada, where it is inaccessible to visit a healthcare provider. Platforms such as the CANVAS network can continue to be used to monitor for potential safety signals and participants who experience a health event severe enough to warrant a healthcare visit can be contacted by a health professional (via telephone or video call) to discuss their health status and also seek treatment for their AEFI. This will help attract a larger sample of participants from specific high-risk groups with enough statistical power to draw accurate inferences. Most importantly, we must develop and update existing methods for data collection to ensure that novel techniques using online surveillance systems are validated.

Given the wide accessibility to information in this era, we have witnessed an emergence of vaccine-related misinformation. [80] Therefore, the findings from this thesis analyses should

be disseminated with the scientific community and general community members using an appropriate knowledge translation framework [81, 82]. This may help promote vaccine acceptance and uptake each year, especially among high-risk groups.

Chapter 7: Conclusion

The findings from this thesis found no association between the seasonal influenza vaccine and severe health events in children and pregnant people. The findings are similar to previous studies conducted in this field; however, a significant difference is that the study design of the CANVAS network includes an unvaccinated control group. This provided the opportunity to determine the rate in a vaccinated group and compare it to the background rate of health events in an unvaccinated group. The findings help reassure the public that seasonal influenza vaccines do not pose an increased risk to children and pregnant people. Since the monitoring period from this analysis was only limited to 7 days, it is plausible that increased cases of AEFIs might have been detected with a longer monitoring period and a larger sample.

Bibliography

1. Paules, C. and K. Subbarao, *Influenza.* Lancet, 2017. **390**(10095): p. 697-708.
2. Organization, W.H. *Influenza (Seasonal)*. 2018 [cited 2022 January 15]; Available from: https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal).
3. Jefferson, T., et al., *Vaccines for preventing influenza in healthy children.* Cochrane Database Syst Rev, 2018. **2**(2): p. Cd004879.
4. Quach, T.H.T., N.A. Mallis, and J.F. Cordero, *Influenza Vaccine Efficacy and Effectiveness in Pregnant Women: Systematic Review and Meta-analysis.* Matern Child Health J, 2020. **24**(2): p. 229-240.
5. Lafond, K.E., et al., *Global Role and Burden of Influenza in Pediatric Respiratory Hospitalizations, 1982-2012: A Systematic Analysis.* PLoS Med, 2016. **13**(3): p. e1001977.
6. Schanzer, D.L., J.M. Langley, and T.W. Tam, *Hospitalization attributable to influenza and other viral respiratory illnesses in Canadian children.* Pediatr Infect Dis J, 2006. **25**(9): p. 795-800.
7. Schanzer, D.L., J.M. Langley, and T.W. Tam, *Influenza-attributed hospitalization rates among pregnant women in Canada 1994-2000.* J Obstet Gynaecol Can, 2007. **29**(8): p. 622-9.
8. Dawood, F.S., et al., *Epidemiology and Clinical Outcomes of Hospitalizations for Acute Respiratory or Febrile Illness and Laboratory-Confirmed Influenza Among Pregnant Women During Six Influenza Seasons, 2010-2016.* J Infect Dis, 2020. **221**(10): p. 1703-1712.
9. Krammer, F., et al., *Influenza.* Nat Rev Dis Primers, 2018. **4**(1): p. 3.
10. Petrova, V.N. and C.A. Russell, *The evolution of seasonal influenza viruses.* Nat Rev Microbiol, 2018. **16**(1): p. 47-60.
11. Carrat, F. and A. Flahault, *Influenza vaccine: the challenge of antigenic drift.* Vaccine, 2007. **25**(39-40): p. 6852-62.
12. Kissling, E., et al., *I-MOVE multicentre case-control study 2010/11 to 2014/15: Is there within-season waning of influenza type/subtype vaccine effectiveness with increasing time since vaccination?* Euro Surveill, 2016. **21**(16).
13. Ferdinands, J.M., et al., *Intraseason waning of influenza vaccine protection: Evidence from the US Influenza Vaccine Effectiveness Network, 2011-12 through 2014-15.* Clin Infect Dis, 2017. **64**(5): p. 544-550.
14. Puig-Barbera, J., et al., *Waning protection of influenza vaccination during four influenza seasons, 2011/2012 to 2014/2015.* Vaccine, 2017. **35**(43): p. 5799-5807.
15. Ray, G.T., et al., *Intraseason Waning of Influenza Vaccine Effectiveness.* Clin Infect Dis, 2019. **68**(10): p. 1623-1630.
16. Canada, P.H.A.o., *Statement on Seasonal Influenza Vaccine for 2013-2014: An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)*, in *Can Commun Dis Rep*. 2013. p. 1-37.
17. Canada, P.H.A.o. *Statement on Seasonal Influenza Vaccine for 2014-2015*. 2014 [cited 2021 May 1]; Available from: https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/statement-on-seasonal-influenza-vaccine-2014-2015.html.

18. Canada, P.H.A.o., *Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2015-2016*. 2015, Public Health Agency of Canada: Ottawa.
19. Canada, P.H.A.o., *Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2016-2017*. 2016, Public Health Agency of Canada: Ottawa.
20. Canada, P.H.A.o., *Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2017–2018*. 2017, Public Health Agency of Canada: Ottawa.
21. Canada, P.H.A.o., *Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2018–2019*. 2018, Public Health Agency of Canada: Ottawa.
22. Canada, P.H.A.o., *Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2019–2020*. 2019, Public Health Agency of Canada: Ottawa.
23. Canada, P.H.A.o., *Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2020–2021*. 2020.
24. Canada, A., *Canada Product Monograph: FLUMIST® Influenza Vaccine (live, attenuated)*. 2014.
25. Canada, A., *Canada Product Monograph: FLUMIST® QUADRIVALENT Influenza Vaccine (live, attenuated)*. 2016.
26. Canada, A., *Canada Product Monograph: FLUMIST® QUADRIVALENT Influenza Vaccine (live, attenuated)*. 2017.
27. Organization, W.H. *Recommendations for influenza vaccine composition*. 2022 [cited 2022 January 15]; Available from: https://www.who.int/teams/global-influenza-programme/vaccines/who-recommendations.
28. Tsai, T.F., *MF59 adjuvanted seasonal and pandemic influenza vaccines.* Yakugaku Zasshi, 2011. **131**(12): p. 1733-41.
29. Inc., N.P.C., *Canada Product Monograph: FLUAD PediatricTM and FLUAD® (Influenza Vaccine, Surface Antigen, Inactivated, Adjuvanted with MF59C.1)*. 2016.
30. Inc., S.C., *Canada Product Monograph: FLUAD Pediatric® and FLUAD® (Influenza Vaccine, Surface Antigen, Inactivated, Adjuvanted with MF59C.1)*. 2017.
31. Canada, G.o. *Clinical trials and drug safety*. 2020 [cited 2021 June 1]; Available from: https://www.canada.ca/en/health-canada/services/clinical-trials.html.
32. Canada, G.o. *Guidance Document For Clinical Trial Sponsors: Clinical Trial Applications*. 2016 [cited 2021 June 1]; Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/clinical-trials/clinical-trial-sponsors-applications.html.
33. Canada, G.o. *Guidance Document: Part C, Division 5 of the Food and Drug Regulations "Drugs for Clinical Trials Involving Human Subjects" (GUI-0100)*. 2019 [cited 2022 February 27]; Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-clinical-practices/guidance-documents/guidance-drugs-clinical-trials-human-subjects-gui-0100/document.html#a3.
34. Canada, G.o. *Vaccine safety and pharmacovigilance: Canadian Immunization Guide*. 2019 [cited 2021 June 15]; Available from: https://www.canada.ca/en/public-

health/services/publications/healthy-living/canadian-immunization-guide-part-2-vaccine-safety/page-2-vaccine-safety.html.
35. Canada, G.o. *Biologic and Radiopharmaceutical Drugs Directorate*. 2021 [cited 2021 June 1]; Available from: https://www.canada.ca/en/health-canada/corporate/about-health-canada/branches-agencies/health-products-food-branch/biologic-radiopharmaceutical-drugs-directorate.html.
36. Canada, G.o. *Guidance document: Annual update of seasonal influenza vaccines*. 2020 [cited 2021 May 6]; Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/annual-update-seasonal-influenza-vaccines.html#s2.1.
37. Ismail, S.J., et al., *Canada's National Advisory Committee on Immunization (NACI): evidence-based decision-making on vaccines and immunization.* Vaccine, 2010. **28 Suppl 1**: p. A58-63.
38. Canada, G.o. *Supply and Distribution of Influenza Vaccine in Canada*. 2017 [cited 2022 February 28]; Available from: https://www.canada.ca/en/public-health/services/immunization/supply-distribution-influenza-vaccine-canada.html.
39. Canada, P.H.A.o., *Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2017–2018 ADDENDUM – Influvac® Use in Children*. 2017, Public Health Agency of Canada: Ottawa.
40. Canada, P.H.A.o., *Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2018–2019 Supplemental Statement - Afluria Tetra® - An Advisory Committee Statement (ACS)*. 2018, Public Health Agency of Canada: Ottawa.
41. Organization, W.H. *Pharmacovigilance*. 2021 [cited 2021 May 6]; Available from: https://www.who.int/medicines/areas/quality_safety/safety_efficacy/safety/en/.
42. Organization, W.H. *Adverse events following immunization (AEFI)*. 2021 [cited 2021 May 6]; Available from: https://www.who.int/vaccine_safety/initiative/detection/AEFI/en/.
43. Canada, G.o. *Adverse events following immunization: Canadian Immunization Guide*. 2020 [cited 2021 May 7]; Available from: https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-2-vaccine-safety/adverse-events-following.html#a.
44. Ahmadipour, N., E. Toth, and B.J. Law, *Canada's Vaccine Vigilance Working Group.* Can Commun Dis Rep, 2014. **40**(Suppl 3): p. 37-40.
45. Celentano, D.D., et al., *Gordis epidemiology*. 6th ed. 2019, Philadelphia, PA U6 - ctx_ver=Z39.88-2004&ctx_enc=info%3Aofi%2Fenc%3AUTF-8&rfr_id=info%3Asid%2Fsummon.serialssolutions.com&rft_val_fmt=info%3Aofi%2Ffmt%3Akev%3Amtx%3Abook&rft.genre=book&rft.title=Gordis+epidemiology&rft.au=Celentano%2C+David+D&rft.au=Szklo%2C+M&rft.au=Gordis%2C+Leon&rft.date=2019-01-01&rft.pub=Elsevier&rft.externalDocID=9865545&paramdict=en-US U7 - eBook: Elsevier.
46. Canada, G.o. *Canadian Adverse Events Following Immunization Surveillance System (CAEFISS)*. 2019 [cited 2021 May 1]; Available from: https://www.canada.ca/en/public-health/services/immunization/canadian-adverse-events-following-immunization-surveillance-system-caefiss.html.

47. Heininger, U., et al., *Guide to active vaccine safety surveillance: Report of CIOMS working group on vaccine safety - executive summary.* Vaccine, 2017. **35**(32): p. 3917-3921.
48. Bettinger, J.A., et al., *The Canadian Immunization Monitoring Program, ACTive (IMPACT): Active surveillance for vaccine adverse events and vaccine-preventable diseases.* Can Commun Dis Rep, 2014. **40**(Suppl 3): p. 41-44.
49. McCarthy, J., et al., *Canadian vaccine research networks: Vaccine safety resources for Canada.* Can Commun Dis Rep, 2015. **41**(Suppl 1): p. 18-23.
50. Halsey, N.A., et al., *The safety of influenza vaccines in children: An Institute for Vaccine Safety white paper.* Vaccine, 2015. **33 Suppl 5**: p. F1-F67.
51. Bettinger, J.A., et al., *2017/18 and 2018/19 seasonal influenza vaccine safety surveillance, Canadian National Vaccine Safety (CANVAS) Network.* Euro Surveill, 2020. **25**(22).
52. Dodds, L., et al., *The association between influenza vaccine in pregnancy and adverse neonatal outcomes.* J Obstet Gynaecol Can, 2012. **34**(8): p. 714-720.
53. Legge, A., et al., *Rates and determinants of seasonal influenza vaccination in pregnancy and association with neonatal outcomes.* Cmaj, 2014. **186**(4): p. E157-64.
54. Chambers, C.D., et al., *Safety of the 2010-11, 2011-12, 2012-13, and 2013-14 seasonal influenza vaccines in pregnancy: Birth defects, spontaneous abortion, preterm delivery, and small for gestational age infants, a study from the cohort arm of VAMPSS.* Vaccine, 2016. **34**(37): p. 4443-9.
55. Ribeiro-Vaz, I., et al., *How to promote adverse drug reaction reports using information systems - a systematic review and meta-analysis.* BMC Med Inform Decis Mak, 2016. **16**: p. 27.
56. Lapphra, K., S. Dobson, and J.A. Bettinger, *Acceptability of Internet adverse event self-reporting for pandemic and seasonal influenza immunization among health care workers.* Vaccine, 2010. **28**(38): p. 6199-202.
57. Harris, P.A., et al., *Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support.* J Biomed Inform, 2009. **42**(2): p. 377-81.
58. Hosmer, D.W., et al., *Applied logistic regression*. Third;3. Aufl.; ed. 2013, Hoboken, New Jersey: Wiley.
59. Haber, P., et al., *Post-licensure surveillance of quadrivalent inactivated influenza (IIV4) vaccine in the United States, Vaccine Adverse Event Reporting System (VAERS), July 1, 2013-May 31, 2015.* Vaccine, 2016. **34**(22): p. 2507-12.
60. Shimabukuro, T.T., et al., *Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS).* Vaccine, 2015. **33**(36): p. 4398-405.
61. Daley, M.F., et al., *The safety of live attenuated influenza vaccine in children and adolescents 2 through 17 years of age: A Vaccine Safety Datalink study.* Pharmacoepidemiol Drug Saf, 2018. **27**(1): p. 59-68.
62. Belshe, R.B., et al., *Live attenuated versus inactivated influenza vaccine in infants and young children.* N Engl J Med, 2007. **356**(7): p. 685-96.
63. Caspard, H., et al., *Evaluation of the safety of live attenuated influenza vaccine (LAIV) in children and adolescents with asthma and high-risk conditions: a population-based prospective cohort study conducted in England with the Clinical Practice Research Datalink.* BMJ Open, 2018. **8**(12): p. e023118.

64. Bettinger, J.A., et al., *Rapid online identification of adverse events after influenza immunization in children by PCIRN's National Ambulatory Network.* Pediatr Infect Dis J, 2014. **33**(10): p. 1060-4.
65. Ackerson, B.K., et al., *Agreement between medical record and parent report for evaluation of childhood febrile seizures.* Vaccine, 2013. **31**(27): p. 2904-9.
66. Tisnado, D.M., et al., *What Is the Concordance between the Medical Record and Patient Self-Report as Data Sources for Ambulatory Care?* Medical Care, 2006. **44**(2): p. 132-140.
67. Fowles, J.B., E.J. Fowler, and C. Craft, *Validation of claims diagnoses and self-reported conditions compared with medical records for selected chronic diseases.* J Ambul Care Manage, 1998. **21**(1): p. 24-34.
68. Inc., S.C., *Canada Product Monograph: AFLURIA® TETRA Quadrivalent Inactivated Influenza Vaccine (Split Virion)*. 2019.
69. Inc., S.C., *Canada Product Monograph: AGRIFLU® (Influenza Vaccine, Surface Antigen, Inactivated)*. 2019.
70. Inc., G., *Canada Product Monograph: FLULAVAL TETRA (2019-2020) Quadrivalent Influenza Vaccine (Split Virion, Inactivated)*. 2019.
71. Inc., G., *Canada Product Monograph: FLUVIRAL (2019-2020) Trivalent Influenza Vaccine (Split Virion, Inactivated)*. 2019.
72. Inc., S.P., *Canada Product Monograph: FLUZONE® Quadrivalent Influenza Virus Vaccine Quadrivalent Types A and B (Split Virion)*. 2018.
73. Inc., B.P., *Canada Product Monograph: INFLUVAC® Influenza vaccine, surface antigen, inactivated*. 2015.
74. Munoz, F.M., et al., *Safety and immunogenicity of three seasonal inactivated influenza vaccines among pregnant women and antibody persistence in their infants.* Vaccine, 2020. **38**(33): p. 5355-5363.
75. Nordin, J.D., et al., *Maternal safety of trivalent inactivated influenza vaccine in pregnant women.* Obstetrics & Gynecology, 2013. **121**(3): p. 519-25.
76. Nordin, J.D., et al., *Maternal influenza vaccine and risks for preterm or small for gestational age birth.* J Pediatr, 2014. **164**(5): p. 1051-1057 e2.
77. Donahue, J.G., et al., *Inactivated influenza vaccine and spontaneous abortion in the Vaccine Safety Datalink in 2012-13, 2013-14, and 2014-15.* Vaccine, 2019. **37**(44): p. 6673-6681.
78. Ahmed, M.A., et al., *Investigating the association of receipt of seasonal influenza vaccine with occurrence of anesthesia/paresthesia and severe headaches, Canada 2012/13-2016/17, the Canadian Vaccine Safety Network.* Vaccine, 2020. **38**(19): p. 3582-3590.
79. Bettinger, J.A., et al., *Successful methodology for large-scale surveillance of severe events following influenza vaccination in Canada, 2011 and 2012.* Euro Surveill, 2015. **20**(29): p. 21189.
80. Larson, H.J., *The biggest pandemic risk? Viral misinformation.* Nature (London), 2018. **562**(7727): p. 309-309.
81. Straus, S.E., J. Tetroe, and I. Graham, *Defining knowledge translation.* CMAJ, 2009. **181**(3-4): p. 165-8.
82. Grimshaw, J.M., et al., *Knowledge translation of research findings.* Implementation Science, 2012. **7**(1): p. 50.

Appendices

Appendix A Categories for describing participant's most severe symptom reported in their online survey from 2014/2015 to 2019/2020.

Symptoms	Child Sample	Pregnant People Sample
Non-Pregnancy Related		
Injection Site Reaction	X	X
Unwell (i.e., tiredness, weakness, muscle aches, joint stiffness, fatigue, or chills)	X	X
Gastrointestinal (i.e., nausea, vomiting, diarrhea, or stomach pain)	X	X
Fever (i.e., temperature ≥38.0°C or >=100.0°F)	X	X
Headache or Migraine	X	X
Hoarseness (i.e., raspy, or strained voice)	X	X
Sore Throat	X	X
Chest Tightness / Discomfort	X	X
Difficulty Breathing / Shortness of breath without throat/tongue swelling	X	X
Wheezing	X	X
Cough	X	X
Croup	X	X
Runny Nose	X	X
Nasal Congestion / Sinus congestion	X	X
Throat Swelling and/or tongue with difficulty breathing or swallowing	X	X
Face Swelling (excluding eyelids)	X	X
Eye Swelling	X	X
Eye Redness	X	X
Eye Pain	X	X
Itchy Eyes	X	X
Eye Discharge	X	X
Ear Symptoms (i.e., earache, ear pain)	X	X
Rash or Hives	X	X
Shingles	X	X
Rapid Heart Rate (i.e., pounding, racing heart or palpitations)	X	X
Neurological (i.e., numbness, tingling, decreased or burning sensation)	X	X
Low Blood Pressure (i.e., dizziness, vertigo, light-headedness)	X	X
Fainting	X	X
Seizure or Convulsion	X	X
Anaphylaxis	X	X
Febrile Seizure	X	X
Persistent Crying (longer than 3 hours)	X	
Difficulty Eating	X	
Urinary Symptoms	X	X
Other	X	X
Pregnancy Related		
Stillbirth or Miscarriage		X
Preterm Labour (regular contractions starting >3 weeks before due date)		X
Preterm Birth (delivery of infant > 3 weeks before due date)		X
High Blood Pressure		X
Eclampsia		X
Vaginal Spotting / Vaginal Bleeding		X
Abnormal Fetal Heart Rate		X
Pregnancy-Related Other		X

Appendix B. Number of seasonal influenza vaccines received in the last 2 years by year, child data from 2013/2014 to 2019/2020 in vaccinated participants only.

Immunization History[1]	2013/2014 n (%)	2014/2015 n (%)	2015/2016 n (%)	2016/2017 n (%)	2017/2018 n (%)	2018/2019 n (%)	2019/2020 n (%)	Total n (%)
0	**125 (0.65)**	**185 (0.96)**	**156 (0.81)**	**203 (1.05)**	**345 (1.78)**	**205 (1.06)**	**368 (1.90)**	**1,587 (8.20)**
IIV	87 (0.45)	99 (0.51)	99 (0.51)	150 (0.78)	307 (1.59)	166 (0.86)	368 (1.90)	1,276 (6.59)
LAIV	38 (0.20)	86 (0.44)	57 (0.29)	53 (0.27)	38 (0.20)	39 (0.20)	N/A[2]	311 (1.61)
1	**270 (1.40)**	**293 (1.51)**	**182 (0.94)**	**300 (1.55)**	**654 (3.38)**	**482 (2.49)**	**720 (3.72)**	**2,901 (14.99)**
IIV	130 (0.67)	130 (0.67)	97 (0.50)	164 (0.85)	536 (2.77)	389 (2.01)	720 (3.72)	2,166 (11.19)
LAIV	140 (0.72)	163 (0.84)	85 (0.44)	136 (0.70)	118 (0.61)	93 (0.48)	N/A[2]	735 (3.80)
2	**1,046 (5.41)**	**1,269 (6.56)**	**1,156 (5.97)**	**1,592 (8.23)**	**3,349 (17.31)**	**2,943 (15.21)**	**3,509 (18.13)**	**14,864 (76.81)**
IIV	346 (1.79)	323 (1.67)	280 (1.45)	587 (3.03)	2,597 (13.42)	2,215 (11.45)	3,509 (18.13)	9,857 (50.94)
LAIV	700 (3.62)	946 (4.89)	876 (4.53)	1,005 (5.19)	752 (3.89)	728 (3.76)	N/A[2]	5,007 (25.87)
Total	**1,441 (7.45)**	**1,747 (9.03)**	**1,494 (7.72)**	**2,095 (10.83)**	**4,348 (22.47)**	**3,630 (18.76)**	**4,597 (23.75)**	**19,352 (100.00)**
IIV	563 (2.91)	552 (2.85)	476 (2.46)	901 (4.66)	3,440 (17.78)	2,770 (14.31)	4,597 (23.75)	13,299 (68.72)
LAIV	878 (4.54)	1,195 (6.18)	1,018 (5.26)	1,194 (6.17)	908 (4.69)	860 (4.44)	N/A[2]	6,053 (31.28)

IIV: Inactivated Influenza Vaccine

LAIV: Live Attenuated Influenza Vaccine

[1] Survey did not capture whether it was the first or second dose for children recommended for two doses of the vaccine within the same influenza season.

[2] LAIV was recommended for use but not available in Canada

Appendix C. Severe health events[1] by immunization history, child data from 2013/2014 to 2019/2020 in participants who received IIV.

Immunization History[2]	Severe Health Event[1]		
	N	Yes (%)	No (%)
0	1,276	100 (7.84)	1,176 (92.16)
1	2,166	171 (7.89)	1,995 (92.11)
2	9,857	673 (6.83)	9,184 (93.17)
Total	**13,299**	**944 (7.10)**	**12,355 (92.90)**

[1] Severe health event: Prevented/stopped activities or missed school or saw healthcare provider
[2] Survey did not capture whether it was the first or second dose for children recommended for two doses of the vaccine within the same influenza season.

Appendix D. Severe health events[1] by immunization history, child data from 2013/2014 to 2018/2019 in participants who received LAIV.

Immunization History[2]	Severe Health Event[1]		
	N	Yes (%)	No (%)
0	280	21 (7.50)	259 (92.50)
1	725	61 (8.41)	664 (91.59)
2	4,979	254 (5.10)	4,725 (94.90)
Total	**5,984[3]**	**336 (5.61)**	**5,648 (94.39)**

[1] Severe health event: Prevented/stopped activities or missed school or saw healthcare provider
[2] Survey did not capture whether it was the first or second dose for children recommended for two doses of the vaccine within the same influenza season.
[3] Excludes 69 child participants from 6-to-23 months who received the LAIV

Appendix E. Univariate logistic regression modelling severe health events[1] with covariates as explanatory variables by IIV status, data from 2013/2014 to 2019/2020.

Variables	IIV			Unvaccinated		
	Estimate	Standard Error	OR (95% CI)	Estimate	Standard Error	OR (95% CI)
Sex						
Male	-	-	Reference	-	-	Reference
Female	-0.1330	0.0677	0.88 (0.77, 1.00)	0.0382	0.0830	1.04 (0.88, 1.22)
Age						
10-14 years old	-	-	Reference	-	-	Reference
5-9 years old	0.1849	0.1155	1.20 (0.96, 1.51)	0.0928	0.1154	1.10 (0.88, 1.38)
2-4 years old	0.5398	0.1111	**1.72 (1.38, 2.13)**	0.4575	0.1169	**1.58 (1.26, 1.99)**
6-23 months	0.5589	0.1177	**1.75 (1.39, 2.20)**	0.5498	0.1785	**1.73 (1.22, 2.46)**
Year						
2019/2020	-	-	Reference	-	-	Reference
2018/2019	0.0636	0.0950	1.07 (0.89, 1.28)	-0.3557	0.1136	**0.70 (0.56, 0.88)**
2017/2018	0.1277	0.0878	1.14 (0.96, 1.35)	-0.1945	0.1362	0.82 (0.63, 1.08)
2016/2017	0.3157	0.1313	**1.37 (1.06, 1.77)**	-0.4703	0.1669	**0.63 (0.45, 0.87)**
2015/2016	0.2278	0.1773	1.26 (0.89, 1.78)	-0.2636	0.1509	0.77 (0.57, 1.03)
2014/2015	0.1475	0.1711	1.16 (0.83, 1.62)	-0.6980	0.973	**0.50 (0.34, 0.73)**
2013/2014	-0.3837	0.2094	0.68 (0.45, 1.03)	-0.1974	0.1641	0.82 (0.60, 1.13)
Site						
Calgary	-	-	Reference	-	-	Reference
Vancouver	0.2078	0.1507	1.23 (0.92, 1.65)	0.1894	0.1666	1.21 (0.87, 1.68)
Toronto	-0.8839	0.2960	**0.41 (0.23, 0.74)**	-0.4889	0.3270	0.61 (0.32, 1.16)
Ottawa	-0.2072	0.3462	0.81 (0.41, 1.60)	0.7037	0.4398	2.02 (0.85, 4.79)
Quebec City	-0.0997	0.1193	0.91 (0.72, 1.14)	-0.9576	0.2049	**0.38 (0.26, 0.57)**
Sherbrooke	-0.0690	0.1025	0.93 (0.76, 1.14)	-0.5856	0.1196	**0.56 (0.44, 0.70)**
Halifax	0.2171	0.5254	1.24 (0.44, 3.48)	0.4055	0.3367	1.50 (0.78, 2.90)
Immunization History[2]						
2	-	-	Reference	N/A	N/A	N/A
1	0.1568	0.0891	1.17 (0.98, 1.39)			
0	0.1488	0.1116	1.16 (0.93, 1.44)			

IIV: Inactivated Influenza Vaccine
OR: Odds Ratio
CI: Confidence Interval
[1] Severe health event: prevented/stopped activities or missed school or saw healthcare provider
[2] Not considered for multivariable logistic regression since it was asked to vaccinated participants only

Appendix F. Univariate logistic regression modelling severe health events[1] with LAIV status and additional covariates as explanatory variables, data from 2013/2014 to 2018/2019.

Variables	LAIV			Unvaccinated		
	Estimate	Standard Error	OR (95% CI)	Estimate	Standard Error	OR (95% CI)
Sex						
Male	-	-	Reference	-	-	Reference
Female	-0.0226	-0.1124	0.98 (0.78, 1.22)	0.1738	0.1022	1.19 (0.97, 1.45)
Age						
10-14 years old	-	-	Reference	-	-	Reference
5-9 years old	0.4953	0.1823	**1.64 (1.15, 2.35)**	0.0418	0.1345	1.04 (0.80, 1.36)
2-4 years old	0.9968	0.1813	**2.71 (1.90, 3.87)**	0.4451	0.1376	**1.56 (1.19, 2.04)**
Year						
2018/2019	-	-	Reference	-	-	Reference
2017/2018	-0.2091	0.2268	0.81 (0.52, 1.27)	0.1501	0.1422	1.16 (0.88, 1.54)
2016/2017	0.2841	0.1933	1.33 (0.91, 1.94)	-0.1969	0.1800	0.82 (0.58, 1.17)
2015.2016	0.1945	0.2029	1.22 (0.82, 1.81)	0.0266	0.1595	1.03 (0.75, 1.40)
2014/2015	0.1425	0.1979	1.15 (0.78, 1.70)	-0.4275	0.2162	0.65 (0.43, 1.00)
2013/2014	-0.0747	0.2213	0.93 (0.60, 1.43)	0.1539	0.1706	1.17 (0.84, 1.63)
Site						
Calgary	-	-	Reference	-	-	Reference
Vancouver	0.7267	0.2127	**2.07 (1.36, 3.14)**	0.4381	0.1810	**1.55 (1.09, 2.21)**
Toronto	0.7926	0.6164	2.21 (0.66, 7.40)	-0.3066	0.3466	0.74 (0.37, 1.45)
Quebec City	0.0293	0.1764	1.03 (0.73, 1.46)	-0.6750	0.2413	**0.51 (0.32, 0.82)**
Sherbrooke	0.2611	0.1305	**1.30 (1.01, 1.68)**	-0.5244	0.1400	**0.59 (0.45, 0.78)**
Immunization History[2]						
2	-	-	Reference	N/A	N/A	N/A
1	0.5348	0.1485	**1.71 (1.28, 2.28)**			
0	0.4099	0.2359	1.51 (0.95, 2.39)			

LAIV: Live Attenuated Influenza Vaccine
OR: Odds Ratio
CI: Confidence Interval
[1] Severe health event: Prevented/stopped activities or missed school or saw healthcare provider
[2] Not considered for multivariable logistic regression since it was asked to vaccinated participants only

Appendix G. Description for "other" most severe symptom category, child data from 2014/2015 to 2019/2020.

Other Severe Symptom[1]					
IIV	N	LAIV	N	Unvaccinated[2]	N
Hand, foot, and mouth disease	2	Ankle swelling	1	Strep throat	4
Mouth sore	2	Hand, foot, and mouth disease	1	Appendicitis	2
Chicken pox	1	Nosebleed	1	Low saturation	2
Edema over the whole body	1	Pimples	1	Adenitis	1
Fractured coccyx	1	Scarlet fever	1	Ankle pain and swelling	1
Grunting	1	Sleeping difficulty	1	Bump in the groin	1
Infection in the groin	1	Tonsillitis	1	Broken tooth	1
Swelling on legs and red patches	1	**Total**	**7**	Mouth sores	1
Tremor	1			Chicken pox	1
Yeast infection	1			Hand, foot, and mouth disease	1
Total	**12**			Head injury	1
				Hernia	1
				Injured finger	1
				Pimples	1
				Total	**19**

IIV: Inactivated Influenza Vaccine

LAIV: Live Attenuated Influenza Vaccine

[1] Most severe symptom was asked to participants who indicated a severe health event

[2] Unvaccinated participants in the IIV and LAIV group combined

Appendix H. Descriptions of "multiple" most severe symptom category for IIV group, child data from 2014/2015 to 2019/2020.

Vaccinated Group			
Symptom 1	Symptom 2	Symptom 3	N
Cough	Runny Nose		3
Cough	Congestion		2
Cough	Unwell		2
Fever	Cough		2
Fever	Unwell		2
Gastrointestinal	Low Blood Pressure		2
Runny Nose	Congestion		2
Unwell	Headache		2
Congestion	Other (Anorexia)		1
Cough	Gastrointestinal		1
Cough	Sore Throat		1
Fever	Sore Throat		1
Fever	Injection Site Reaction		1
Fever	Congestion		1
Fever	Hives		1
Unwell	Persistent Crying		1
Headache	Ear Symptom		1
Gastrointestinal	Unwell		1
Sore Throat	Ear Symptom		1
Gastrointestinal	Congestion		1
Wheezing	Other (Eczema)		1
Fever	Ear Symptom		1
Fever	Headache		1
Fever	Gastrointestinal		1
Sore Throat	Congestion		1
Runny Nose	Congestion	Unwell	1
Cough	Fever	Gastrointestinal	1
Fever	Unwell	Gastrointestinal	1
Fever	Unwell	Difficulty Eating	1
Fever	Unwell	Headache	1
Gastrointestinal	Unwell	Injection Site Reaction	1
Injection Site Reaction	Fever	Unwell	1
Wheezing	Cough	Croup	1
Total			**44**

IIV: Inactivated Influenza Vaccine

Appendix I. Descriptions of "multiple" most severe symptom category for LAIV group, child data from 2014/2015 to 2019/2020.

Vaccinated Group					
Symptom 1	Symptom 2	Symptom 3	Symptom 4	Symptom 5	N
Fever	Cough				2
Cough	Gastrointestinal				1
Cough	Runny Nose				1
Congestion	Fever				1
Unwell	Runny Nose				1
Fever	Other (Amorphous)				1
Fever	Other (Itching)				1
Fever	Headache				1
Gastrointestinal	Difficulty Eating				1
Headache	Rash				1
Headache	Gastrointestinal				1
Unwell	Runny Nose				1
Cough	Congestion	Fever			1
Congestion	Cough	Other (Sleep)			1
Congestion	Runny Nose	Cough			1
Fever	Unwell	Difficulty Eating			1
Runny Nose	Congestion	Unwell			1
Runny Nose	Sore Throat	Cough			1
Fever	Unwell	Cough	Runny Nose	Gastrointestinal	1
Total					**20**

LAIV: Live Attenuated Influenza Vaccine

Appendix J. Descriptions of "multiple" most severe symptom category for unvaccinated group, child data from 2014/2015 to 2019/2020.

Unvaccinated Group		
Symptom 1	Symptom 2	N
Cough	Difficulty Breathing	2
Cough	Runny Nose	2
Congestion	Runny Nose	2
Cough	Congestion	1
Cough	Fever	1
Cough	Difficulty Eating	1
Cough	Wheezing	1
Gastrointestinal	Runny Nose	1
Gastrointestinal	Headache	1
Gastrointestinal	Fever	1
Low Blood Pressure	Wheezing	1
Sore Throat	Difficulty Breathing	1
Total		**15**

Appendix K. Most severe symptoms reported in the online survey and the telephone follow-up report, child data from 2016/2017 to 2019/2020.

Most Severe Symptom Reported in Online Survey	N	Most Severe Symptom Reported in Telephone Report	N (%)[1]
Fever	31	Fever	24 (77.42)
		Cough	2 (6.45)
		Ear Symptoms	2 (6.45)
		Gastrointestinal	1 (3.23)
		Headache	1 (3.23)
		Shingles	1 (3.23)
Gastrointestinal	22	Gastrointestinal	19 (86.36)
		Ear Symptoms	2 (9.09)
		Fever	1 (4.55)
Injection Site Reaction[2]	17	Injection Site Reaction[2]	17 (100.00)
Ear Symptoms	16	Ear Symptoms	12 (75.00)
		Fever	3 (18.75)
		Croup	1 (6.25)
Cough	15	Cough	9 (60.00)
		Fever	3 (20.00)
		Congestion	1 (6.67)
		Ear Symptoms	1 (6.67)
		Croup	1 (6.67)
Hives	13	Hives	12 (92.31)
		Injection Site Reaction[2]	1 (7.69)
Unwell	5	Injection Site Reaction[2]	3 (60.00)
		Unwell	1 (20.00)
		Ear Symptoms	1 (20.00)
Sore Throat	4	Sore Throat	3 (75.00)
		Fever	1 (25.00)
Breathing Difficulty	4	Breathing Difficulty	4 (100.00)
Croup	4	Croup	2 (50.00)
		Cough	1 (25.00)
		Breathing Difficulty	1 (25.00)
Red Eyes	3	Red Eyes	2 (66.67)
		Unwell	1 (33.33)
Headache	3	Headache	1 (33.33)
		Fever	1 (33.33)
		Hives	1 (33.33)
Wheezing	3	Wheezing	3 (100.00)
Runny Nose	3	Ear Symptoms	2 (66.67)
		Red Eyes	1 (33.33)
Face Swelling	2	Face Swelling	1 (50.00)
		Hives	1 (50.00)
Urinary Symptoms	2	Urinary Symptoms	1 (50.00)
		Gastrointestinal	1 (50.00)
Congestion	1	Gastrointestinal	1 (100.00)
Itchy Eyes	1	Red Eyes	1 (100.00)
Eye Tears	1	Red Eyes	1 (100.00)
Seizure	1	Seizure	1 (100.00)
Difficulty Eating	1	Difficulty Eating	1 (100.00)
Total	**152**	**Total**	**152 (100.00)**

IQR: Interquartile range

[1] Denominator is the total sample of the most severe symptom in the online survey

[2] Asked to vaccinated participants only.

Appendix L. Immunization history in vaccinated pregnant participants in the last two years, data from 2016/2017 to 2019/2020.

Number of Vaccines Received	2016/2017 n (%)[1]	2017/2018 n (%)[1]	2018/2019 n (%)[1]	2019/2020 n (%)[1]	Total n (%)[1]
0	22 (1.63)	38 (2.81)	37 (2.74)	73 (5.40)	170 (12.57)
1	25 (1.85)	50 (3.70)	64 (4.73)	72 (5.33)	211 (15.61)
2	189 (13.98)	263 (19.45)	238 (17.60)	281 (20.78)	971 (71.82)
Total	**236 (17.46)**	**351 (25.96)**	**339 (25.07)**	**426 (31.51)**	**1,352 (100.00)**

[1] Percentages are calculated based on the total vaccinated sample (n=1,352).

Appendix M. Number of seasonal influenza vaccines received in the last 2 years by severe health event[1] status, pregnancy data from 2016/2017 to 2019/2020 in vaccinated participants only.

Immunization History	Severe Health Event[1]		
	N	Yes (%)	No (%)
0	170	5 (2.94)	165 (97.06)
1	211	7 (3.32)	204 (96.68)
2	971	46 (4.74)	925 (95.26)
Total	**1,352**	**58 (4.29)**	**1,294 (95.71)**

[1] Severe health event: prevented/stopped activities or missed school or saw healthcare provider

Appendix N. Univariate logistic regression modelling severe health event[1] with covariates as explanatory variables by vaccination status, pregnancy data from 2017/2018 to 2019/2020.

Variables	Vaccinated			Unvaccinated		
	Estimate	Standard Error	OR (95% CI)	Estimate	Standard Error	OR (95% CI)
Trimester						
1st	-	-	Reference	-	-	Reference
2nd	-0.2401	0.3728	0.79 (0.38, 1.63)	-1.3031	0.5958	**0.27 (0.09, 0.87)**
3rd	-0.5332	0.4181	0.59 (0.26, 1.33)	-0.4772	0.5242	0.62 (0.22, 1.73)
Age						
30-49 years old	-	-	Reference	-	-	Reference
15-29 years old	-0.1123	0.3326	0.89 (0.47, 1.72)	-0.7696	0.6226	0.46 (0.14, 1.57)
Year						
2019/2020	-	-	Reference	-	-	Reference
2018/2019	-0.4986	0.3948	0.61 (0.28, 1.32)	-0.7349	0.5827	0.48 (0.15, 1.50)
2017/2018	-0.3602	0.3729	0.70 (0.34, 1.45)	0.0249	0.5163	1.03 (0.37, 2.82)
2016/2017	0.2726	0.3592	1.31 (0.65, 2.66)	-0.5860	0.5835	0.56 (0.18, 1.74)
Site						
Calgary	-	-	Reference	-	-	Reference
Vancouver	0.4513	0.3604	1.57 (0.78, 3.18)	-0.2231	0.6948	0.80 (0.21, 3.12)
Toronto	-0.3948	0.4680	0.67 (0.27, 1.69)	-0.7087	0.8051	0.49 (0.10, 2.39)
Quebec City	-1.4255	0.4979	**0.24 (0.09, 0.64)**	-1.3218	0.8007	0.27 (0.06, 1.28)
Sherbrooke	-1.0023	0.4642	**0.37 (0.15, 0.91)**	-0.3185	0.5847	0.73 (0.23, 2.29)
Halifax	-1.1740	0.7452	0.31 (0.07, 1.33)	0.5754	0.5639	1.78 (0.59, 5.37)
Immunization History[2]						
2	-	-	Reference	N/A	N/A	N/A
1	0.1420	0.5950	1.15 (0.36, 3.70)			
0	0.5139	0.4796	1.67 (0.65, 4.28)			

OR: Odds Ratio

CI: Confidence Interval

[1] Severe health event: Prevented/stopped activities or missed school or saw healthcare provider

[2] Not considered for multivariable logistic regression since it was asked to vaccinated participants only

Appendix O. Descriptions for "multiple" most severe symptom category for vaccinated group, pregnancy data from 2016/2017 to 2019/2020.

	Vaccinated Group	
Symptom 1	Symptom 2	N
Congestion	Runny Nose	2
Gastrointestinal	Difficulty Eating	1
Sore Throat	Cough	1
Unwell	Gastrointestinal	1
Unwell	Congestion	1
Total		**6**