THE USE AND NEUROLOGICAL SAFETY OF THE QUADRIVALENT HUMAN PAPILLOMAVIRUS (HPV) VACCINE: THE ONTARIO GRADE 8 HPV VACCINE COHORT STUDY

by

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Abstract

The quadrivalent (q-) human papillomavirus (HPV) vaccine is praised for its near perfect efficacy of 98% in the per-protocol population and minimal safety concerns. Adherence to the dosing schedule of 0, 2 and 6 months outside clinical trials has not yet been described. Furthermore, clinical trials were underpowered to detect rare, but serious, adverse events including convulsions, seizures and epilepsy in young girls targeted by American and Canadian national advisory committees.

This retrospective cohort study followed Grade 8 girls eligible for Ontario’s HPV immunization program during the 2007/08 to 2010/11 campaign years. Using Ontario’s immunization and health databases, baseline characteristics, qHPV vaccination, dates of qHPV vaccination and diagnoses of serious neurological events were identified for each cohort member. The proportions of girls who initiated and completed the qHPV vaccine program were determined. Adherence to the recommended dosing intervals and for ‘time-to-series completion’ was calculated as the proportion of eligible girls whose number of days between doses complied with the recommended dosing interval. A self-matched, case only approach was used to estimate the age-adjusted rate ratio (RR) of neurological events in the 0-30 day period following qHPV vaccination. The primary study endpoint was a composite of the first occurrence of a convulsion, seizure or epilepsy. Secondarily, an epileptic seizure only endpoint was assessed, as were the influence of a number of predisposing risk factors.

An overall uptake of 50.24% was observed, of which, 87.02% received at least three doses. Adherence to the recommended dosing interval was most difficult in scheduling of the second dose (70.80%). There was no increased risk observed for the
primary endpoint in the 0-30 days following qHPV vaccination (RR 1.01, 95% CI 0.92-1.10). However, this association was modified in girls with predisposing risk factors for epilepsy. There was an increased risk observed for the epileptic seizure only endpoint (RR 1.64, 95% CI 1.28-2.10).

In Ontario, the overall uptake of the qHPV vaccine is low. Once initiated, series completion is high, with the majority receiving the vaccine in a timely manner. A risk for epileptic seizures following vaccination may be limited to girls with predisposing risk factors.
Co-Authorship

This thesis presents the work of Ms. W. Ting Lim in collaboration with her advisors, Dr. Kimberly A. Sears and Dr. Linda E. Lévesque.

**Manuscript 1**: Human Papillomavirus (HPV) Vaccination Status and Dose Timing in a Publicly Funded Immunization Program: The Ontario Grade 8 HPV Vaccine Cohort Study. Dr. Lévesque is accredited for the idea to describe and assess the uptake, series completion and adherence to the dose scheduling of the quadrivalent HPV (qHPV) vaccine. The statistical analysis was conducted by Ms. Lim, with the support and guidance of Ms. Lindsey Colley and Dr. Lévesque. The interpretation of results and writing of the manuscript were the work of Ms. Lim, with conceptual and editorial feedback from Dr. Lévesque and Dr. Sears.

**Manuscript 2**: The Risk of Serious Neurological Events Associated with the Use of the Quadrivalent Human Papillomavirus (HPV) Vaccine: The Ontario Grade 8 HPV Vaccine Cohort Study. The idea to assess the risk for serious neurological events following qHPV vaccination was discussed and decided upon by Ms. Lim and Dr. Lévesque. The statistical analysis was conducted by Ms. Lim with the guidance and support of Ms. Colley and Dr. Lévesque. The interpretation of results and writing of the manuscript were the work of Ms. Lim, with conceptual and editorial feedback from Dr. Lévesque and Dr. Sears.

Ms. Lim wrote the other chapters of the thesis (introduction, literature review, methods, general discussion and appendices), with editorial feedback and advice from Dr. Lévesque and Dr. Sears.
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<tbody>
<tr>
<td>ACCS</td>
<td>Ambulatory Care Classification System</td>
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<tr>
<td>AEFI(s)</td>
<td>Adverse Event(s) Following Immunization</td>
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<tr>
<td>AIS</td>
<td>Adenocarcinoma <em>in situ</em></td>
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<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CIHI</td>
<td>Canadian Institute for Health Information</td>
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<tr>
<td>CIN</td>
<td>Cervical Intraepithelial Neoplasia</td>
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<tr>
<td>CNS</td>
<td>Central Nervous System</td>
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<tr>
<td>DAD</td>
<td>Discharge Abstract Database</td>
</tr>
<tr>
<td>DTaP</td>
<td>Diphtheria, Tetanus and Acellular Pertussis</td>
</tr>
<tr>
<td>DTP</td>
<td>Diphtheria, Tetanus and Whole-Cell Pertussis</td>
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<tr>
<td>ED</td>
<td>Emergency Department</td>
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<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>(q)HPV</td>
<td>(Quadrivalent) Human Papillomavirus</td>
</tr>
<tr>
<td>ICD-9 or -10CA</td>
<td>International Classification of Diseases, 9<em>th</em> or 10<em>th</em>-Canadian Enhancement Code Revisions</td>
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<tr>
<td>ICES</td>
<td>Institute for Clinical Evaluative Sciences</td>
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<tr>
<td>IKN</td>
<td>ICES Key Number</td>
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<tr>
<td>ILAE</td>
<td>International League Against Epilepsy</td>
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<tr>
<td>IQR</td>
<td>Interquartile Range</td>
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<tr>
<td>IRIS</td>
<td>Immunization Record Information System</td>
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<tr>
<td>KFL&amp;A</td>
<td>Kingston, Frontenac, Lennox and Addington Public Health</td>
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<tr>
<td>LPHA(s)</td>
<td>Local Public Health Agency(-ies)</td>
</tr>
<tr>
<td>MMR</td>
<td>Measles, Mumps and Rubella</td>
</tr>
<tr>
<td>MOHLTC</td>
<td>Ministry of Health and Long-Term Care</td>
</tr>
<tr>
<td>NACRS</td>
<td>National Ambulatory Care Reporting System</td>
</tr>
<tr>
<td>NES</td>
<td>Non-Epileptic Events/Seizures</td>
</tr>
<tr>
<td>NNH</td>
<td>Number Needed to Harm</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
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<tr>
<td>NPV</td>
<td>Negative Predictive Value</td>
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<td>OHIP</td>
<td>Ontario Health Insurance Plan</td>
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<tr>
<td>PPV</td>
<td>Positive Predictive Value</td>
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<tr>
<td>RCTs</td>
<td>Randomized Controlled Trials</td>
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<tr>
<td>RPDB</td>
<td>Registered Persons Database</td>
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<tr>
<td>RR</td>
<td>Rate Ratio</td>
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<tr>
<td>SCCS</td>
<td>Self-Controlled Case Series</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>SES</td>
<td>Socioeconomic Status</td>
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<tr>
<td>US</td>
<td>United States</td>
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<tr>
<td>VAERS</td>
<td>Vaccine Adverse Events Reporting System</td>
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<tr>
<td>VaIN</td>
<td>Vaginal Intraepithelial Neoplasia</td>
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<tr>
<td>VIN</td>
<td>Vulvar Intraepithelial Neoplasia</td>
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<tr>
<td>VLPs</td>
<td>Virus-Like Particles</td>
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Chapter 1

Introduction

1.1 Thesis Introduction

Seizures may be epileptic or non-epileptic. Epileptic seizures are transient and spontaneous interruptions of normal brain function caused by disorganized and abnormally excited electrical signals in the brain, whereas non-epileptic seizures are clinical manifestations presumed to be unrelated to an abnormal and excessive discharge of neurons in the brain.\textsuperscript{1}

Recurrent epileptic seizures are characteristic of the neurological disorder known as epilepsy.\textsuperscript{1, 2} Many, if not all, epileptic seizures involve loss of awareness and some may cause convulsions (i.e., uncontrollable twitching or shaking of the body);\textsuperscript{1-3} thus, the terms convulsion and seizure are commonly used interchangeably. The World Health Organization has estimated that around 50 million people of all ages worldwide are affected by this disease.\textsuperscript{4} The incidence of epilepsy in Canada has been poorly studied. One study estimated the overall incidence rate for children aged 1 month to 16 years in Nova Scotia to be 41 per 100,000 person-years;\textsuperscript{5} this is similar to the rate estimated by a well-recognized incidence study in Rochester, Minnesota, USA.\textsuperscript{6} The prevalence of epilepsy in Canada has been better examined, and in Ontario, studies have consistently reported a prevalence of 5-6 per 1,000 persons.\textsuperscript{7, 8}

In children, a diagnosis of epilepsy is typically made when a child has had at least two or more unprovoked seizures; epileptic seizures may be experienced by a person who does not have epilepsy. This diagnostic criterion is based on the observation that the risk
of seizure recurrence increases to 40-50% after the first seizure, and up to 80% after a second seizure.\textsuperscript{9-11} Epilepsy has been associated with increased risk for premature mortality,\textsuperscript{12} decreased quality of life,\textsuperscript{13} comorbid somatic conditions such as stomach/intestinal ulcers, stroke, urinary incontinence, bowel disorders, migraines, Alzheimer’s disease, and chronic fatigue,\textsuperscript{14} psychiatric and behavioral problems (e.g., anxiety and depression),\textsuperscript{15} and decreased cognitive function including learning disabilities\textsuperscript{16}. In comparison with other chronic diseases, people with epilepsy are more likely to see a family doctor, specialist, or psychologist/counselor, visit the emergency room, and be admitted to hospital.\textsuperscript{8} Standardized mortality ratios, commonly determined to compare mortality rates of those with epilepsy to a referent population, are highest amongst children with epilepsy.\textsuperscript{16} Additionally, people with epilepsy suffer greatly from enacted or perceived stigma that is based on misconceptions and misunderstandings of the disease.\textsuperscript{15, 17, 18}

A convulsion following syncope (fainting) is known as a non-epileptic physiological seizure or an anoxic seizure. These convulsive attacks are due to physiological disturbances in brain function rather than electrical disturbances;\textsuperscript{1} however, differentiation between epileptic and non-epileptic seizures has proven to be difficult as they share clinical features and on occasion, non-epileptic seizures may trigger epileptic events\textsuperscript{19, 20}. Due to frequent misdiagnosis, the incidence of physiological non-epileptic seizures is unknown.

Although rare, convulsions, seizures and epilepsy have been reported following immunization with vaccines, including the quadrivalent (q-) human papillomavirus (HPV) vaccine (Gardasil\textsuperscript{®}). By December 31, 2008, the Vaccine Adverse Events
Reporting System (VAERS), a passive surveillance system that was implemented by the United States (US) Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC), had received 12,424 reports of adverse events following Gardasil® vaccination in the US; 772 (6.2%) of these reports were considered to be serious in nature. Of these 772 serious event reports, 8.8% were identified as convulsions. These reports have raised concerns regarding the qHPV vaccine’s potential to cause serious neurological events.

Numerous clinical trials have established the efficacy of the qHPV vaccine for preventing HPV infections and pre-cancerous cervical lesions; unfortunately, these trials were underpowered to assess the risk of rare, but serious, adverse events including neurological events such as convulsions, seizures, and epilepsy. Moreover, less than 5% of participants in these trials were under the age of 16. These findings suggest that information about the safety of this vaccine is limited, particularly for the younger populations targeted by provincial HPV immunization programs.

1.2 Objectives
The objectives of this thesis were as follows:

1. To assess the uptake, series completion and the adherence to dose interval recommendations of the qHPV vaccine administered to Grade 8 girls in school-based clinics in Ontario, Canada.

2. To assess the risk of neurological events, including convulsions, seizures and epilepsy, following immunization with the qHPV vaccine within Ontario’s Grade 8 HPV immunization program.
1.3 Thesis Organization

This thesis conforms to the guidelines outlined by the Queen’s University School of Graduate Studies\textsuperscript{23} and Department of Community Health and Epidemiology\textsuperscript{24}. The following chapter of this thesis provides a literature review outlining current evidence background information for vaccine-related adverse events, with emphasis on the qHPV vaccine and neurological events. The third chapter of this thesis is a detailed description of the methods used, including information on the data sources and statistical methods employed. The fourth chapter presents the first thesis study of two, which describes the uptake and series completion of the qHPV vaccination program, as well as the adherence to the recommended qHPV dosing schedule in school-based clinics in Ontario. The fifth chapter presents the second thesis study, which assesses the risk of neurological events, including convulsions, seizures and epilepsy, following qHPV vaccination. The sixth and final chapter of this thesis contains a summary of both studies, and is followed by a general discussion and conclusions.

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Chapter 2

Literature Review

2.1 Vaccines and Adverse Events

Vaccines are biological preparations intended to prevent future infections of disease in an individual. If the vaccine is successful, when the host is exposed to the pathogen in the future, a specific immune response will be immediate and sufficiently strong to kill the invading organism before it has the opportunity to multiply and cause disease. The active component of a vaccine is an infectious disease antigen that has been altered from its original form to induce specific and active immune response.¹ Vaccines may be classified as live attenuated (e.g. polio, measles, mumps and rubella), killed whole organisms (e.g. polio, pertussis), or subunit (e.g. hepatitis B, human papillomavirus (HPV)) vaccines.²

In some individuals, the initial immune response to the vaccine may be exaggerated and result in vaccine-induced adverse events. Adverse events following immunization (AEFIs) are defined as any undesirable experience associated with the use of a vaccine in a patient; they may be local or systemic, immediate or delayed, inconsequential or serious. An AEFI is considered to be serious when the event following use of the vaccine (1) results in death, (2) is life-threatening, (3) requires inpatient hospitalization or prolongation of existing hospitalization, (4) results in significant, persistent, or permanent disability, (5) results in a congenital anomaly, or (6) requires intervention to prevent permanent impairment or damage.³ AEFIs may be attributable to impurities derived from the active vaccine component, the production process or
additives used in vaccine formulation such as adjuvants. Adjuvants are non-antigens that are used to enhance the immunogenicity of the co-administered antigenic component, and thus, may also cause an exaggerated immune response in an individual resulting in an adverse event. For example, aluminum-containing adjuvants, like that contained in the quadrivalent HPV (qHPV) vaccine, have the potential to cause local and systemic adverse events and have even been implicated in the development of autoimmune diseases.

Studies published to date have provided both experimental and clinical evidence to suggest that activation of the immune system may promote epileptic seizure onset. It is commonly accepted that infection with a virus may pose a risk for seizure onset as the immune response triggered by an infection may cause viral encephalitis (inflammation of the brain). Vezzani and Granata reviewed experimental and clinical evidence to conclude that inflammation may be a common factor contributing, or predisposing, to the occurrence of seizures in various forms of epilepsy with differing aetiologies; however, they noted that when the original description of the disease did not include the presence of specific pathogens (viral particles or bacteria), the initial trigger of the inflammatory response in the brain remained unknown. From the evidence they presented, they were able to suggest that the immune/inflammatory response trigger may either be within the central nervous system (CNS) or that the CNS was a target of immune/inflammatory response that originated within peripheral lymphoid tissues. A few years later, Riazi et al. proposed that peripheral inflammation could induce a corresponding inflammatory response in the brain and consequently cause transient or long-term effects on seizure susceptibility either through the disruption of the blood-brain barrier thereby altering
cerebral neurotransmission or other mechanisms, such as the direct effects of cytokines on neurons. In addition, evidence suggests that it may be the chronic inflammation of the brain that predisposes an individual to the occurrence of an epileptic seizure, although the etiologically relevant risk window is unknown.

Although evidence suggests biological plausibility for an epileptic seizure to occur following vaccination, it is also highly possible that a seizure following immunization may be a reflex anoxic seizure. A reflex anoxic seizure is a non-epileptic physiological seizure also known as “syncope attack” or “convulsive syncope”. Often, this type of seizure is triggered by a painful or frightening stimulus including venepuncture (i.e., needle injections), which, by vagal stimulation, causes pronounced bradycardia and subsequent relative cerebral ischemia (insufficient circulation to the brain), thereby inducing an anoxic seizure. Syncope-induced seizures are therefore likely to occur shortly after vaccination. Moreover, it is important to note that it has been suggested that a syncope attack may induce epileptic seizures, the biological mechanism for epileptic anoxic seizures is unknown.

2.2 HPV Vaccine and Adverse Events

2.2.1 Clinical Trials

Before a vaccine is made available on the market, it must undergo clinical trials to determine and evaluate its efficacy and safety. Rambout et al. conducted a systematic review and meta-analysis of 6 premarketing randomized controlled trials (RCTs) of the prophylactic qHPV vaccine and of another bivalent HPV vaccine. As RCTs are generally designed to establish a treatment’s efficacy, the primary objective of the
meta-analysis was to determine the vaccines’ efficacies in preventing HPV infection and pre-cancerous cervical disease. A brief section addressing the occurrence of adverse events from these RCTs reported that the majority of adverse events reported were minor, and that the incidence of serious adverse events and death were balanced between the vaccine and control groups. Although adverse events reported in premarketing trials were generally minor, it is important to bear in mind that RCTs follow a relatively small number of individuals in comparison to the numbers that will actually be exposed to the treatment once commercially available. Even when pre-licensure trials follow thousands of subjects, they are not large enough to detect rare adverse events; thus, it is of no surprise that a systematic review conducted by our research group found that RCTs for the qHPV vaccine were underpowered (<80%) to detect rare, but serious, adverse events.

2.2.2 Vaccine Adverse Event Reporting System: A Post-Marketing Surveillance System

Recognizing that vaccine trials are too small to detect rare adverse events, the United States (US) Food and Drug Administration (FDA), in collaboration with the Centers for Disease Control and Prevention (CDC), implemented the Vaccine Adverse Event Reporting System (VAERS) in 1990. VAERS is a passive surveillance system that relies on the submission of voluntary reports of illness after vaccination, and is used to detect early safety signals and generate hypotheses about possible new adverse events or changes in frequency of known ones for any US-licensed vaccine; this is a key component of post-licensure vaccine safety surveillance. VAERS may be useful for detecting rare adverse events in a cost-effective and timely manner, as well as identifying potential risk factors for specific AEFIs, however, this system of post-marketing
surveillance has a number of important limitations. The limitations include: 1) an inability to assess causality; 2) use of reports that are not standardized and often provide inadequate information or lack of verification of the adverse event; 3) under- and over-reporting of events due to the voluntary nature of this system resulting in a potential misrepresentation of the numerator for calculation of incident rate; 4) lack of an appropriate denominator for calculating incident rates; 5) lack of information on adverse events in unvaccinated persons; and 6) confounding from the concomitant use of other drugs and/or concomitant disease.\textsuperscript{19-22} Despite these important limitations, a number of post-marketing vaccine safety studies have been carried out;\textsuperscript{23, 24} these have been criticized and their conclusions called into question.\textsuperscript{21}

VAERS is only able to provide information on the temporal sequence of a suspected adverse event. The only requirement to submit a report is that the administration of the vaccine must precede the onset of the adverse event; the association only needs to be suspected and does not need to be established.\textsuperscript{21} Although temporality is essential to attribute causation, more information and evidence is needed. Chen \textit{et al.} list strength of association, analytical bias, biological gradient/dose-response, statistical significance, consistency, and biological plausibility/coherence as the basis for assessing causality for most rare vaccine adverse events;\textsuperscript{25} the fulfillment of these criteria is not possible using data from VAERS.

There is a significant amount of variability of reporting standards to VAERS. The submissions are not formal case reports, but mere descriptions of symptoms and signs temporally associated with the vaccination(s);\textsuperscript{21} often, the information provided is incomplete or inaccurate.\textsuperscript{19, 21} The lack of information does not provide a high degree of
diagnostic certainty for studies wishing to use these data. Additionally, the events reported have not been verified to have occurred. An investigation of deaths reported to VAERS found that the actual cause of death was significantly different from that reported for 24% of cases; there was even one case where the subject of the report did not actually die.

Since VAERS relies solely on voluntary submissions of AEFIs, this database is prone to an under- and over-reporting of AEFIs. Under-reporting may occur if the adverse event is delayed post-vaccination and/or if the association between the vaccine and the adverse event has not been made. Reporting bias, whereby events occurring soon after vaccination are more likely to be reported than those occurring later, is a common problem with post-marketing surveillance systems such as VAERS that rely on voluntary reporting of adverse events. There are a few selected adverse events for specified vaccines that are required to be reported by vaccine providers as associations have already been established; however, for most AEFIs, VAERS is likely to capture only a small proportion of all suspected AEFIs. On the other hand, media reporting of a suspected association may influence the amount of reporting to VAERS and result in an over-reporting of events. Also, the longer a vaccine is on the market, the more the levels of reporting to VAERS decrease, as it has been shown that new vaccines tend to have higher reporting rates than older vaccines. These influences on reporting rates clearly highlight the limitations of voluntary passive surveillance systems such as VAERS. Furthermore, the over- and under-reporting of events, and the lack of verification of diagnoses, result in an unstable and unreliable numerator for calculating the incidence rate of an AEFI.
Incidence rates not only require that the number of events for the numerator be valid, they also require knowledge of the number of people “at risk” or “exposed” (i.e., those who actually received the vaccine) for the numerator; information that cannot be determined from VAERS\(^21\). At best, investigators may be able to calculate a “reporting rate” for an AEFI where the proportion of reports per doses of vaccine distributed/sold is determined. Even then, the rate calculated is not an accurate representation of a true incidence rate as the investigator does not know if all doses distributed/sold were administered or how many individuals received multiple doses of the vaccine during the year;\(^21\) the latter representing a significant problem for vaccines requiring multiple doses, such as the qHPV vaccine. Without true incidence rates, relative risks for adverse events associated with specific vaccines cannot be reliably estimated.

An important limitation associated with using the VAERS registry for the evaluation of serious adverse events, is the lack of information on serious adverse events in unvaccinated persons.\(^19\text{-}22\) Without information on the unvaccinated group, there is no comparator group data to determine a relative risk for serious adverse events. In a hepatitis B post-marketing study by Geier \textit{et al.}, researchers attempted to overcome this limitation by using another vaccine as a “control” group;\(^23\) however, differences in immunization ages for each vaccine may lead to confounding, and AEFIs may simply be reflecting the background risk of illness in that age group\(^21\). Even if both vaccines were administered to similar age groups, the resulting relative risk calculated would not be of any significance since relative risks are a ratio of the incidence rates, and incidence rates cannot be calculated from VAERS due to its voluntary nature and lack of appropriate denominator.\(^19\text{-}21\) More importantly, the relative risk calculated would merely indicate
whether one vaccine has a greater incidence or reporting rate of a specific AEFI than the other, rather than provide information on the independent risk associated with the vaccine under study. For example, a relative risk of 1.0 for neurological events could indicate that neither vaccine causes a neurological event or that both cause harm.

Lastly, confounding by other drug use and disease may be present amongst the reports submitted to VAERS. Since information on a subject’s drug use or present condition/disease does not have to be disclosed, the occurrence of an adverse event may actually be caused by these underlying factors rather than by the vaccine itself.

With the limitations listed above, VAERS should only be used to detect early warnings signs and generate, not test, hypotheses regarding vaccine safety.

2.2.2.1 Neurological Events in VAERS

Reports to VAERS of tonic-clonic (jerking) movements and seizure-like activity that may be experienced with syncope (fainting) warranted a label revision for the qHPV vaccine, Gardasil®, in 2009. An exploration of the VAERS databases also revealed reports of new epilepsy diagnoses following immunization with the qHPV vaccine.

2.2.3 Observational Studies

As the qHPV vaccine is relatively new, no observational studies have yet to be conducted to determine whether neurological events reported to date including convulsions, seizures or epilepsy, are a coincidence or a consequence of being immunized with the qHPV vaccine. However, observational studies assessing the risk for febrile seizures (i.e., epileptic seizures associated with a significant rise in body temperature in children under the age of 5 years) following diphtheria, tetanus and whole-
cell pertussis (DTP), and measles, mumps and rubella (MMR) vaccinations have been conducted, and both vaccines have been found to be associated with increased risks for febrile seizures. Although the compositions of these vaccines are not equivalent to that of the qHPV vaccine and febrile seizures cease to occur after the age of 5, these associations may still provide insight to the potential risk for neurological events following the qHPV vaccine.

Neurological events have been linked to DTP vaccination since 1933. In 1983, Hirtz et al. followed 39 children and found an increased risk for febrile seizures. More than half of the children were reported to have a personal or family history of febrile seizures, but none appeared to have an increased risk for the development of afebrile seizures and/or epilepsy. In 1995, Farrington et al. assessed the risk for febrile seizures following DTP using the self-controlled case series (SCCS) analysis method. Using three different risk windows, an increased risk for febrile seizures was found 0-3 days following DTP vaccination. Another study, using a traditional Cox proportional-hazards regression found an increased risk for febrile seizures only on the day of vaccination. In addition, consistent with the findings of Hirtz et al., this study found those with a personal or family history of febrile seizures were at greater risk for febrile seizures but were not at a higher risk for subsequent seizures or neurodevelopmental disabilities. These findings are further supported by a review, conducted by the Institute of Medicine in the US, which found no increase in risk for afebrile seizures. A review of the safety of childhood vaccinations by Chen et al. state the established risk for febrile seizures following DTP vaccination is about 2 to 3 times greater. The occurrence of febrile seizures following DTP has been attributed to the whole-cell pertussis component of the
vaccine; the vaccine has since been altered to utilize acellular pertussis (DTaP), and has shown a decrease in the risk for febrile seizures.25,34

Similar to DTP vaccination, vaccination against MMR has been associated with a risk for febrile seizures; however, the time at which a seizure is likely to occur is not as immediate as seen with DTP vaccination. Farrington et al. found an increased risk for febrile seizures 6-11 days following MMR vaccination,31 while Barlow et al. detected an increased risk 8-14 days following vaccination32. Like DTP vaccination, the risk is greater in those with a personal or family history of febrile seizures and individuals are not at increased risk for subsequent seizures, epilepsy or neurodevelopmental disabilities.25,32,35

2.3 Nature of the Outcome: Serious Neurological Events

Convulsions are described as a rapid and uncontrollable shaking of the body caused by the repeated contraction and relaxation of the person’s muscles. Convulsions are a common symptom of a seizure, and typically, the terms are used interchangeably. Seizures may be epileptic or non-epileptic. The International League Against Epilepsy (ILAE) has defined “epileptic seizures” as a clinical manifestation presumed to result from an abnormal and excessive discharge of a set of neurons in the brain, which consists of sudden and transitory abnormal phenomena including alterations of consciousness, motor sensory, autonomic or psychic events, perceived by the patient or an observer.36 Febrile seizures are a subtype of “epileptic seizures occurring in childhood after one month of age, associated with a febrile illness not caused by an infection of the central nervous system, without previous neonatal seizures or a previous unprovoked seizure, and not meeting criteria for other acute symptomatic seizures”.36 Since the onset of
seizures due to febrile illness after the age of 6 years is considered unusual, epileptic attacks which occur in a setting of fever after the age of 5, should not be classified or documented as a febrile seizure (P.L. Carlen, FRCPC, MD, personal communication, July 28, 2012).

“Non-epileptic events/seizures (NES)” are clinical manifestations presumed to be unrelated to an abnormal and excessive discharge of a set of neurons of the brain, including: (a) physiological disturbances in brain function (vertigo or dizziness, syncope, sleep and movement disorders, transient global amnesia, migraine, enuresis), and (b) psychogenic seizures or “pseudoseizures” (non-epileptic sudden behavioural episodes). The differential diagnosis of a true epileptic seizure and NES is usually based solely on the clinical history of the patient. The gold standard method to differentiate between NES and epileptic seizures is to record the seizure on video while simultaneously monitoring the individual with an electroencephalogram (EEG); however, even then, it is sometimes difficult to determine which type of seizure is being dealt with. Therefore, possible neurological events following vaccination include epileptic and physiological non-epileptic seizures, while psychogenic NES represent a source of misclassification.

Epileptic seizures may be the most worrisome AEFI; however, physiological NES, particularly anoxic seizures, are the most probable. Anoxic seizures, as explained earlier, may be triggered by a painful or frightening stimulus such as needle injections and occur primarily in females. The likelihood of an anoxic seizure is further supported by the observation that 30-40% of adolescent syncope reports to VAERS described signs of jerking or other seizure-like activity. Anoxic seizures are difficult to clinically differentiate from epileptic convulsions. A list of historical and event features that...
differentiate these convulsive syncope attacks and seizures can be found in Table 2.1. Furthermore, anoxic seizures and epileptic seizures may co-exist, though this is rare.\textsuperscript{8-11} Despite difficulty in differentiating the two seizure types, both are biologically plausible AEFI{s}, and therefore, should not be of any concern for misclassification.

Psychogenic NES represent a source of misclassification of the seizure event. Psychogenic NES may precipitate as a result of immediate triggers such as panic or exposure to sudden sensory stimuli; however, they are believed to arise in response to difficulties in the individual’s life such as abuse or neglect rather than an underlying pathophysiology,\textsuperscript{41} and are just as likely to occur in absence of vaccination. The incidence of psychogenic NES is estimated to be anywhere between 0.91 and 3.03 per 100,000 person-years.\textsuperscript{11} Adolescent females and young adults are most often affected by psychogenic NES;\textsuperscript{11} a 4:1 female to male ratio is estimated for its incidence in those over the age of 10\textsuperscript{42}. The prevalence of psychogenic NES has been estimated to be 2-33 per 100,000 persons.\textsuperscript{43} The correct diagnosis of psychogenic NES is often delayed as differentiating it from epileptic seizures based on history is difficult. A list of historical and event features that may be used to differentiate psychogenic NES and seizures can be found in Table 2.2. This delay leads to an increased risk for iatrogenic complications of anticonvulsant use, delayed referral to psychiatric treatment and potential exposure to unnecessary emergency therapies.\textsuperscript{11} Due to the diagnostic delay, a relatively high prevalence of psychogenic NES patients are referred to epilepsy centres (15-30%).\textsuperscript{39} With the differentiation between epileptic and psychogenic seizures being so difficult, psychogenic NES represent a source of non-differential misclassification, biasing the
potential association between vaccination and neurological events towards a null association.

2.3.1 Incidence

The incidence of epilepsy has consistently shown a bimodal age distribution, where incidence is high in the first year of life, decreases during childhood to reach a relatively stable and low rate in adulthood, but increases drastically in the elderly.\textsuperscript{44-46} Epilepsy is also commonly found to occur in males more frequently;\textsuperscript{44-48} however, there have been a few studies that have found minor to no difference between gender incidences\textsuperscript{44}. There is conflicting evidence addressing racial differences in the incidence and prevalence of epilepsy.\textsuperscript{48} The prevalence of epilepsy across socioeconomic status (SES) has been observed to be higher in those of lower SES; however, the potential association between epilepsy and SES has been inadequately studied; hence there is little definitive evidence to explain this trend.\textsuperscript{47} Anoxic seizures are found to be more common in adolescent females; however, given the amount of misclassification, the incidence of is difficult to estimate and is therefore unknown.\textsuperscript{8}

2.3.2 Etiologically Relevant Time Window

The time period following vaccination in which a convulsion or seizure must occur to be etiologically attributed to the vaccine depends on the underlying biological mechanism for the adverse event. Information available from vaccine safety studies or voluntary case-reports, such as those contained in VAERS, may also help estimate the timing and duration of this “risk window” if the pathophysiology is not fully understood.
Anoxic seizures are considered acute adverse events, so it would be expected that the etiologically relevant risk window would occur soon after vaccination. Conversely, the hypothesized pathophysiology of epileptic seizures following immunization suggests that these seizures may have a delayed risk window. Notably, febrile seizures following DTP and MMR vaccinations have been observed to occur immediately to a few days following vaccination.\textsuperscript{31, 32}

To determine the appropriate etiological risk window for serious neurological events following qHPV vaccination, a descriptive analysis of the VAERS database was conducted. The VAERS reports illustrated the occurrence of serious neurological events including convulsions, seizures and new diagnoses of epilepsy for females aged 6-29 years were most likely to be reported within 30 days of vaccination (Figure 2.1).\textsuperscript{28}

2.3.3 Risk Factors in Young Females

The risk for epileptic seizure occurrence, excluding febrile seizure, has been associated with genetic, congenital and developmental conditions, family history of epilepsy, head or brain trauma, neoplasm (tumour), CNS infection, and personal history of febrile seizures. Race/ethnicity may also be a potential risk factor; this has yet to be confirmed given the limited nature of the evidence.

Genetic, congenital and developmental conditions may predispose an individual to have epileptic seizures in childhood, adolescence or young adulthood.\textsuperscript{44, 47, 49, 50} The most commonly recognized conditions include cerebral palsy and mental retardation. Cerebral palsy is a term used to describe a group of non-progressive disorders affecting body movement and/or muscle coordination. The incidence of cerebral palsy is due to an insult to or anomaly of the developing brain. Epilepsy is estimated to develop in one third
of cerebral palsy or mentally retarded patients; its development may simply be clinical manifestations (symptoms) of the underlying cerebral abnormality. Other conditions that may be cross-diagnosed with epilepsy, and subsequently pose as risk factors, include tuberous sclerosis, Down syndrome and lupus erythematosus. In the Rochester study, 4% of cases were attributed to congenital or genetic abnormalities. An individual may also be genetically predisposed to developing epilepsy if a family history of epilepsy is present. Family history of epilepsy has been evaluated through cohort and case-control studies to show a two- to three-fold increased increase for epilepsy.

Histories of head or brain trauma, the presence of a brain tumour and CNS infections have been suggested as potential risk factors for epilepsy. The Rochester study found 5% of epilepsy cases were due to head trauma, 4% to brain tumour and 3% to infectious diseases. Epilepsy resulting from brain injury may be referred to as posttraumatic epilepsy. In most cases, the risk of seizures appears greatest in the first year after trauma, and subsequently decreases thereafter. Unfortunately, a review of posttraumatic epilepsy studies indicated that many had limited their follow-up to the occurrence of only one seizure, and subsequent diagnosis of epilepsy was therefore unknown. Brain tumours are the most common type of solid tumour found in children; like genetic or congenital conditions, epileptic seizures may be a clinical manifestation of the underlying disease. The risk of epileptic seizures due to CNS infection is dependent on the infective agent. Some may experience acute symptomatic seizures at the time of infection; this occurrence is associated with an additional increase in risk for epilepsy in subsequent years.
If an individual has a history of febrile seizures, they are believed to be at higher risk for epilepsy; however, it has also been suggested otherwise. The suggestion is that rather than being considered a causal factor, febrile seizures should be considered a marker for either genetic predisposition or for a pre-existing cerebral lesion. Furthermore, studies following those who experienced febrile seizures following DTP or MMR vaccination have found no subsequent risk for epilepsy. With opposing evidence, febrile seizures are a potential risk factor for epilepsy that requires further research.

The race/ethnicity of an individual is a potential risk for epilepsy. A literature review conducted by Sander and Shorvon claimed to have found several reports showing high prevalence rates in Black African and non-white populations, and alluded to the conclusion that race/ethnicity was an established risk factor. When these reports were investigated, it was found that Sander and Shorvon drew conclusions from many studies that were of small sample size, poor epidemiological methods, and/or black-only populations; thus, rendering their conclusions questionable. A more recent review of epilepsy in North America reviewed studies with better epidemiological methods for the association between race/ethnicity and epilepsy, but found conflicting evidence. Additional studies are needed to determine whether race/ethnicity is a true risk factor.

A physiological NES occurring in young females is most likely a result of a syncope episode (i.e., anoxic seizure). Syncope is a consequence of any decreases in cerebral perfusion and may be caused by orthostasis, cardiac arrhythmias, and cardiac outflow obstructions or may be neurally mediated. Examples of neurally mediated syncope include vasovagal faints, carotid sinus hypersensitivity and situational faints, all
of which are a result of inappropriate bradycardia and hypotension. Situational fainted are
of particular interest as they may occur with physical pain, such as the prick of a needle, or
frightening situations, such as anticipating the pain from a needle, in healthy
individuals with normal blood pressure.\textsuperscript{11} There are no known risk factors for syncope-
related physiological NES.

\section*{2.4 Nature of the Exposure: qHPV Vaccine and Program}

\textsuperscript{\textregistered} is a qHPV vaccine used to prevent infections caused by HPV Types 6,
11, 16 and 18 and diseases associated with these HPV types including cervical cancer,
vulvar and vaginal cancer, genital warts (condyloma acuminata), cervical
adenocarcinoma \textit{in situ} (AIS), cervical intraepithelial neoplasia (CIN) grades 1, 2 and 3,
vulvar intraepithelial neoplasia (VIN) grades 2 and 3, and vaginal intraepithelial
neoplasia (VaIN) grades 2 and 3.\textsuperscript{57} Efficacy of the vaccine is known to be 98\% (95\%
confidence interval, CI 86-100\%) in a per-protocol susceptible population and 44\% (95\%
CI, 26-58\%) in an intention-to-treat population.\textsuperscript{58} The vaccine is approved for use in
females aged 9-26 years and is most effective when administered prior to the start of
sexual activity when exposure to HPV is highest.\textsuperscript{57} Like all vaccines, Gardasil\textsuperscript{\textregistered} contains
both medicinal and non-medicinal ingredients. The medicinal active ingredients, or
“antigenic components”, of the vaccine are highly purified virus-like particles (VLPs) of
the recombinant major capsid (L1) protein of HPV types 6, 11, 16 and 18.\textsuperscript{59} Non-
medicinal ingredients include sodium chloride, L-histidine, polysorbate 80 (PS-80),
sodium borate, water, and most importantly, amorphous aluminium hydroxyphosphate
sulphate adjuvant. As mentioned previously, both the active component and the adjuvant,
an ingredient used to enhance the immunogenicity of the co-administered antigenic component, may cause an exaggerated immune response leading to an adverse event.²

Gardasil® was approved for use in Canada in 2006 by Health Canada after the careful review of data on quality, safety and efficacy. According to the Summary Basis Decision document for Gardasil® released by Health Canada, twelve clinical trials were used to assess the efficacy and safety of this vaccine, four of which were considered pivotal in the decision-making process.⁵⁹ Based on the results of these trials, Health Canada concluded that adverse events reported by trial subjects were generally well tolerated, with the most common being injection-site adverse events including pain, swelling, and erythema due to L1 VLPs and/or aluminium adjuvant contained in the vaccine. Furthermore, the proportion of subjects who reported serious adverse events was comparable between those vaccinated with Gardasil® and those who were vaccinated with a placebo. However, most studies used an adjuvanted placebo which may have attenuated differences between the two treatments as adverse events can also be due to the adjuvant.

Four pivotal studies evaluated a total of 20,541 women aged 16-26 years at enrolment.⁵⁹ The decision to approve the vaccine in age groups younger than 16 (i.e., 9-15 years) was based on the demonstration of non-inferiority of immunogenic data in the younger group compared with the older group.⁵⁹ It should be noted that one of the four pivotal studies was conducted in two parts, wherein the second part of the study did test the vaccine in females aged 13-24 years (mean age was 20.0 years), and likely contributed to the approval of the vaccine in younger age groups. Nevertheless, a systematic review conducted by our research group determined that less than 5% of
participants in these trials were under the age of 16.\textsuperscript{18} Although little evidence is available on the safety of the vaccine in younger age groups, the Ontario Ministry of Health and Long-Term Care implemented a fully funded HPV immunization program aimed at Grade 8 girls, typically aged 12-13 years\textsuperscript{60}. This is the age at which many girls are undergoing puberty, during which, hormone levels change. There has been extensive research conducted to describe the interactions between the neuroendocrine and immune systems. During puberty, estrogens levels increase, affecting the activity of the immune system.\textsuperscript{61, 62} This interaction could be beneficial with regard to vaccination programs targeting females undergoing puberty as estrogens enhance the humoral immune response,\textsuperscript{61} increasing the ability of the body to produce antibodies for future protection. Unfortunately, it is also known that a number of autoimmune diseases develop during periods when reproductive function is undergoing pronounced changes,\textsuperscript{61, 62} therefore, the interaction between the neuroendocrine and immune systems may also introduce a risk for vaccination programs in these young girls. Whether this could potentiate a risk for epileptic seizures is unknown; however, the lack of safety evidence for the grade 8 population is still a concern as the incidence of epilepsy varies by age\textsuperscript{44-46, 63}.

HPV vaccination is voluntary and is provided through school-based clinics by public health nurses.\textsuperscript{60} The vaccine is recommended by the manufacturer to be administered intramuscularly as three separate doses at 0, 2 and 6 months; however, the manufacturer also states that clinical studies have shown efficacy if the vaccine is given within a one year period, and a grace period of one month for Dose 2 (i.e., month 1 to month 3 in the vaccination regimen) and a period of two months for Dose 3 (i.e., month 4 to month 8 in the vaccination regimen) do not impact the immune responses for the
vaccine. Each dose is administered and documented by the public health nurse present. The vaccination status of each individual is captured in the Immunization Record Information System (IRIS) databases maintained by Ontario’s 36 Local Public Health Agencies (LPHAs), and thus represents the biological exposure status of the individual.

The qHPV vaccine is comparable to the hepatitis B vaccination as both are administered to similar age groups, require multiple doses to acquire immunity and are recombinant vaccines suspended with an aluminum adjuvant. Despite these similarities, using hepatitis B immunization as a comparator would not be appropriate to determine the risk of neurological events or other serious adverse events, nor would any other vaccine available. As previously mentioned, the relative risk compares the incidence of serious adverse events of one vaccine to another, but does not indicate the actual risk of the vaccine to cause serious adverse events in the general population as both vaccines could have identical risk profiles and would show no relative difference in incidence rates; thus, having no significance.

With the qHPV vaccine being relatively new, little is known about the characteristics of those who obtain the vaccine. There is currently one study that was conducted to describe the characteristics of individuals who initiated the HPV vaccination and those who did not. Characteristics positively associated with HPV vaccine initiation were higher neighbourhood income and educational level (i.e., SES), number of visits to a physician, history of the flu vaccine and a history of sexually transmitted diseases. Having a male primary provider and the number of hospitalizations were found to be inversely correlated with HPV vaccine initiation.
Race/ethnicity was also suspected to be correlated to HPV vaccine uptake; blacks and Asians were less likely than whites to receive the vaccine, and while Hispanic girls aged 9-12 years were more likely to initiate the vaccine, Hispanic women aged 18-26 years were less likely to initiate the vaccine. The investigators suggested the difference observed in the study could be due to access to care, cultural attitude toward HPV, cervical cancer or vaccination, and/or physician-patient communication. It must be noted that information on race/ethnicity was missing for approximately half of the subjects. In attempt to resolve this issue, a multiple imputation using a previously validated algorithm was used. This imputation would assign a race/ethnicity for individuals by using hospital-based service utilization, geocoding methods, spoken language and surname criteria for Hispanics and Asians. When the multiple imputation for race/ethnicity was performed, the Asian race/ethnicity was not associated with HPV initiation. This indicated a need for more studies to understand whether a racial disparity truly exists in HPV vaccination.

Chun et al. also investigated whether the history of immune-related conditions of females was correlated to the initiation of the HPV vaccine. The immune-related conditions evaluated were: 1) rheumatoid conditions; 2) asthma; 3) general allergy including hay fever, eczema, contact dermatitis, urticaria, food allergies, and unspecified allergy; 4) drug allergy; 5) number of infections including urinary tract, respiratory tract, intestinal, and skin; and 6) antibiotic use for bacterial infections. The investigators found that subjects who might be at greater risk of immune-related adverse outcomes were not underrepresented among vaccine recipients (i.e., those with immune-related conditions were just as likely to initiate the vaccine), and thus concluded that those with immune-
related conditions were not less likely to initiate the HPV vaccine (i.e., not a determinant of vaccine uptake).

2.5 Confounders and Effect Modifiers

Potential confounders that have been shown to be associated with both the receipt of the HPV vaccine and serious neurological adverse events are age, race/ethnicity and SES. Age is likely a confounder as both the administration of the qHPV vaccine and the incidence of epilepsy and physiological non-epileptic seizures are age-dependent. Race/ethnicity and SES represent potential confounders as the association between each factor and either the exposure or outcome is not well established. Although race/ethnicity has been proposed as a risk factor for epileptic seizures, it is not a well-established risk factor as studies are limited and have conflicting results. Furthermore, race/ethnicity data was missing for approximately 50% of subjects in the study describing correlates of the HPV vaccine uptake,\(^6^6\) limiting the significance of the study’s finding. SES is currently only seen to have an association with the prevalence rates of epilepsy,\(^4^7\) this makes it difficult to determine whether it is in fact a predictive factor or simply a result of the costs associated with having epilepsy; thus, we cannot be certain whether SES will confound the association.

History of the flu vaccine and sexually transmitted diseases, and the number of visits to a physician are only seen to be associated with HPV vaccine uptake. Although, an association between these factors and the risk of neurological events may seem unlikely, they may still be potential confounders. These factors may indicate certain health behaviours which may be indirectly related to a predisposition for epileptic seizures, and thus may also be considered potential confounders. Conversely, family
history of epileptic seizures, associated with only the outcome of interest, may also be a potential confounder as parents of eligible girls may be concerned of the safety of their daughters and are consequently more likely to withhold vaccination.

Given the limited body of literature available on the association between the qHPV vaccine and the risk of neurological events, few potential effect modifiers have been identified. Once an individual has had an epileptic seizure, the recurrence risk is 20-35% in the subsequent 5 years. After two epileptic seizures, recurrence risk for subsequent seizures increases greatly. A history of epileptic seizures may therefore modify the association under study if the likelihood of having a seizure is higher in vaccinated girls. Other potential effect modifiers include genetic and developmental conditions (cerebral palsy, mental retardation, tuberous sclerosis, Down syndrome, lupus erythematosus), history of febrile seizures, history of head trauma, history of CNS infection and race/ethnicity. All of these risk factors may modify the effect of the qHPV vaccine with regards to the risk of convulsions and epileptic seizures.

2.6 Conclusion

The qHPV vaccine has been commended for its achievement in exhibiting nearly perfect efficacy in a per-protocol population. Clinical trial protocols ensured participants received each qHPV vaccine dose according to a recommended schedule of 0, 2 and 6 months; however, information on the adherence to this recommended dose schedule in practice is unknown and may have important implications on the effectiveness and safety of the vaccine. Surveys have consistently shown that the safety of the HPV vaccine is an important determinant of HPV vaccine acceptance. The occurrence of a convulsion or seizure following vaccination can be very frightening to both the individual and their
parents. Given reports of serious neurological events in the VAERS database, the biological plausibility of these events and the lack of power to detect such adverse reactions in clinical trials, epidemiologic studies are needed to determine whether serious neurological events reported to date are truly associated with vaccine use or are merely coincidental. Additional evidence regarding the safety of the HPV vaccine will allow parents to make informed decisions about the risks and benefits of this vaccine for their daughters. The results of this study may also aid decision makers and health care providers in the delivery of the HPV immunization program.

2.7 References


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Table 2.1 List of historical and event features that differentiate syncope and seizure from Selvitelli et al. (2011)

<table>
<thead>
<tr>
<th></th>
<th>Syncope</th>
<th>Epileptic Seizure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-ictal features</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>More common</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Ictal features</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of Consciousness</td>
<td>Common</td>
<td>Common, depends on seizure type</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>Possible</td>
<td>Possible</td>
</tr>
<tr>
<td>Frequency of ictus</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Precipitation by stress</td>
<td>Uncommon</td>
<td>More common</td>
</tr>
<tr>
<td>Head turning</td>
<td>Uncommon</td>
<td>More common</td>
</tr>
<tr>
<td>Occurrence after prolonged sitting or standing</td>
<td>More common</td>
<td>Less common</td>
</tr>
<tr>
<td><strong>Post-ictal features</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>More common</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>
Table 2.2 List of history and event features that differentiate psychogenic non-epileptic attacks and epileptic seizure from Selvitelli et al. (2011)

<table>
<thead>
<tr>
<th>Historical features</th>
<th>Psychogenic Attacks</th>
<th>Epileptic Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td>Older</td>
<td>Younger</td>
</tr>
<tr>
<td>Gender predominance</td>
<td>Female</td>
<td>None</td>
</tr>
<tr>
<td>History of abuse</td>
<td>Common</td>
<td>Less common</td>
</tr>
<tr>
<td>History of pain syndromes or event in waiting or examining room</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>History of prior psychiatric treatment</td>
<td>Common</td>
<td>Less common</td>
</tr>
<tr>
<td>History of anticonvulsant therapy</td>
<td>Typically fewer medication trials and less polytherapy</td>
<td>Typically more medication trials and greater polytherapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event features</th>
<th>Psychogenic Attacks</th>
<th>Epileptic Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of event</td>
<td>Longer (typically &gt;2 minutes)</td>
<td>Shorter (typically 1-2 minutes)</td>
</tr>
<tr>
<td>Sleep occurrence</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Ictal behaviors (pelvic thrusting, side-to-side head movements, gradual onset, asymmetric/asynchronous limb movements, variable amplitude, crying)</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Ictal heart rate</td>
<td>Stable</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Ictal urinary incontinence and tongue bite</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Ictal eye closure</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Post-ictal confusion</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Post-ictal whisper or partial motor responses</td>
<td>Common</td>
<td>Not seen</td>
</tr>
<tr>
<td>Post-ictal breathing patterns</td>
<td>Often rapid, shallow, soft and irregular</td>
<td>Deep and prolonged inspiratory/expiratory phases, regular and loud, often with snoring</td>
</tr>
</tbody>
</table>
Figure 2.1 Daily average neurological event report rates to Vaccine Adverse Events Reporting System (VAERS) for days following qHPV vaccination – last updated December 14, 2011.

* Daily Report Rate = Number of Events Reported (for specified onset interval) divided by Length of Onset Interval
Chapter 3

Methods

3.1 Overview of Study

A population-based cohort of all girls aged 12-13 years and eligible during the first four years (2007/08-2010/11) of Ontario’s Grade 8 human papillomavirus (HPV) immunization program was formed using the province’s administrative health databases. Cohort members were followed from September 01 of their eligible school year (cohort entry) until their date of death, the date their immunization records were transferred for record linkage (May to August 2011), or the end of the study (March 31, 2011). The vaccination status of each cohort member was ascertained using the Immunization Record Information System (IRIS) databases maintained by Ontario’s Local Public Health Agencies (LPHAs). For the analysis of vaccination status and dose timing, the outcomes of interest were vaccine uptake, series completion, between dose time intervals and time-to-series completion. For the safety analysis, the primary outcome included the occurrence of convulsions, seizures and epilepsy. The outcomes were identified using the Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD), National Ambulatory Care Reporting System (NACRS) and the Ontario Health Insurance Plan (OHIP) database. To assess the association between the quadrivalent HPV (qHPV) vaccine and the outcome of interest, the self-controlled case series (SCCS) method, developed for the post-marketing evaluation of adverse events following immunization, was employed.
3.2 Data Sources and Quality

This study used four of Ontario’s administrative health databases as well as, IRIS. The Institute for Clinical Evaluative Sciences (ICES-Central) provided access to the province’s databases via ICES-Queen’s to retrieve individual-level health-related information for research purposes. To ensure the confidentiality of administrative data held at ICES, personal identifiers are replaced with a unique encrypted ICES Key Number (IKN). The encrypted IKN is unique to each individual across the different datasets, permitting record linkage across databases and across time.

3.2.1 Registered Persons Database (RPDB)

This database is updated bi-monthly and provides basic information on all Ontario residents with a health card number. These data are collected by the Ministry of Health and Long-Term Care (MOHLTC), and have been enriched by ICES using their other data holdings. The main data elements contained in the RPDB include demographics (e.g., date of birth, sex), geographic information (e.g., postal code), neighbourhood income quintile, a proxy for family income derived by record linking postal codes to Canadian Census data, and date of last contact with the health care system. Sex and date of birth were used for the identification of the qHPV vaccination birth cohorts through linkage with IRIS. In addition, this database was the primary source of patient demographic and geographic information. Most information held within the RPDB is considered accurate; however, some geographic information provided by the MOHLTC is sometimes out-of-date or incorrect. To obtain more accurate postal codes, ICES updates information in the RPDB using data from its other holdings (e.g., DAD, NACRS). Information obtained from this database included IKN, birth month and year, sex, income quintile and place of
residence. Data from January 1\textsuperscript{st}, 1994 (the earliest date of birth of cohort members) to March 31, 2011 (end of study) were used for this thesis.

3.2.2 Canadian Institute for Health Information’s Discharge Abstract Database (DAD)

This database is updated annually and contains detailed records of all hospitalizations.\textsuperscript{2} A reabstraction study of the DAD found that demographic data and most procedure were coded with high sensitivity (>80\%) and near perfect specificity (>95\%); however, co-morbidities were generally poorly documented.\textsuperscript{4} The main data elements include patient demographics, clinical data (e.g., diagnoses, procedures) and administrative data (e.g., admission category, length of stay). DAD was the primary source for hospitalization information of cohort members. Variables obtained were IKN, admission and discharge dates, and diagnosis code (documented using the International Classification of Diseases 10\textsuperscript{th}-Canadian Enhancement Code Revisions, ICD-10CA) and type. Data collected from January 1994 to March 2011 were used for this thesis.

3.2.3 National Ambulatory Care Reporting System (NACRS)

NACRS is updated annually and provides information on patient visits to hospital and community-based ambulatory care (i.e., day surgery, outpatient clinics and emergency departments).\textsuperscript{2} NACRS was the primary source of information regarding emergency department (ED) visits. The main data elements used included clinical data, administrative data, financial data, and service-specific data elements for day surgery and emergency. Variables obtained were IKN, visit date, diagnosis code and type. Data collected from July 2000 (when Ontario adopted ED reporting) to March 2011 were used for the performed analyses.
Data collecting methods for ED visits vary across facilities, which may affect the accuracy of information provided. CIHI conducted re-abstraction and inter-rater reliability studies and found high agreement in non-clinical data including demographic, financial, institutional, visit and assessment data (these data were not provided). Also, these studies found high agreement rates for determining a patient’s main problem (85.5±1.9% agreement) and reason for visit (72.5±7.5% agreement); however ICD-10CA diagnostic coding of the “Main Problem” and “Reason for Visit” had low agreement rates (68.8±3.2% and 59.3±6.7% agreement, respectively).  

3.2.4 Ontario Health Insurance Plan (OHIP) Database

This database contains detailed information on physician claims for health services covered under OHIP. This database also provides information on lab tests ordered and visits to specialists but may not have a record of all visits made to a family doctor as approximately 6% of Ontario physicians do not have a fee-for-service practice and instead belong to a capitated practice where a set sum of money is provided for each patient on the physician’s roster. OHIP records at ICES are updated bi-monthly; approximately 97% of the claims having service dates in a given month are submitted to the MOHLTC within 3 months of the service date, and approximately 99.7% of claims are available after 6 months. Validation of this database has not yet been conducted, although the validity of some diagnoses have been undertaken as needed. The main data elements in the OHIP database include encrypted patient (IKN) and physician identifiers, code for service provided, the date of service and the associated diagnosis (ICD-9 based coding), and the fee paid to the physician. Data collected from January 1994 to March 2011 were used for this thesis.
3.2.5 Immunization Record Information System (IRIS)

The IRIS database, a copy of which is maintained by each of Ontario’s 36 LPHAs, was originally developed by the MOHLTC to track and record immunizations mandated under the Immunization of School Pupils Act (1982) for all school-aged children in the province. In addition to mandatory vaccines, IRIS is used to maintain records on other childhood vaccines, particularly those that are publicly funded, such as the qHPV vaccine, whether administered at a school clinic, a LPHA, or a physician’s office. The IRIS databases from 22 of 34 participating LPHAs were transferred to ICES and record linked to created a provincial childhood immunization database. The main data elements contained in this database include demographics (e.g., date of birth, sex, school), vaccine type and immunization date. This database was used to determine individuals’ qHPV vaccination status, date of qHPV vaccination and vaccination history for other vaccines.

As parents/guardians are required to provide their child’s immunization records to the LPHA when the child transfers from a school in a different health unit, IRIS is considered up-to-date. A recent re-abstraction study of the Kingston, Frontenac, Lennox and Addington Public Health (KFL&A) IRIS database demonstrated that this database is both valid and accurate in capturing individual’s HPV vaccination status with a sensitivity of 99.8% (95% confidence interval, CI 99.3-99.9), a specificity of 97.7% (95% CI 96.3-98.7), and an accuracy of 98.6% for vaccination dates.

3.3 Cohort Selection

The eligible population for Ontario’s HPV vaccination program is girls in Grade 8. Unfortunately, an individual’s grade is not captured by any of the available databases.
Consequently, the RPDB was used to identify birth cohorts, a proxy for a girl’s grade, as girls entering Grade 8 must turn 13 by December 31st of that year. For example, girls born in 1994 would have been in Grade 8 for the 2007/08 program year, those born in 1995 for the 2008/09 program, and so on. Eligible girls were excluded if their immunization records were not available at the time of the analysis and if they had died prior to cohort entry. In addition, cohort members with duplicate HPV vaccination entries with mismatched vaccination dates were also excluded; the latter is due to self-reporting of vaccination history for girls moving from one health unit to another. Cohort members were followed from September 1st of their Grade 8 year (cohort entry or t0) until the earliest of the following: date of transfer of immunization records to ICES (May to August 2011), date of death or the end of the study (March 31, 2011).

3.4 Ascertainment of Exposure

HPV vaccination status and date of vaccination of each cohort member were ascertained using the provincial IRIS database. IRIS provides information on biological exposure as each dose is documented by the public health nurse who administers the vaccine. As previously discussed, an assessment of the timing of serious neurological events following HPV vaccination demonstrated that the period of highest risk following vaccination appeared to be 30 days. As such, this time period was considered the aetiologically relevant “exposure time window” or “risk period”. Consequently, the time periods preceding and following the “risk period” were analyzed as unexposed follow-up time for the safety analysis.
3.5 Ascertainment of Outcome

The study evaluated the association between the exposure to the qHPV vaccine and the risk of serious neurological events. The primary study endpoint was a composite of the first occurrence of convulsions, epilepsy and seizures after cohort entry. This was done to try and account for the possibility that: (1) epileptic seizures may have been misdiagnosed or miscoded as general convulsions, \(^\text{12}\) (2) non-epileptic seizures may have been mistaken for epileptic seizures, \(^\text{13, 14}\) and (3) that tonic-clonic, seizure-like activity is well recognized as accompanying syncope, \(^\text{15}\) which is a common and accepted adverse event following immunization. These outcomes were identified using ICD-9 and 10CA diagnostic codes found in the DAD, NACRS and OHIP databases (Appendix A). The identification of epileptic seizures using ICD coding have been validated in the DAD database and Ambulatory Care Classification System (ACCS) database, a database similar to NACRS. \(^\text{12}\) Positive and negative predictive values (PPV and NPV) for ICD-9 coding in DAD were 98% and 99%, respectively, and 99% and 97% in ACCS. PPV and NPV for ICD-10CA coding in DAD were 98% and 99%, respectively, and 100% and 90% in ACCS.

3.6 Statistical Analysis

3.6.1 Descriptive Analysis

A descriptive analysis was conducted to describe the profile of cohort members and compare vaccinated and unvaccinated girls with regards to socio-demographics, medical history, history of health services utilization and vaccination history. Calculation of the average number of days in hospital included the days in hospital after birth for those born in an Ontario hospital as it is typical for the mother and infant to remain in
hospital for recovery. Additionally, if a hospitalization resulted in same day admission and discharge, this hospitalization did not contribute to the average days in hospital. The ICD-9, ICD-10CA and OHIP diagnosis codes used to identify the specified covariates in Appendix A. The DAD and NACRS databases capture multiple diagnostic codes for each visit. Due to the low agreement rate for coding of the “Main Problem” in NACRS, only the first code recorded was used (i.e., first diagnostic position). The number of codes needed from DAD to accurately capture medical history has not been validated. Since few diagnostic codes were present beyond the tenth diagnostic position, two definitions of the medical conditions of interest were compared; one limited to the first five diagnostic positions and the other using the first 10 diagnostic positions. As there was little to no difference in the prevalence of the specified conditions using either definition, medical conditions were ascertained using the first five diagnostic positions.

3.6.2 Analysis of qHPV Vaccination Status and Dose Timing

In addition to describing the profile of cohort members, the first manuscript evaluated the extent to which a publicly funded, school clinic-based HPV immunization program was able to adhere to the recommended dosing schedule that established the vaccine’s efficacy. As the study end date was March 31, 2011, the majority of the 1997 birth cohort, corresponding to the 2010/11 vaccination program, had not received the third and final dose of the qHPV immunization program in school; thus, the analysis was restricted to girls born between 1994 and 1996. For this analysis, vaccine uptake (i.e., series initiation) was defined as having received at least one dose, while series completion was defined as having received all 3 doses during follow up. The number of days between the first and second dose (“Dose 1” and “2”), and the second and third dose
(“Dose 3”) was calculated for each girl who received at least two and three doses, respectively, and categorized into groups that reflected the recommended dosing schedule (0, 2 and 6 months) and the allowed between dose grace period of 1 month (30 days) between Dose 1 and 2, and 2 months (60 days) between Dose 2 and 3. As such, the interval between Dose 1 and 2 was categorized as: (i) too short (<30 days), (ii) as recommended (30-90 days), and (iii) too long (>90 days), and the interval between Dose 2 and 3 as: (i) too short (<60 days), (ii) as recommended (60-180 days), and (iii) too long (>180 days). Similarly, “time-to-series completion” was calculated as the number of days between Dose 1 and 3 for girls who received at least 3 doses and was also categorized taking into account the allowed grace period of 60 days. In addition to the allowed grace period, the efficacy of the vaccine was demonstrated in individuals who received all 3 doses within a one year period, and was therefore considered as an “acceptable” time interval. “Time-to-series completion” was categorized as: (i) too short (<120 days), (ii) as recommended (120-240 days), (iii) acceptable (241-365 days), and (iv) too long (>365 days).

3.6.3 Analysis of Neurological Events Following qHPV Vaccination

Traditionally, cohort data is analyzed using time-to-event Cox Proportional Hazards regression. However, since little is known about the factors that predict the outcomes of interest as well as those influencing vaccine uptake or avoidance in the Ontario Grade 8 population, the traditional cohort analysis may be prone to significant confounding. In addition, potential confounders such as race, SES, and family history are not captured by administrative health databases, further increasing the potential for confounding. Consequently, a self-matched analysis (SCCS) method was employed for
the primary analysis of the association between qHPV vaccination and the risk of serious neurological complications.

The SCCS method, similar to the case-crossover design, is a case-based, self-matched approach where cases are compared to themselves over time; however, contrastingly, it is derived from the cohort rather than the case-control model. This analytical technique allows for the complete control of all known, unknown and unmeasured individual-level confounders that are time-independent. The application of the SCCS method requires 3 key assumptions: (1) events arise in a non-homogeneous (random) Poisson process; (2) the occurrence of an event must not alter the probability of subsequent exposure; and (3) the occurrence of the event of interest must not censor or affect the observation period. The latter assumption has been shown to be quite robust to deviations, particularly with regards to non-repeating events.

For the SCCS analysis, each vaccinated case’s observation time was divided into control (i.e., unexposed person-time) and risk (i.e., exposed person-time) periods, based on the a priori chosen exposure risk window of 0-30 days following immunization. As such, the 30 days following each vaccine dose was classified as “exposed” and all other follow-up time as “unexposed”. The incidence rate during “exposed” person-time was compared to that during “unexposed” time using conditional Poisson regression. To control for the potentially confounding effects of age, non-vaccinated cases were included in the analysis. Subsequently, the analysis was stratified on the basis of important risk factors for neurological complications including history of seizures and/or convulsions, previous head trauma, history of CNS infections, Down syndrome, mental retardation, cerebral palsy and tuberous sclerosis to assess potential effect modification.
3.6.4 Sensitivity Analysis

Sensitivity analyses were conducted to account for any uncertainty regarding the assumptions and choices made for the primary analysis, as well as to assess the impact of potential sources of misclassification due to the outcome definition and the choice of the exposure risk window.

The primary analysis was conducted considering only the first occurrence of convulsion, epilepsy or recurrent seizure; however, the SCCS analysis is designed to allow for multiple occurrences of the outcome. Consequently, the analysis was repeated considering all occurrences (i.e., events) reported in any of the 3 data sources (OHIP, NACRS, DAD). Furthermore, the primary analysis assumed that the risk for convulsion and seizure after each dose was equal. However, it is conceivable that the risk of a serious neurological complication could increase with each subsequent dose administered; thus, a dose response analysis was conducted.

Disease classification in the OHIP (physician claims) database uses a modified ICD-9 system; diagnosis codes are truncated to 3 digits and therefore do not provide the same level of detail or precision for the outcome definition. Thus, this modified coding system increased the potential for misclassification in the identification of convulsions as the diagnostic code for convulsions also captures episodes ataxia, vertigo and headache (excluding tension headache of migraine). To assess the effect of outcome misclassification introduced by the use of OHIP data, the analysis was repeated using only cases identified through DAD and NACRS. The biological mechanism through which an epileptic seizure could precipitate by vaccination is likely different from that for NES. Thus, the inclusion of convulsions in the outcome definition of the primary analysis
may have introduced misclassification bias. As such, the analysis was repeated whereby only epileptic seizures were considered for the case definition, and again, only considering convulsions (including febrile seizures and excluding those also captured as an epileptic seizure case) for the case definition.

Syncope is often observed with the occurrence of a convulsion or epileptic seizure. Conversely, convulsions may result from the onset of syncope. The sequence of events may be difficult to determine, and may result in misclassification of convulsions. To evaluate the potential for this source of outcome misclassification, the SCCS analysis was repeated to assess the association of the first occurrence of syncope captured by the 3 data sources (diagnosis code listed in Appendix A).

The exposure risk window used in the primary analysis was chosen on the basis that reporting rates to VAERS decreased to approximately 1 report per day after 30 days; however, it was noted that a high number of these reports occurred within a day of the vaccination.\textsuperscript{11} Furthermore, a 0-42 day risk period has been used by others to study the risk of neurological complications with other vaccines (L.E. Lévesque, BScPhm, MSc, PhD, personal communication, September 14, 2011). Consequently, the SCCS analysis was repeated using exposure risk windows of 0-1 day, 2-30 days and 31-42 days to address potential sources of exposure misclassification from the choice of the primary exposure risk window.

All statistical analyses were performed using Statistical Analysis Software (SAS) version 9.2 (SAS Institute Inc., Cary, NC).
3.7 Ethical Considerations

This study used administrative health databases, and thus posed no risk to the health of an individual. All data provided by Ontario’s Health Units (IRIS databases), as well as that available through ICES, were rendered anonymous by ICES-Central. To ensure the confidentiality of these data while facilitating record linkage across databases, each individual was identified using a unique encrypted number (IKN). As such, access to any potentially identifying information was not possible. The IKN was present in each database and therefore served as the linking variable. Record-linkage and all analyses were conducted at the secured ICES satellite unit located at Queen’s University (ICES-Queen’s). As a prescribed entity under Section 45(1) of Ontario’s Personal Health Information Protection Act (2004), ICES is allowed to collect and use personal health information without consent for the purposes of analysis and compiling statistical information related to management, evaluation or monitoring of the health care system. All data are held in a highly-secured facility that is subject to review, audit and approval by the office of Ontario’s Information and Privacy Commissioner. All study results, whether in public presentation or written format, were reported in aggregate form only. Ethics approval for the qHPV vaccine study was obtained from the ICES internal review committee and the Sunnybrook Health Sciences Service Research Ethics Board. Ethics approval from the Queen’s University Research Ethics Board in accordance with the Tri-Council Policy Statement on the Ethical Conduct of Research Involving Humans was obtained. A copy of the Queen’s Research Ethics Board approval may be found in Appendix B.
3.8 References


Chapter 4

Human Papillomavirus (HPV) Vaccination Status and Dose Timing in a Publicly Funded Immunization Program: The Ontario Grade 8 HPV Vaccine Cohort Study

4.1 Preface to the Manuscript

This chapter contains the first of two manuscripts of this thesis addressing the use and neurological safety of the quadrivalent (q-) human papillomavirus (HPV) vaccine for a cohort of Grade 8 girls residing in Ontario, Canada. Specifically, the following manuscript assesses the level of uptake and series completion for the HPV vaccine and the extent of adherence to the recommended dosing intervals.

As mentioned in Chapter 2, the qHPV vaccine is known to have an efficacy of 98% in the per-protocol susceptible population following a dosing schedule of 0, 2 and 6 months. Currently, the adherence to the recommended dosing schedule is unknown. The following study addresses this knowledge gap by exploring the time intervals between doses administered and the “time-to-series completion”. This study is based on the first 3 years of the qHPV vaccination program in Ontario and relies entirely on data from administrative health and vaccination databases.
ABSTRACT

Background: The quadrivalent (q-) human papillomavirus (HPV) vaccine has shown efficacy of 98% in the per-protocol population when administered at 0, 2 and 6 months. However, adherence to the recommended dosing schedule outside of clinical trials has not yet been evaluated. In addition, little is known about the uptake and series completion of this vaccine when delivered through publicly funded, school-based clinics.

Methods: This retrospective cohort study followed Grade 8 girls eligible to receive the qHPV vaccine during the 2007/08 to 2009/10 campaign years of Ontario’s HPV immunization program. Using Ontario’s immunization and health databases, baseline characteristics, HPV vaccination status and dates of vaccination of each cohort member was ascertained. The proportion of girls who initiated (uptake) and completed the qHPV vaccine series was calculated as the number of eligible girls receiving at least one dose divided by the total number of eligible girls and the number receiving all three doses during follow up divided by the number of girls who initiated the program, respectively. Adherence to the recommended dosing interval between the three doses of the vaccine and for “time-to-series completion” was calculated as the proportion of eligible girls whose number of days between doses complied with the recommended dosing interval.

Results: Overall uptake of the qHPV vaccine was low at 50.24%, with the first campaign year having the lowest observed uptake, but series completion was consistently high at 84.90% to 88.23%. Adherence to the recommended dosing interval was 70.80% between
the first and second doses and 94.81% between the second and third doses. Over 95% completed the series within the recommended one year period.

**Conclusions:** In Ontario, the overall uptake of the qHPV vaccine is low; however, among those who initiate the immunization program, the series completion rate is high, with the majority of eligible girls receiving the vaccine in a timely manner.
INTRODUCTION

The human papillomavirus (HPV) is a common sexually transmitted virus with over 100 types. Two high-risk types of this virus, types 16 and 18, cause 70% of cervical cancers,\(^1,2\) while low risk viruses, types 6 and 11, are responsible for 90% of genital warts.\(^3\) In 2006, Canada and the United States (US) approved a quadrivalent HPV (qHPV) vaccine for use in females aged 9-26 years to prevent infection with these four strains of HPV and HPV-related diseases.\(^4,5\)

The efficacy of the qHPV vaccine for the prevention of cervical intraepithelial neoplasia (CIN) grade 2 or 3, adenocarcinoma in situ (AIS), or invasive carcinoma of the cervix, with the detection of HPV-16, HPV-18, or both in one or more of three adjacent sections of the same lesion has been shown to be 98% (95% CI 86-100) in the per-protocol population.\(^6\) This nearly perfect efficacy was established following a dosing schedule of 0, 2 and 6 months. However, adherence to the recommended qHPV dose schedule outside of clinical trials has not yet been evaluated. In addition, little is known about the uptake and series completion of this vaccine when delivered through publicly funded, school-based clinics.

The aim of this study was to assess the timing of doses of the qHPV vaccine administered to Grade 8 girls in school-based clinics in Ontario, Canada, and evaluate vaccine uptake and series completion in this population.

METHODS

Ontario’s Grade 8 HPV Vaccination Program
In 2007, the Ontario government initiated a publicly funded HPV immunization program to provide free qHPV vaccinations to all Grade 8 girls through school-based clinics coordinated by the province’s 36 Local Public Health Agencies (LPHAs). This voluntary vaccination program normally requires parental consent and eligible girls have until the end of August of their Grade 8 year to initiate the vaccine series, and until the end of Grade 9 to complete it. The three doses are generally administered at school by public health nurses in September/October, November/December, and March/April of each school year. Eligible girls are also able to obtain the vaccine at their LPHA (e.g., personal preference or absent from school on a clinic day) or through their family physician who obtains the free doses from the LPHA.

Study Population and Design

A population-based, retrospective cohort of girls eligible for the first four years of Ontario’s HPV immunization program (2007/08-2010/11 campaign years) was identified using the administrative health and immunization databases of Ontario, Canada. Because school grade is not available in these databases, the cohort was identified using birth year as girls entering Grade 8 must turn 13 by December 31st of that year; the birth cohorts therefore consisted of all girls born between 1994 and 1997 and residing in Ontario at the beginning of their Grade 8 year. Cohort members were followed from September 1st of their eligible school year (cohort entry) until their date of death, the date their immunization records were transferred for record linkage (May to August 2011) or the end of the study (March 31, 2011), whichever came first.
Eligible girls whose immunization records were not available at the time of the analysis (i.e., data not yet transferred from their LPHAs) were excluded from the cohort, as were those who had died prior to cohort entry (but were still listed in the population registry database). For the purposes of the current study, the cohort was restricted to the first three years of the HPV vaccination program (2007/08-2009/10 campaign years) as a result of the study end date occurring before the conclusion of the 1997 birth cohort’s Grade 8 school year.

_Data Sources_

For this study, the following administrative health databases were used: (1) the Registered Persons Database (RPDB) for information on socio-demographics and health insurance coverage, (2) the Canadian Institute for Health Information’s (CIHI) Discharge Abstract Database (DAD) for detailed information on hospitalizations including dates of hospitalizations, diagnoses and procedures, (3) the National Ambulatory Care Reporting System (NACRS) database for information on emergency department (ED) visits including dates and primary diagnosis, and (4) the Ontario Health Insurance Plan (OHIP) database for information on physician services claims. These databases, described elsewhere in detail, were developed as a result of Ontario’s universal health care programs offered to residents of the province, and have been used extensively in health research, including in post-marketing evaluations of drug and vaccine safety. Residents of Ontario are represented in each of these databases by a unique encrypted identifier, thus permitting complete record linkage at the level of the individual across databases and across time.
Information on all mandatory and optional vaccinations for school-aged children, including the qHPV vaccine, was obtained using the Immunization Record Information System (IRIS) database maintained by each of the province’s 36 LPHAs. The IRIS database was developed by the Ontario Ministry of Health and Long-Term Care (MOHLTC) to track and record immunizations of school-aged children mandated under the *Immunization of School Pupils Act (1982).* As a result, each of the province’s 36 IRIS databases contains individual-level information on all HPV vaccine doses administered through the publicly funded program. The IRIS database of each health unit was transferred to the Institute for Clinical Evaluative Sciences (ICES) under Data Sharing Agreements to create a provincial immunization database that was record linked with the province’s administrative health databases. A recent re-abstraction of the Kingston, Frontenac, Lennox and Addington Public Health (KFL&A) IRIS database demonstrated that IRIS is both valid and accurate in capturing individuals’ HPV vaccination status with a sensitivity of 99.8% (95% CI 99.3-99.9), a specificity of 97.7% (95% CI 96.3-98.7), and an accuracy of 98.6% for the vaccination dates. Residents of Ontario are represented in each of these databases by a unique encrypted identifier, thus permitting complete record linkage at the level of the individual across databases and across time.

*HPV Vaccination Status and Timing*

The HPV vaccination status and date of vaccination of each cohort member was ascertained using the IRIS database. HPV vaccine uptake was defined as having received at least one dose, whereas series completion required the receipt of all three doses during
cohort follow up. The number of days between the first and second dose (“Dose 1” and “2”) and the second and third dose (“Dose 3”) was calculated for each girl who received at least two and three doses, respectively, and categorized into groups that reflected the recommended dosing schedule (0, 2 and 6 months) and the allowed between dose grace period of 1 month (30 days) between Dose 1 and 2, and 2 months (60 days) between Dose 2 and 3. As such, the interval between Dose 1 and 2 was categorized as: (i) too short (<30 days), (ii) as recommended (30-90 days), and (iii) too long (>90 days), and the interval between Dose 2 and 3 as: (i) too short (<60 days), (ii) as recommended (60-180 days), and (iii) too long (>180 days). Similarly, “time-to-series completion” was calculated as the number of days between Dose 1 and 3 for girls who received at least 3 doses and was also categorized taking into account the allowed grace period of 60 days. In addition to the allowed grace period, the efficacy of the vaccine was demonstrated in individuals who received all 3 doses within a one year period, and was therefore considered as an “acceptable” time interval. “Time-to-series completion” was categorized as: (i) too short (<120 days), (ii) as recommended (120-240 days), (iii) acceptable (241-365 days), and (iv) too long (>365 days).

Baseline Characteristics

The baseline characteristics of cohort members were ascertained between birth and cohort entry using the RPDB, DAD, NACRS, OHIP and IRIS databases and included socio-demographics, vaccination history, medical history and patterns of health care utilization.
The socio-demographic factors considered included age at cohort entry, place of residence (urban/rural), and neighbourhood income. Place of residence and neighbourhood income were obtained by linking a girl’s postal code at cohort entry with the 2006 Canadian Census data. Neighbourhood incomes were categorized into provincial quintiles and place of residence into urban (≥10,000 persons) or rural (<10,000 persons).19

Vaccination history was ascertained using the IRIS database and included information on both optional and mandatory vaccines. In addition, whether HPV vaccination before cohort entry occurred and how many doses were given was determined.

Cohort members’ medical histories were established by identifying conditions leading to a hospitalization (DAD database), an ED visit (NACRS database), or an outpatient physician visit (OHIP database). The International Classification of Diseases, 9th and 10th-Canadian Enhancement Code Revisions (ICD-9 and 10CA) and OHIP diagnostic codes were used to identify the medical conditions listed in Appendix 1. DAD and NACRS allow for multiple diagnosis codes to be recorded for each visit, however, in view of the low agreement rates for the coding of a persons’ “main problem” in NACRS,12 only the first code recorded was used. The number of codes needed from DAD to accurately capture medical history has not been validated. Since few diagnostic codes were present beyond the tenth diagnostic position, two definitions of the medical conditions of interest were compared; one limited to the first five diagnostic positions and the other using the first 10 diagnostic positions. As there was little to no difference in the
prevalence of the specified conditions using either definition, medical conditions were ascertained using the first five diagnostic positions.

The indicators of health care utilization that were examined included the number of outpatient physician visits, number of hospital admissions and days hospitalized, the number of “same day surgeries” and ED visits. Calculations of the number of hospital admissions and days hospitalized included the birth admission. In addition, hospitalizations with the same date of admission and discharge were not included in the calculation of the number of days hospitalized to avoid the possibility of double-counting.

Ethics

This study was approved by Queen’s University Health Sciences Research Ethics Board and Sunnybrook Health Sciences Centre’s Ethics Review Board.

Statistical Analysis

Cross-tabulations were used to compare the baseline characteristics of unvaccinated and vaccinated girls.

The proportion of girls who initiated (uptake) and completed the qHPV vaccine series was calculated as the number of eligible girls receiving at least one dose divided by the total number of eligible girls and the number receiving all three doses during follow up divided by the number of girls who initiated the program, respectively.

Adherence to the recommended dosing interval between the three doses of the qHPV vaccine and for “time-to-series completion” was calculated as the proportion of
eligible girls whose number of days between doses complied with the recommended
dosing interval. In addition, the proportion of girls whose dosing interval was shorter or
longer than recommended was also calculated.

All statistical analyses were performed using Statistical Analysis Software (SAS)

RESULTS

The study cohort consisted of 111,798 Grade 8 girls born between 1994 and 1996
and eligible for Ontario’s HPV vaccination program (Figure 4.1). After record linking the
study cohort with the IRIS database, it was discovered that a small number of eligible
girls had duplicate HPV vaccination records with non-matching vaccination dates
(N=232 or 0.21%). These girls were excluded from the cohort as the correct vaccination
date could not be readily identified, thereby leaving 111,566 Grade 8 girls available for
the analysis. The duplicate records are due to parental self-reports of vaccination status
when girls move from one LPHA to another. Cohort members were a mean age of 13.17
years at cohort entry, and were followed for an average of 2.60 years. Cohort members
included in the current study represented a geographically diverse population of eligible
girls (Figure 4.2).

The baseline characteristics of HPV vaccinated and unvaccinated girls were
similar with respect to place of residence, neighbourhood income quintile, and medical
history but differed with respect to vaccination history and pattern of health care
utilization (Table 4.1). In particular, vaccinated girls were at least 1.5 times more likely to
have previously received an optional vaccine. In addition, vaccinated girls were more likely to see a family physician but were less likely to have been hospitalized. A total of 865 girls initiated the HPV vaccine prior to cohort entry and were removed from subsequent analyses.

Overall, 50.24% of eligible girls received at least one dose of the qHPV vaccine during the first three years of the province’s publicly funded vaccination program. HPV vaccine uptake was the lowest in the first year of the immunization program 46.56%, 53.54% (p<0.0001) and 50.65% (p<0.0001) in 2007/08, 2008/09 and 2009/10, respectively. Of those who initiated the HPV vaccine series, the vast majority received at least 3 doses (87.02%) (Table 4.2). There was a small number of girls who received more than the recommended three doses, with 73 (0.13%) having received four to five doses. This pattern of usage was consistent across all three years of the immunization program (Figure 4.3).

The pattern of the HPV vaccine dosing schedule and time-to-series completion is shown in Figure 4.4. Dose 2 was administered an average of 2.81 months (SD 1.45) following Dose 1, and Dose 3 an average of 4.21 months (SD 1.62) following Dose 2. For those who received all three doses, the average time to series completion was 6.88 months (SD 2.00), with the majority of Grade 8 girls completing their series within 4 to 8 months and over 95% completing the series within a year (Figure 4.5). The analyses were repeated to exclude those who received more than 3 doses during follow-up and yielded similar estimates.
DISCUSSION

This study described the uptake of the qHPV vaccine, its dose series completion and its dose administration timing in 111,566 girls in Ontario, Canada. To the best of our knowledge, this is the first study to assess the timing of HPV dose administration, particularly in the context of a publicly funded, school-based immunization program. Of those who initiated their HPV vaccination series, most received and completed the recommended 3-dose series within a time frame that is considered “acceptable” according to the manufacturer’s guidelines. Surprisingly, it was observed that a small percentage (0.13%) of girls who initiated the immunization program went on to receive upwards of five vaccine doses.

This study showed an overall uptake of 50.24% in the first three years of Ontario’s HPV immunization program; this is consistent with reported provincial HPV vaccine uptake rates\textsuperscript{20}. The first year of the program had the lowest uptake; however, subsequent years have not shown much improvement. Some provinces, such as the Atlantic provinces and Quebec, have reported uptake rates as high as 83 to 88%, while others, such as Manitoba and Alberta, have reported rates similar those in Ontario at 50-55%.\textsuperscript{21} Reasons for variation across the country are unknown; however, this variation may point to the need for Ontario public health agencies to change their current strategy in the promotion and provision of the qHPV vaccine to improve its uptake. Perhaps it is the target age group that requires reconsideration, or it may simply be a matter of increasing the promotional efforts made by the public health agencies. Ontario should look to the practices of other provinces, such as Quebec or the Atlantic provinces which have >80% uptake of the vaccine,\textsuperscript{21} to improve its uptake rate. On the other hand, as
parental concerns regarding the safety and long term effects of this vaccine has been identified as a major determinant of HPV vaccine uptake in a number of studies, facilitating the development of the necessary infrastructure to carry out post-marketing safety analyses needs to be given serious consideration.

On the other hand, since effectiveness of the HPV vaccine is, in part, dependent on the number of doses the girl receives, it is comforting to know that approximately 90% of vaccinated girls completed their immunization series; this is the highest series completion rate that has been reported to date, including rates reported in varying populations with different follow-up times.22-29 This finding may be due to differences in health care systems, and may highlight the benefits of offering the HPV vaccine through publicly funded school-based clinics. Moreover, this completion rate may be further augmented in the near future as a recent announcement declared that Ontario would be expanding their “catch up program” to allow female students who did not receive or finish the HPV vaccine series in Grade 8 to receive publicly funded HPV vaccine until the end of Grade 12.30

Although, it may be of concern that approximately 10% of girls do not complete the vaccination series, it was equally disconcerting to note that some girls received more than the recommended three HPV vaccine doses, with up to five doses received by some. These cases may be the result of administrative errors or erroneous self-reports of HPV vaccination history by parents or the girls themselves (e.g., forgetting they had already received three doses) as extra-immunization in children has been found to often occur when multiple immunization providers are involved,31 communication, including documentation, has been demonstrated as key factor for the occurrence of pediatric
medication errors, and parental recall for vaccinations requiring more than one dose has been observed to be poor. The clinical impact of receiving excess doses is unknown; however, this may present an economical issue as financial resources are spent on providing unnecessary doses for free to these girls. These findings provide evidence for the need to improve immunization record keeping and information sharing practices in Ontario.

The qHPV vaccine is recommended by the manufacturer to be administered intramuscularly as three separate doses at 0, 2 and 6 months. Clinical studies conducted by the manufacturer have shown sustained vaccine efficacy even when a grace period of 1 month for Dose 2, and 2 months for Dose 3 is applied to the dosing interval, provided the vaccine series is completed within one year. Although the majority of eligible Grade 8 girls received their vaccine doses within the recommended dosing intervals, some girls received the vaccine too early or too late. These situations may occur for various reasons. Perhaps the girl was not present at school at the time of vaccination and subsequently received the vaccine from a family physician or the public health unit, and in doing so, modified the dose timing; or perhaps scheduling of clinic dates may have postponed due to holidays or unforeseen school field trips. Unfortunately, the clinical impact of dosing deviations is currently unknown. It will therefore be important for future studies to evaluate the effectiveness and/or safety of the qHPV vaccine when doses are given outside of the recommended time frames.

The limitations of this study include the potential for loss to follow-up bias, the potential for inaccurate HPV vaccination dates, and the possibility that the results may not be easily generalized to other populations.
Studies using population databases may be susceptible to loss to follow-up when subjects migrate to a jurisdiction that is not captured by the databases used. In this study, the completion of the vaccination series may be unknown if a girl moved out of the province of Ontario, or to a public health region whose immunization records were not available at the time of the analysis. However, as nearly 90% of cohort members completed their HPV vaccine series, losses to follow-up are unlikely to be an important source of bias.

Another potential limitation of the use of administrative databases is the possibility of misclassification bias due to inaccurate information, such as the date of HPV vaccination. Fortunately, a recent re-abstraction study found that HPV vaccination dates captured in IRIS were 98.6% accurate in the KFL&A region.\textsuperscript{17} It may be argued that the accuracy of the IRIS database of one LPHA may not be generalized to other IRIS databases; however, as it is a high priority of the public health unit to obtain accurate immunization information for all individuals enrolled in Ontario schools, it is unlikely that the other IRIS databases were considerably less accurate.

Lastly, the results of this study of a publicly funded, school clinic based HPV immunization program may not be generalized to other jurisdictions. Other countries may not offer the qHPV vaccine for free, and while other provinces in Canada also offer free HPV immunization programs, the age targeted by other provincial programs varies;\textsuperscript{34} thus, the results of this study may not be applicable to other jurisdictions and populations.
CONCLUSION

In Ontario, the overall uptake of the qHPV vaccine is low; however, among those who initiate the immunization program, the series completion rate is high, with the majority of eligible girls receiving the vaccine in a timely manner. This is the first study to describe the scheduling of HPV dose administration. Low uptake provides evidence for the improvement of Ontario’s current promotion and provision strategy of the qHPV vaccine, while extra-immunizations suggest improvement in the immunization record keeping and information sharing practices in Ontario. Future studies should investigate the factors associated with low uptake rate, incorrect dose timing and excess doses, as well as the efficacy and safety of this vaccine when received outside of the recommended dose scheduling.

REFERENCES


Figure 4.1 Cohort flow diagram
Figure 4.2 Geographic representation of immunization data transferred from local public health units at the time of the analysis

The green regions represent health units who immunization records were available at the time of the analysis. The pink regions represent health units whose immunization records were transferred after the analysis had begun.
Table 4.1 Baseline characteristics of Grade 8 girls vaccinated and unvaccinated with the qHPV vaccine in Ontario, Canada

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Vaccinated (N=56 024)</th>
<th>Unvaccinated (N=55 542)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td><strong>Socio-Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td>13.17 (0.28)</td>
<td>13.17 (0.29)</td>
</tr>
<tr>
<td>Follow-up (years), mean (SD)</td>
<td>2.57 (0.80)</td>
<td>2.62 (0.83)</td>
</tr>
<tr>
<td>Deaths during follow-up</td>
<td>13 (0.02)</td>
<td>16 (0.03)</td>
</tr>
<tr>
<td>Place of residence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>47 344 (84.51)</td>
<td>45 398 (81.74)</td>
</tr>
<tr>
<td>Rural</td>
<td>8642 (15.43)</td>
<td>8230 (14.82)</td>
</tr>
<tr>
<td>Missing°</td>
<td>38 (0.07)</td>
<td>1914 (3.45)</td>
</tr>
<tr>
<td><strong>Income Quintile</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st (lowest)</td>
<td>8092 (14.44)</td>
<td>8736 (15.73)</td>
</tr>
<tr>
<td>2nd</td>
<td>10 445 (18.64)</td>
<td>9552 (17.20)</td>
</tr>
<tr>
<td>3rd</td>
<td>12 695 (22.66)</td>
<td>11 169 (20.11)</td>
</tr>
<tr>
<td>4th</td>
<td>12 821 (22.88)</td>
<td>12 150 (21.88)</td>
</tr>
<tr>
<td>5th (highest)</td>
<td>11 771 (21.01)</td>
<td>11 804 (21.25)</td>
</tr>
<tr>
<td>Missing°</td>
<td>200 (0.36)</td>
<td>2131 (3.84)</td>
</tr>
<tr>
<td><strong>Vaccination History</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Mandatory Vaccinations§</td>
<td>55 482 (99.03)</td>
<td>53 078 (95.56)</td>
</tr>
<tr>
<td><strong>Optional Vaccinations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>48 580 (86.71)</td>
<td>32 056 (57.71)</td>
</tr>
<tr>
<td>Meningococcal C</td>
<td>44 346 (79.16)</td>
<td>25 786 (46.43)</td>
</tr>
<tr>
<td>Both</td>
<td>41 644 (74.33)</td>
<td>23 530 (42.36)</td>
</tr>
<tr>
<td><strong>Both Mandatory§ and Optional Vaccinations</strong></td>
<td>41 379 (73.86)</td>
<td>23 315 (41.98)</td>
</tr>
<tr>
<td><strong>Initiated HPV Vaccination</strong></td>
<td>411 (0.73)</td>
<td>454 (0.82)</td>
</tr>
<tr>
<td>Prior to Cohort Entry (t0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Dose</td>
<td>303 (73.72)</td>
<td>63 (13.88)</td>
</tr>
<tr>
<td>2 or 3 Doses×</td>
<td>108 (26.28)</td>
<td>391 (86.12)</td>
</tr>
<tr>
<td>From 1st dose to t0 (days), median (IQR)</td>
<td>173 (79-231)</td>
<td>336 (306-508)</td>
</tr>
<tr>
<td>From last dose to t0 (days), median (IQR)</td>
<td>139 (54-223)</td>
<td>154.5 (332-111)</td>
</tr>
<tr>
<td><strong>Medical History</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergy (Anaphylaxis)</td>
<td>601 (1.07)</td>
<td>607 (1.09)</td>
</tr>
<tr>
<td>Category</td>
<td>Count 1</td>
<td>Count 2</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>Asthma/Bronchitis/Pneumonia (all types)</td>
<td>40,391 (72.10%)</td>
<td>38,307 (68.97%)</td>
</tr>
<tr>
<td>Autoimmune Disorders</td>
<td>2832 (5.05%)</td>
<td>2803 (5.05%)</td>
</tr>
<tr>
<td>Neoplasms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain Neoplasm</td>
<td>48 (0.09%)</td>
<td>50 (0.09%)</td>
</tr>
<tr>
<td>Other</td>
<td>6,998 (12.49%)</td>
<td>6,626 (11.93%)</td>
</tr>
<tr>
<td>Congenital Anomalies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Down Syndrome</td>
<td>276 (0.49%)</td>
<td>346 (0.62%)</td>
</tr>
<tr>
<td>Tuberous Sclerosis</td>
<td>716 (1.28%)</td>
<td>813 (1.46%)</td>
</tr>
<tr>
<td>Other</td>
<td>6,638 (11.85%)</td>
<td>6,461 (11.63%)</td>
</tr>
<tr>
<td>Diseases of the Central Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral Palsy</td>
<td>179 (0.32%)</td>
<td>339 (0.61%)</td>
</tr>
<tr>
<td>Epilepsy/Recurrent Seizures*</td>
<td>1,667 (2.98%)</td>
<td>1,952 (3.51%)</td>
</tr>
<tr>
<td>Other</td>
<td>4,404 (7.86%)</td>
<td>4,239 (7.63%)</td>
</tr>
<tr>
<td>Head Injury and Trauma</td>
<td>10,503 (18.75%)</td>
<td>10,137 (18.25%)</td>
</tr>
<tr>
<td>Human Immunodeficiency</td>
<td>43 (0.08%)</td>
<td>41 (0.07%)</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection of the Central Nervous System</td>
<td>354 (0.63%)</td>
<td>373 (0.67%)</td>
</tr>
<tr>
<td>Sexually Transmitted Infections</td>
<td>1,904 (3.40%)</td>
<td>1,885 (3.39%)</td>
</tr>
<tr>
<td>Other</td>
<td>49,824 (88.93%)</td>
<td>47,731 (85.94%)</td>
</tr>
<tr>
<td>Mental/Behavioral Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental Retardation</td>
<td>296 (0.53%)</td>
<td>466 (0.84%)</td>
</tr>
<tr>
<td>Other</td>
<td>18,820 (33.59%)</td>
<td>18,698 (33.66%)</td>
</tr>
<tr>
<td>Newborn Seizure/Convulsions</td>
<td>12,329 (22.01%)</td>
<td>11,316 (20.37%)</td>
</tr>
<tr>
<td>Perinatal Complications**</td>
<td>16,496 (29.44%)</td>
<td>15,431 (27.78%)</td>
</tr>
<tr>
<td>Health Care Utilization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient Visits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (0-40)</td>
<td>17,356 (30.98%)</td>
<td>20,748 (37.35%)</td>
</tr>
<tr>
<td>Med-low (41-80)</td>
<td>24,328 (43.42%)</td>
<td>22,344 (40.23%)</td>
</tr>
<tr>
<td>Med-high (81-130)</td>
<td>11,277 (20.13%)</td>
<td>9,779 (17.61%)</td>
</tr>
<tr>
<td>High (≥131)</td>
<td>3,063 (5.47%)</td>
<td>2,671 (4.81%)</td>
</tr>
<tr>
<td>Family/General/Pediatric Physician†</td>
<td>55,650 (99.33%)</td>
<td>54,786 (98.64%)</td>
</tr>
<tr>
<td>Low (1-50)†</td>
<td>27,605 (49.60%)</td>
<td>30,124 (54.98%)</td>
</tr>
<tr>
<td>Med (51-115)†</td>
<td>24,852 (44.66%)</td>
<td>21,926 (40.02%)</td>
</tr>
<tr>
<td>Category</td>
<td>Low (0-1)</td>
<td>Med (2)</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>43 278 (77.25)</td>
<td>9001 (16.07)</td>
</tr>
<tr>
<td>In hospital at cohort entry ≤10</td>
<td>31 826 (56.81)</td>
<td>21 148 (37.75)</td>
</tr>
<tr>
<td>Days in Hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (0-2 days)</td>
<td>31 826 (56.81)</td>
<td>21 148 (37.75)</td>
</tr>
<tr>
<td>Med (3-10 days)</td>
<td>31 826 (56.81)</td>
<td>21 148 (37.75)</td>
</tr>
<tr>
<td>High (≥11 days)</td>
<td>31 826 (56.81)</td>
<td>21 148 (37.75)</td>
</tr>
<tr>
<td>Same Day Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (0)</td>
<td>43 375 (77.42)</td>
<td>11 322 (20.21)</td>
</tr>
<tr>
<td>Med (1-2)</td>
<td>43 375 (77.42)</td>
<td>11 322 (20.21)</td>
</tr>
<tr>
<td>High (≥3)</td>
<td>43 375 (77.42)</td>
<td>11 322 (20.21)</td>
</tr>
<tr>
<td>Emergency Department Visits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (0)</td>
<td>4507 (8.04)</td>
<td>38 831 (69.31)</td>
</tr>
<tr>
<td>Med-low (1-3)</td>
<td>4507 (8.04)</td>
<td>38 831 (69.31)</td>
</tr>
<tr>
<td>Med-high (4-10)</td>
<td>4507 (8.04)</td>
<td>38 831 (69.31)</td>
</tr>
<tr>
<td>High (≥11)</td>
<td>4507 (8.04)</td>
<td>38 831 (69.31)</td>
</tr>
</tbody>
</table>

**SD** = Standard Deviation; **IQR** = Interquartile Range

* Expressed as N (%) unless otherwise stated
† Missing because postal code in RPDB did not exist at the time of the 2006 census
$ Matthew convulsions
$ Includes status epilepticus
\* Includes newborn seizures/convulsions
† Percentage of those who have seen a medical doctor of the specified specialty at least once
‡ Calculated based on those who have seen a medical doctor of the specified specialty at least once
Table 4.2 Overall qHPV vaccine uptake, series completion and the frequency of the number of doses received

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uptake</td>
<td>55 613 (50.24)</td>
</tr>
<tr>
<td>Series Completion</td>
<td></td>
</tr>
<tr>
<td>1 dose</td>
<td>1847 (3.32)</td>
</tr>
<tr>
<td>2 doses</td>
<td>5373 (9.66)</td>
</tr>
<tr>
<td>3 doses</td>
<td>48 320 (86.89)</td>
</tr>
<tr>
<td>4 or 5 doses</td>
<td>73 (0.13)</td>
</tr>
</tbody>
</table>
Figure 4.3 Frequency of the number of doses received according to immunization program year
Figure 4.4 Patterns of the qHPV vaccine dosing schedule and time-to-series completion
Figure 4.5 Patterns of adherence to recommended dosing schedule and time-to-series completion of the qHPV vaccine
Chapter 5

The Risk of Serious Neurological Events Associated with the Use of the Quadrivalent Human Papillomavirus (HPV) Vaccine: The Ontario Grade 8 HPV Cohort Study

5.1 Preface to the Manuscript

This chapter contains the second of two manuscripts of this thesis addressing the use and neurological safety of the quadrivalent (q-) human papillomavirus (HPV) vaccine in Ontario. The focus of this manuscript is on the potential adverse neurological effects of the HPV vaccine that could not be detected in randomized controlled trials because of small sample sizes.

As discussed in Chapter 2, convulsions, seizures and epilepsy were selected as the study endpoints due to frequent reporting of these events to the Vaccine Adverse Events Reporting System (VAERS), and because neurological events have been associated with other vaccines.

The factors that predict the outcomes of interest as well as those influencing vaccine uptake or avoidance have not been extensively studied. Furthermore, potential confounders such as race/ethnicity, socioeconomic status (SES) and family history of epilepsy are not captured by administrative health databases. As such, this study employed a self-matched analysis known as the self-controlled case series method, an analytical technique known to control for all known, unknown and unmeasured time-independent confounders.
Following the manuscript, the results and discussion of additional sensitivity analyses undertaken to address the robustness of the findings of the primary analysis are presented.
5.2 Manuscript: The Risk of Serious Neurological Events Associated with the Use of the Quadrivalent Human Papillomavirus (HPV) Vaccine: The Ontario Grade 8 HPV Vaccine Cohort Study

ABSTRACT

Background: Passive surveillance has suggested a possible association between the quadrivalent (q-) human papillomavirus (HPV) vaccine and neurological events. The risk of serious neurological events such as those reported with the qHPV vaccine has been established with other vaccines; however, to date, no study has evaluated the risk of these events following qHPV vaccination.

Methods: This retrospective cohort study followed Grade 8 girls eligible to receive the qHPV vaccine during the 2007/08 to 2010/11 campaign years of Ontario’s HPV immunization program. Using Ontario’s immunization and health databases, dates of qHPV vaccination and diagnoses of serious neurological events were identified for each cohort member. A self-matched, case only approach was used to estimate the age-adjusted rate ratio (RR) of neurological events in the 0-30 day period following qHPV vaccination. The primary study endpoint was a composite of the first occurrence of a convulsion, seizure or epilepsy. Secondarily, an epileptic seizure only endpoint was assessed, as were the influence of a number of predisposing risk factors.

Results: There was no increased risk observed for the composite endpoint of serious neurological events in the 0-30 days following qHPV vaccination (RR 1.01, 95% CI 0.92-1.10). However, girls with predisposing risk factors for epilepsy including history of epileptic seizures, cerebral palsy and Down syndrome did experience an elevated risk following vaccination (RR 1.50, 95% CI 1.13-1.99; RR 2.11, 95% CI 0.95-4.67; and RR...
3.09, 95% CI 1.42-6.72, respectively). An increased risk was observed for the epileptic seizure only endpoint (RR 1.64, 95% CI 1.28-2.10); this was time-dependent as risk was highest immediately post-vaccination (RR 2.55, 95% CI 1.26-5.15 for the period 0-1 day), and diminished thereafter (RR 1.57, 95% CI 1.21-2.04 and RR 1.13, 95% CI 0.85-1.50 in the 2-30 days and 31-60 days following vaccination, respectively).

Conclusions: The use of the qHPV vaccine was associated with an increased risk for seizures among Grade 8 girls. This risk may be limited to girls with predisposing risk factors for epilepsy. Further studies are needed to delineate the type of seizures involved in such reactions as early seizures likely represent injection-related reactions rather than vaccine-induced reactions.
INTRODUCTION

The human papillomavirus (HPV) is a common sexually transmitted virus with over 100 types. Two high-risk types of this virus, types 16 and 18, cause 70% of cervical cancers,\(^1\),\(^2\) while low risk viruses, types 6 and 11, are believed to cause 90% of genital warts\(^3\). In 2006, Canada and the United States (US) approved a quadrivalent HPV (qHPV) vaccine for use in females aged 9-26 years to prevent infection with these four HPV types and associated diseases.\(^4\),\(^5\) The vaccine is most effective when administered before onset of sexual activity; thus, national advisory committees currently recommend that girls be immunized between the ages of 9-13 in Canada and 11-12 in the US.\(^6\),\(^7\)

Although randomized controlled trials of the HPV vaccine suggest the vaccine is safe and effective,\(^8\) these trials were underpowered to detect rare, but serious, adverse events\(^9\). Additionally, the average age of female participants was 20 years, with less than 5% under the age of 16;\(^9\) this further emphasizes the limited amount of safety evidence for the young age group targeted by national advisory committees’ recommendations. It is therefore not surprising that parental concerns about the safety of the HPV vaccine have been found to be an important determinant of non-uptake of this vaccine.\(^10\)-\(^12\)

Reports to the US Vaccine Adverse Events Reporting System (VAERS) have suggested a possible association between the vaccine and neurological events including convulsions, seizures and epilepsy.\(^13\) Although no observational studies evaluating this association have been conducted to date, the risk of neurological events following immunization is not a novel hypothesis as febrile seizures (i.e., epileptic seizures associated with a significant rise in body temperature) are believed to be causally associated with vaccine use and has been reported following the administration of the
diphtheria, tetanus and whole-cell pertussis (DTP), the measles, mumps and rubella (MMR) vaccine, and a newly marketed meningococcal A vaccine.\textsuperscript{14-22}

This population-based, retrospective cohort study assessed the risk of convulsions, seizures and epilepsy following immunization with the qHPV vaccine.

**METHODS**

*Ontario’s Grade 8 HPV vaccination program*

In 2007, the Ontario government announced the start of a three-year, $117 million program to provide free qHPV vaccinations to all Grade 8 girls through school-based clinics coordinated by the province’s 36 Health Units;\textsuperscript{23} this publicly funded vaccination program is now in its fifth year. This voluntary vaccination program usually requires parental consent and eligible girls have until the end of August of their Grade 8 year to initiate the three dose series, and until the end of Grade 9 to complete the series. The HPV vaccine is typically administered at school clinics by public health nurses in September/October, November/December, and March/April of each school year. Eligible girls can also obtain the vaccine at the Health Unit or through their family physician who obtains the vaccine from the Health Unit.

*Data Sources*

For this study, the following databases were used: (1) the Registered Persons Database (RPDB) for information on socio-demographics and health insurance coverage of residents of Ontario (Canada’s most populous province), (2) the Canadian Institute for Health Information’s (CIHI) Discharge Abstract Database (DAD) for detailed
information on hospitalizations, (3) the National Ambulatory Care Reporting System (NACRS) database for information on emergency department (ED) visits, and (4) the Ontario Health Insurance Plan (OHIP) database for information on physician services claims. These databases, described elsewhere in detail, were developed to maintain records on the universal health care programs offered to residents of the province, and have been used extensively in health research, including in post-marketing evaluations of drugs and vaccines. In addition, the Immunization Record Information System (IRIS) database was used for information on vaccinations. The IRIS database, maintained by each individual Health Unit, was developed by the Ontario Ministry of Health and Long-Term Care (MOHLTC) to track and record immunizations of school-aged children. As a result, the IRIS databases contain individual-level information on all qHPV vaccine doses administered through the province’s publicly funded program. The IRIS database of each health unit was transferred to the Institute for Clinical Evaluative Sciences (ICES) under Data Sharing Agreements to create a provincial immunization database that was record linked with the province’s administrative health databases. A recent re-abstraction of the Kingston, Frontenac, Lennox and Addington Public Health (KFL&A) IRIS database demonstrated that IRIS is both valid and accurate in capturing individuals’ HPV vaccination status with a sensitivity of 99.8% (95% CI 99.3-99.9), a specificity of 97.7% (95% CI 96.3-98.7), and an accuracy of 98.6% for the vaccination dates. Such low levels of misclassification can be explained by the necessity of health units to track and record immunizations of school-aged children mandated under the Immunization of School Pupils Act (1982). Residents of Ontario are represented in each of these
databases by a unique encrypted identifier, thus permitting complete record linkage at the level of the individual across databases and across time.

Study Population and Design

This population-based, retrospective cohort study was analyzed using a self-matched approach known as the self-controlled case-series method. The cohort consisted of girls eligible for the first four years of Ontario’s publicly funded Grade 8 HPV immunization program, beginning with the 2007/08 school year. Because school grade is not available in the administrative databases, the study cohort was identified using birth year as girls entering Grade 8 must turn 13 by December 31st of that year. As such, all girls born between 1994 and 1997 were identified using the insured persons’ population registry (RPDB). Cohort members were followed from September 1st of their eligible school year (cohort entry) until the earliest of the following: date of death, date of transfer of their immunization records for record linkage (May to August 2011) or the end of the study (March 31, 2011).

Eligible girls whose immunization records were not available at the time of the analysis (i.e., data not yet transferred from their health unit) were excluded from the cohort, as were those who had died prior to cohort entry (but were still listed in the population registry database).

HPV Vaccine Exposure

All doses of the qHPV vaccine administered during follow-up were identified using the IRIS database. The dates of administration of individual doses were used to
identify the start of pre-specified periods of follow-up time during which an individual was considered at increased risk of neurological events (i.e., etiologically exposed person-time). These time periods are herein referred to as exposure risk periods. The duration of these periods was based on suggested mechanisms for convulsions and seizures following immunization, the timing of post-vaccination neurological events reported to VAERS, and previous studies of neurological events following vaccination. Unexposed person-time was all follow-up that did not fall within an exposure risk period (Figure 5.1).

**Study End Point**

The outcome of interest was a composite of the first occurrence of a convulsion, seizure or epilepsy [International Classification of Diseases, 10th-Canadian Enhancement Code Revision (ICD-10CA), codes G40, G41, R56.0, R56.8; OHIP fee-for-service medical claims codes 345, 780] anytime after cohort entry. The DAD, NACRS, and OHIP databases were used to identify the study end point.

**Ethics**

This study was approved by Queen’s University Health Sciences Research Ethics Board and Sunnybrook Health Sciences Centre’s Ethics Review Board.

**Statistical Analysis**

Traditionally, cohort data are analyzed using time-to-event Cox Proportional Hazards regression. However, since little is known about the risk factors for the
neurological outcomes under study, as well as those influencing vaccine uptake or avoidance in the Ontario Grade 8 population, a traditional Cox analysis may be particularly susceptible to confounding bias. In addition, potential confounders such as race/ethnicity, socioeconomic status (SES), and family history of neurological conditions are not captured by administrative health databases, thereby further increasing the potential for bias. Consequently, the self-controlled case series (SCCS) method was employed to assess the association between qHPV vaccination and the risk of serious neurological events. This self-matched analysis, described in detail elsewhere, offers the advantage of controlling for all time-independent confounders, whether known or unknown, by comparing cases to themselves over time. Furthermore, since the SCCS method is derived from the cohort model, it is possible to control for time effects such as confounding by age by including unvaccinated cases in the analysis. Rate ratios are estimated by comparing the event rate during exposed person-time (exposure risk periods) with that during unexposed time for the same individual. As such, unvaccinated cases do not contribute to the estimation of the rate ratios.

The primary analysis was based on the a priori chosen exposure risk period of 0-30 days following immunization (i.e., day of vaccination to 30 days later). To account for the possibility of confounding by age, unvaccinated cases were also included in the analysis. Incidence rate ratios (RR) and 95% confidence intervals (CI) were estimated using conditional Poisson regression to account for the individual level matching. Subsequently, the analysis was repeated stratified on the basis of: (1) history of epileptic seizures, (2) history of convulsions (including febrile seizures), (3) head trauma and brain injury, (4) central nervous system (CNS) infections, (5) cerebral palsy, (6) mental
retardation, (7) tuberous sclerosis, and (8) Down syndrome to assess potential effect modification.

To test the robustness of the study’s findings under the assumptions made for the primary analysis, the analysis was repeated by first removing any girls who received >3 doses, then by assuming a differential dose effect relationship (i.e., risk differs by dose). The analysis was also repeated to test for the influence of misclassification bias by: (1) using only cases identified through the DAD and NACRS databases; (2) only considering epileptic seizures [ICD-10CA code G40, G41; OHIP code 345] for the case definition; (3) only considering convulsions (including febrile seizures and excluding those also captured as an epileptic seizure case) [ICD-10CA codes R56.0, R56.8; OHIP code 780] for the case definition; and (4) using exposure risk periods of 0-1 day, 2-30 days and 31-42 days following vaccination. Additionally, the association between the qHPV vaccine and syncope [ICD-10CA code R55; OHIP code 785] was assessed to help distinguish between physiological (anoxic) seizures and epileptic seizures since the former is more likely to be accompanied by fainting. Finally, to assess whether age was an important source of confounding, the analysis was repeated excluding unvaccinated cases.

All statistical analyses were performed using Statistical Analysis Software (SAS) version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

The cohort consisted of 145,766 girls with a mean age of 13.17 years at cohort entry, and followed for a median of 2.58 years (interquartile range, IQR 1.58-3.58)
After record linking the study cohort with the IRIS database, it was discovered that a small number of eligible girls had duplicate HPV vaccination records with non-matching vaccination dates (N=232 or 0.16%). These girls were excluded from the cohort as the correct vaccination date could not be readily identified, thereby leaving 145,534 Grade 8 girls available for the analysis. The duplicate records are due to parental self-reports of vaccination status when girls move from one health unit to another.

Vaccinated and unvaccinated girls were similar with respect to socio-demographic characteristics and medical history (diagnostic codes used to identify the medical conditions listed in Appendix 1); however, vaccinated girls were more likely to see a family physician but were somewhat less likely to have been hospitalized (Table 5.1). On the other hand, girls who received the qHPV vaccine were much more likely to have received optional vaccines such as Hepatitis B and Meningococcal C.

During follow-up, a total of 5591 vaccinated cases were identified (Figure 5.3). 87 (1.56%) of these resulted in a visit to the emergency department, and ≤10 (≤0.18%) in a hospitalization. 4.94% of cases (N=276) received 1 dose of the HPV vaccine, 15.04% (N=841) received 2 doses, and 80.02% (N=4474) received at least 3 doses. An additional 5007 unvaccinated cases were identified and included in the analysis to control for confounding by age.

There was no increased risk observed for the composite endpoint of serious neurological events in the 0-30 days following qHPV vaccination (RR 1.01, 95% CI 0.92-1.10). The addition of unvaccinated girls to control for confounding between exposure and age did not change this estimate (age-adjusted RR 1.01, 95% CI: 0.9-1.10). These results were unchanged after excluding girls who received more than 3 doses,
removing cases identified from OHIP, testing for a dose-response, and testing different exposure risk periods. Additionally, there was no association between the qHPV vaccine and syncope. However, the qHPV vaccine was associated with a significantly increased risk of serious neurological events among girls with a history of epileptic seizures, cerebral palsy, and Down syndrome (Figure 5.4).

There was an increased risk observed for the epileptic seizure only endpoint (RR 1.64, 95% CI 1.28-2.10). The risk estimates this endpoint were affected by the length of the exposure risk window, being highest immediately post-vaccination (RR 2.55, 95% CI 1.26-5.15) and diminishing thereafter (Table 5.2). Conversely risk estimates for the convulsion only endpoint were similar to those of the composite endpoint. The incidence pattern of epileptic seizure cases relative to dose administration is shown in Figure 5.5. The average time-to-seizure event following qHPV vaccination ranged from 2-3 weeks.

DISCUSSION

No risk was observed for the composite endpoint of convulsions, seizures and epilepsy in the 0-30 days following qHPV vaccination. However, a significantly increased risk was detected among girls with a history of epileptic seizures, cerebral palsy and Down syndrome, all of which are predisposing risk factors for epilepsy. Sensitivity analyses suggest the use of a composite endpoint may have resulted in significant misclassification as an increased risk 0-30 days post-vaccination was observed when the analysis was restricted to the endpoint of epileptic seizures, but not when the analysis was restricted to convulsions. The risk of seizure was greatest immediately following HPV vaccination, remained elevated and diminished after 30 days. However,
This risk may be limited to girls with predisposing risk factors for these events including history of epileptic seizures, cerebral palsy and Down syndrome, as suggested by the subgroup analyses seen in the composite endpoint; further research is needed to address this hypothesis.

This study is the first population-based observational study to assess the risk of neurological events following qHPV vaccination. To our knowledge, there has only been one study that has assessed the risk of neurological events following HPV vaccination. This study reviewed and described adverse events following HPV immunization reported to VAERS, and found a reporting rate of 0.29 convulsions per 100,000 vaccine doses distributed, which was not greater than the background rates reported with other vaccines. Furthermore, a reporting of 8.2 syncope cases per 100,000 qHPV doses distributed, which investigators claimed was “disproportional” to other vaccines, suggested that some reports of seizures may be anoxic seizures resulting from syncopal episodes. Although the reporting rate for convulsions did not appear greater than the background rates reported with other vaccines, the VAERS study had a number of significant limitations that prevent conclusions from being drawn about the risk for convulsions or seizure-like activity following HPV vaccination. Studies using VAERS reports are limited by the potential for under- and over-reporting of adverse events following vaccination, the lack of information on adverse events rates in unvaccinated persons (comparator group), and confounding from concomitant use of other drugs and/or concomitant disease. The current study on the other hand overcame these limitations with the use of population-based databases and a self-matched analysis. The use of population-based databases removed the potential for under- and over-reporting of events as events
are no longer voluntarily reported and provided information on the incidence of events independent of HPV vaccination (i.e., a comparator group). The use of a self-matched analysis allowed control for known, unmeasured, and unknown time-independent confounders.

This study’s primary outcome definition was a composite of the first occurrence of convulsions, seizures and epilepsy; this was done to try and account for the possibility that: (1) epileptic seizures may have been misdiagnosed or mis-coded as general convulsions,43 (2) non-epileptic seizures may have been mistaken for epileptic seizures,44, 45 and (3) that tonic-clonic, seizure-like activity is well recognized as accompanying syncope46. However, this composite endpoint was found to be highly misclassified as a statistically significant risk was found for epileptic seizures following qHPV vaccination, but there was no risk for the convulsion only endpoint. It has been proposed that peripheral inflammation following immunization could induce a corresponding inflammatory response in the brain and consequently cause transient or long-term effects on seizure susceptibility either through the disruption of the blood-brain barrier thereby altering cerebral neurotransmission or other mechanisms, such as the direct effects of cytokines on neurons.47 Reflex anoxic seizures, a type of non-epileptic seizures, may also be triggered through the subsequent cerebral ischemia of vagal stimulation following needle injections.48 The differing biological mechanisms underlying epileptic and non-epileptic seizures are likely the cause for such high misclassification. We assessed the risk of syncope following quadrivalent vaccination in attempt to distinguish between anoxic seizures and epileptic seizures, and found no association; however, as the primary risk period was 0-30 days, syncope may have been too misclassified to find an
association during this risk period, even if one existed, as the relevant risk period for syncope would likely be the same day.

The risk of epileptic seizures following qHPV vaccination is consistent with the findings of other vaccine studies with regards to both magnitude and risk period. DTP and MMR vaccines have established risks of febrile seizures with RR of 1.8 to 5.7 immediately following vaccination, and RR of 3.0 six to fourteen days post-vaccination, respectively.\textsuperscript{14, 15, 17, 19} This study found a risk of epileptic seizures 0-30 days post-vaccination, with the risk being highest immediately following vaccination (0-1 day) and diminishing after 30 days. The higher risk for epileptic seizures immediately following vaccination suggests the occurrence of anoxic seizures rather than epileptic seizures; thus, caution must be exercised with the use of the term “epileptic seizure” as anoxic seizures may be miscoded as epileptic seizures. Despite this, the adverse neurological events detected were serious enough of warrant contact with the healthcare system. The relative risk increase of post-vaccination seizures observed in this study corresponds to a number needed to harm (NNH) of 389, and must be weighed against the benefits of the qHPV vaccine. Furthermore, as subgroup analyses for the composite endpoint indicated that the elevated risk may be confined to girls with a history of epileptic seizures, cerebral palsy and Down syndrome, future studies are needed to determine whether the risk of seizure we observed is limited to those with predisposing risk factors. If the risk is restricted to those with predisposing risk factors, health care providers may provide caution to parents of girls with predisposed risk, and simultaneously reassure other parents about the vaccine’s neurological safety.
A limitation of this study was the use of a composite endpoint. Misclassification due to the inclusion of convulsions likely made it impossible to observe the association between the qHPV vaccine and epileptic seizures because the analysis was dominated by convulsions endpoints. Disease coding within the OHIP database is truncated to 3 digits, consequently removing precision of disease type and grouping convulsions with ataxia, vertigo and headaches (excluding tension headaches and migraines). Nevertheless, OHIP data were included as it was assumed that the majority of cases of seizure-like activity would be diagnosed in an outpatient clinic setting (i.e., family/general physician or pediatrician). Sensitivity analyses demonstrated that the exclusion of endpoints identified in the OHIP database still resulted in a null effect, however, an increased risk of epileptic seizures was observed when isolated from the composite endpoint. This increased risk for an epileptic seizure only endpoint indicated the composite endpoint was highly misclassified and that the misclassification was not primarily driven by the use of OHIP data.

CONCLUSION

There was an increased risk for seizures 0-30 days following qHPV vaccination among Grade 8 girls. However, this risk may be limited to girls with predisposing risk factors for epilepsy. The use of a composite neurological endpoint including convulsions resulted in significant misclassification. Further studies are needed to delineate the type of seizures involved in such reactions as early seizures likely represent injection-related reactions rather than vaccine-induced reactions.
REFERENCES


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48. Appleton RE. Reflex anoxic seizures: May be frightening to parents but are nothing to worry about. BMJ 1993;307(6898):214-5.
Figure 5.1 Conceptual diagram of the self-controlled case series (SCCS) method
Figure 5.2 Cohort flow diagram
Table 5.1 Baseline characteristics of Grade 8 girls vaccinated and unvaccinated with the qHPV vaccine in Ontario, Canada

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Vaccinated (N=72 798)</th>
<th>Unvaccinated (N=72 736)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td><strong>Socio-demographics</strong></td>
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<td></td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td>13.17 (0.28)</td>
<td>13.17 (0.29)</td>
</tr>
<tr>
<td>Follow-Up (years), median (IQR)</td>
<td>2.58 (1.58-2.58)</td>
<td>2.58 (1.58-3.58)</td>
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<tr>
<td>Deaths during follow-up</td>
<td>14 (0.02)</td>
<td>17 (0.02)</td>
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<tr>
<td>Place of Residence</td>
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<tr>
<td>Urban</td>
<td>61 699 (84.75)</td>
<td>59 463 (81.75)</td>
</tr>
<tr>
<td>Rural</td>
<td>11 056 (15.19)</td>
<td>10 831 (14.89)</td>
</tr>
<tr>
<td>Missing</td>
<td>43 (0.06)</td>
<td>2442 (3.36)</td>
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<tr>
<td>Income Quintile</td>
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<tr>
<td>1st (lowest)</td>
<td>10 298 (14.15)</td>
<td>11 421 (15.70)</td>
</tr>
<tr>
<td>2nd</td>
<td>13 506 (18.55)</td>
<td>12 509 (17.20)</td>
</tr>
<tr>
<td>3rd</td>
<td>16 531 (22.71)</td>
<td>14 537 (19.99)</td>
</tr>
<tr>
<td>4th</td>
<td>16 767 (23.03)</td>
<td>15 965 (21.95)</td>
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<tr>
<td>5th (highest)</td>
<td>15 473 (21.25)</td>
<td>15 581 (21.42)</td>
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<td>Missing</td>
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<td>2723 (3.74)</td>
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<td><strong>Vaccination History</strong></td>
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<tr>
<td>All Mandatory Vaccinations§</td>
<td>72 151 (99.11)</td>
<td>69 611 (95.70)</td>
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<tr>
<td><strong>Optional Vaccinations</strong></td>
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<tr>
<td>Hepatitis B</td>
<td>63 069 (86.64)</td>
<td>40 470 (55.64)</td>
</tr>
<tr>
<td>Meningococcal C</td>
<td>58 166 (79.90)</td>
<td>32 437 (44.60)</td>
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<tr>
<td>Both</td>
<td>54 362 (74.68)</td>
<td>29 317 (40.31)</td>
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<tr>
<td>Both Mandatory§ and Optional Vaccinations</td>
<td>54 040 (74.23)</td>
<td>29 054 (39.94)</td>
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<td><strong>Medical History</strong></td>
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<td>Allergy (Anaphylaxis)</td>
<td>800 (1.10)</td>
<td>873 (1.20)</td>
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<td>Asthma/Bronchitis/Pneumonia (all types)</td>
<td>52 436 (72.03)</td>
<td>50 141 (68.94)</td>
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<td>Autoimmune Disorders</td>
<td>3733 (5.13)</td>
<td>3745 (5.15)</td>
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<td>Neoplasms</td>
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<tr>
<td>Brain Neoplasm</td>
<td>56 (0.08)</td>
<td>74 (0.10)</td>
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<td>Other</td>
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<td>Down Syndrome</td>
<td>348 (0.48)</td>
<td>494 (0.68)</td>
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<td>Value 2</td>
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<tr>
<td>----------------------------------------------</td>
<td>-------------</td>
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<tr>
<td>Tuberous Sclerosis</td>
<td>946 (1.30)</td>
<td>1108 (1.52)</td>
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<td>Other</td>
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<td>8576 (11.79)</td>
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<td>53 042 (72.86)</td>
<td>51 453 (70.74)</td>
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<td>2537 (3.49)</td>
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<td>5604 (7.70)</td>
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<td>Head Injury and Trauma</td>
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<td>13 214 (18.17)</td>
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<td>513 (0.71)</td>
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<td>2435 (3.35)</td>
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<tr>
<td>Other</td>
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<td>62 681 (86.18)</td>
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<tr>
<td>Mental Retardation</td>
<td>377 (0.52)</td>
<td>597 (0.82)</td>
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<td>Other</td>
<td>24 512 (33.67)</td>
<td>24 563 (33.77)</td>
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<td>Newborn Seizure/Convulsions</td>
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<td>15 142 (20.82)</td>
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<td>Perinatal Complications</td>
<td>21 820 (29.97)</td>
<td>20 664 (28.41)</td>
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<td>Outpatient Visits</td>
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<tr>
<td>Low (0-40)</td>
<td>22 581 (31.02)</td>
<td>27 304 (37.54)</td>
</tr>
<tr>
<td>Med-low (41-80)</td>
<td>31 717 (43.57)</td>
<td>29 302 (40.29)</td>
</tr>
<tr>
<td>Med-high (81-130)</td>
<td>14 552 (19.99)</td>
<td>12 640 (17.38)</td>
</tr>
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<td>High (≥131)</td>
<td>3948 (5.42)</td>
<td>3490 (4.80)</td>
</tr>
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<td>Family/General/Pediatric</td>
<td>72 385 (99.43)</td>
<td>71 880 (98.82)</td>
</tr>
<tr>
<td>Physician†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (1-50)‡</td>
<td>36 104 (49.88)</td>
<td>39 809 (55.38)</td>
</tr>
<tr>
<td>Med (51-115)†</td>
<td>32 193 (44.47)</td>
<td>28 525 (39.68)</td>
</tr>
<tr>
<td>High (≥116)‡</td>
<td>4088 (5.65)</td>
<td>3546 (4.93)</td>
</tr>
<tr>
<td>Neurologist†</td>
<td>2694 (3.70)</td>
<td>3169 (4.36)</td>
</tr>
<tr>
<td>Low (1)‡</td>
<td>2231 (82.81)</td>
<td>2497 (78.79)</td>
</tr>
<tr>
<td>Med (2)‡</td>
<td>337 (12.51)</td>
<td>449 (14.17)</td>
</tr>
<tr>
<td>High (≥3)‡</td>
<td>126 (4.68)</td>
<td>223 (7.04)</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (0-1)</td>
<td>56 443 (77.53)</td>
<td>56 656 (77.89)</td>
</tr>
<tr>
<td>Med (2)</td>
<td>11 597 (15.93)</td>
<td>11 020 (15.15)</td>
</tr>
<tr>
<td>Days in Hospital</td>
<td>Low (0-2 days)</td>
<td>Med (3-10 days)</td>
</tr>
<tr>
<td>------------------</td>
<td>----------------</td>
<td>----------------</td>
</tr>
<tr>
<td>In hospital at cohort entry</td>
<td>Low (0)</td>
<td>Med (1-2)</td>
</tr>
<tr>
<td>High (≥3)</td>
<td>4758 (6.54)</td>
<td>27 184 (37.34)</td>
</tr>
<tr>
<td>In hospital at cohort entry</td>
<td>≤10 (0.01)</td>
<td>25 723 (35.36)</td>
</tr>
<tr>
<td>Same Day Surgery</td>
<td>Low (0)</td>
<td>Med (1-2)</td>
</tr>
<tr>
<td>Low (0)</td>
<td>56 338 (77.39)</td>
<td>14 756 (20.27)</td>
</tr>
<tr>
<td>Med (1-2)</td>
<td>57 129 (78.54)</td>
<td>13 990 (19.23)</td>
</tr>
<tr>
<td>Emergency Department Visits</td>
<td>Low (0)</td>
<td>Med-low (1-3)</td>
</tr>
<tr>
<td>Low (0)</td>
<td>4714 (6.48)</td>
<td>50 272 (69.06)</td>
</tr>
<tr>
<td>Med-low (1-3)</td>
<td>4271 (5.87)</td>
<td>51 332 (70.57)</td>
</tr>
<tr>
<td>Med-high (4-10)</td>
<td>3462 (4.76)</td>
<td>3363 (4.62)</td>
</tr>
</tbody>
</table>

SD = Standard Deviation; IQR = Interquartile Range

* Expressed as N (%) unless otherwise stated
† Percentages may not add up to 100% due to rounding
* Expressed as N (%) unless otherwise stated
‡ Missing because postal code in RPDB did not exist at the time of the 2006 census
§ Mandatory vaccinations in Ontario include: measles, mumps, rubella, diphtheria, tetanus and polio
• May include convulsions, and excludes tension headaches and migraines
•• Includes status epilepticus
••• Excludes newborn seizures/convulsions
† Percentage of those who have seen a medical doctor of the specified specialty at least once
‡ Calculated based on those who have seen a medical doctor of the specified specialty at least once
Figure 5.3 Schematic breakdown of events identified within the composite neurological endpoint (N=5591)

“Both” may have occurred as an event may have been captured in multiple databases with non-matching diagnostic codes.
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Vaccinated Cases (N)</th>
<th>Age-Adjusted RR (95% CI)</th>
<th>P-value†</th>
<th>Incidence Rate Ratio (RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous Epileptic Seizure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>380</td>
<td>1.50 (1.13-1.99)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5211</td>
<td>0.97 (0.89-1.07)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous Convulsion/Febrile Seizure§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4437</td>
<td>1.00 (0.91-1.1)</td>
<td>0.314</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1154</td>
<td>1.05 (0.87-1.28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous Head Trauma/Brain Injury</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1287</td>
<td>1.09 (0.91-1.31)</td>
<td>0.160</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>4304</td>
<td>0.98 (0.89-1.09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous Infection of the CNS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>42</td>
<td>1.50 (0.63-3.59)</td>
<td>0.187</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5549</td>
<td>1.01 (0.92-1.10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral Palsy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>43</td>
<td>2.11 (0.95-4.67)</td>
<td>0.034</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5548</td>
<td>1.00 (0.92-1.09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental Retardation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>39</td>
<td>1.29 (0.52-3.17)</td>
<td>0.296</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5552</td>
<td>1.01 (0.92-1.10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuberous Sclerosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>85</td>
<td>0.75 (0.34-1.65)</td>
<td>0.231</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5506</td>
<td>1.01 (0.93-1.11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Down Syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>35</td>
<td>3.09 (1.42-6.72)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5556</td>
<td>1.00 (0.91-1.09)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RR = Incidence Rate Ratio; CI = Confidence Interval

§ Indirectly includes ataxia, vertigo and headaches (excluding tension headaches and migraines) as a result of OHIP diagnostic code use

† P-value for two-sided test of interaction comparing those with and without the risk factor at a significance level of α = 0.05

Figure 5.4 Risk of convulsions, seizures and epilepsy following qHPV vaccination according to the presence of predisposing risk factors
Table 5.2 Risk estimates for various neurological endpoints and exposure risk windows following qHPV vaccination

<table>
<thead>
<tr>
<th>Number of Vaccinated Cases</th>
<th>Immediate Risk Periods</th>
<th>RR (95% CI)</th>
<th>Age-Adjusted RR (95% CI)</th>
<th>Delayed Risk Periods</th>
<th>Age-Adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite Neurological Endpoint</td>
<td>5591</td>
<td>0-30 days</td>
<td>1.01 (0.92-1.10)</td>
<td>1.01 (0.92-1.10)</td>
<td>-</td>
</tr>
<tr>
<td>Epileptic Seizures Only*</td>
<td>484</td>
<td>0 days</td>
<td>-</td>
<td>2.55 (0.95-6.84)</td>
<td>1-30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0-1 days</td>
<td>-</td>
<td>2.55 (1.26-5.15)</td>
<td>2-30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0-2 days</td>
<td>-</td>
<td>1.91 (0.99-3.71)</td>
<td>3-30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0-5 days</td>
<td>-</td>
<td>1.59 (0.95-2.68)</td>
<td>6-30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0-7 days</td>
<td>-</td>
<td>1.60 (1.01-2.51)</td>
<td>8-30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0-30 days</td>
<td>-</td>
<td>1.64 (1.28-2.10)</td>
<td>31-60 days</td>
</tr>
<tr>
<td>Convulsions Only*</td>
<td>5107</td>
<td>0-30 days</td>
<td>-</td>
<td>0.95 (0.86-1.04)</td>
<td>-</td>
</tr>
</tbody>
</table>

RR = Incidence Rate Ratio; CI = Confidence Interval

* As coding for epileptic seizures was considered to be less misclassified, those with both epileptic seizure and convulsion codes were categorized as an “epileptic seizure case” and were subsequently excluded from being a “convulsion case” to create mutually exclusive outcome groups.
Figure 5.5 Schematic representation of epileptic seizure case distribution relative to time of qHPV vaccination for girls having received only 1 dose of the qHPV vaccine (5.4a), girls having received 2 doses (5.4b) and girls having received all 3 doses (5.4c)

Average time-to event (days) and standard deviation (SD) for each exposed risk period is shown.
5.3 Additional Analysis and Discussion

Initially, a sensitivity analysis where all events reported to any of the three data sources was considered, as *a priori* assumptions of conditional Poisson regression for SCCS analysis allows an individual to have multiple events over time. This sensitivity analysis yielded a RR of 0.81 (95% CI 0.75-0.87), indicating a protective effect which did not intuitively make sense. Further discussion amongst investigators for potential reasoning behind the protective effect, concluded that many subsequent events captured, particularly from OHIP billings, were likely to represent follow-up appointment billings rather than “true” incident events. Inclusion of follow-up appointments would artificially inflate the number of events seen in unexposed person-time, and would consequently yield a significantly protect RR.

Once analyses had been completed, it was noted that OHIP inpatient billings were not excluded from the analyses, therefore potentially double counting events that were captured from DAD and/or NACRS. Although, primary analyses only took the first occurrence of neurological events captured across the three data sources, it was feared that criticism for not excluding inpatient billings may affect the results seen. An additional sensitivity analysis was performed where OHIP inpatient billings were excluded; this yielded a RR that was the same as the primary analysis (RR 1.01, 95% CI 0.92-1.10). Therefore, the inclusion of OHIP inpatient billings did not affect the outcome of this study.
Chapter 6

General Discussion

6.1 Introduction

Beginning in 2007, Ontario has invested approximately $39M each year delivering the quadrivalent (q-) human papillomavirus (HPV) vaccine to Grade 8 girls through school clinics. This publicly funded immunization program has the potential to significantly reduce the burden of HPV related disease, however, the success of this program depends, at least in part, on adherence with the recommended dosing schedule that established the vaccine’s efficacy and parental support of this program. Parental concerns regarding the safety of the HPV vaccine have been shown to be an important determinant of vaccine uptake.\textsuperscript{1-4} The objectives of this thesis were to describe and assess the patterns of use, adherence to dose interval recommendations and the neurological safety of the qHPV vaccine. This chapter discusses the key findings of the studies conducted within this thesis, their strengths and limitations, public health implications and future research.

6.2 Summary of Key Findings

The objective of the first study of this thesis was to assess the vaccine uptake, series completion and timing of doses of the qHPV vaccine administered to Grade 8 girls in school-based clinics in Ontario, Canada. This was the first study to describe the timing of dose administration for the qHPV vaccine. This study found an overall uptake rate 50.24\% for the qHPV vaccine, with the first campaign year having the lowest observed uptake. The low uptake rate was consistent with provincial qHPV vaccine uptake rates,\textsuperscript{5}
which is one of the country’s lowest provincial qHPV vaccine uptake rates. Despite low uptake, vaccine series completion was consistently high at 84.90% to 88.23%, being the highest series completion rates that have been reported to date, including rates reported in varying populations with different follow-up times. Overall adherence to the recommended dosing interval was high with over 95% of girls completing the vaccine series within an acceptable one year period; however, there appeared to be some difficulty in scheduling the second dose within two months of the first dose as only 70.80% of girls received their second dose within the recommended timeframe. Furthermore, 73 (0.13%) of girls who initiated the vaccine series were found to have received more than 3 doses of the vaccine.

The objective of the second study of this thesis was to assess the risk of convulsions, seizures and epilepsy following immunization with the qHPV vaccine. This study found no risk for the composite endpoint of convulsions, seizures and epilepsy following administration of the qHPV vaccine (age-adjusted rate ratio, RR 1.01, 95% confidence interval, CI 0.92-1.10). However, girls with predisposing risk factors for epilepsy including history of epileptic seizures, cerebral palsy and Down syndrome did experience an elevated risk following vaccination (age-adjusted RR 1.50, 95% CI 1.13-1.99; RR 2.11, 95% CI 0.95-4.67; and RR 3.09, 95% CI 1.42-6.72, respectively). Sensitivity analyses indicated an increased risk for an epileptic seizure only endpoint (RR 1.64, 95% CI 1.28-2.10), but no risk for a convulsion only endpoint, which highlighted the impact of outcome misclassification when using a composite endpoint for neurological events. However, the risk for epileptic seizures following qHPV vaccination may be confined to those with predisposing risk factors for epilepsy. Furthermore, the
risk for epileptic seizures was time-dependent with the highest risk observed immediately post-vaccination (RR 2.55, 95% CI 1.26-5.15 for the period 0-1 day), and diminishing thereafter (RR 1.57, 95% CI 1.21-2.04 and RR 1.13, 95% CI 0.85-1.50 in the 2-30 days and 31-60 days following vaccination, respectively), suggesting the need to delineate the type of seizures involved in such reactions as early seizures likely represent injection-related reactions rather than vaccine-induced reactions.

6.3 Strengths and Limitations

The strengths of the studies presented in this thesis were the use of population-based administrative databases, validated exposure data, as well as the use of a self-matched analysis to control for unknown and unmeasured confounders. Furthermore, data used were representative of most regions of the province.

Selection bias is an important threat to the validity of cohort studies. By using population-based databases, the entire target population was available for analysis thereby minimizing, but not eliminating the possibility of selection bias. The use of birth cohorts to identify Grade 8 girls eligible for the HPV immunization program may have been a potential source of selection bias as some girls may have been born a year earlier or later due to having failed or skipped a grade. It may be hypothesized that girls who are held a year back may be more likely to experience a neurological event after vaccination and/or those who skip ahead may be less likely to experience an event as school performance may indicate underlying neurological conditions. However, the birth cohort definition was recently evaluated in a re-abstraction study of the Kingston, Frontenac, Lennox and Addington Public Health (KFL&A) data, and found to correctly identify
96.4% of eligible girls (L.E. Lévesque, BScPhm, MSc, PhD, personal communication, September 28, 2011); this is, therefore, an unlikely source of selection bias.

Cohort studies are also susceptible to loss to follow-up bias (selection “out” bias). However the only source of losses to follow-up in this database study is from girls who migrate to an area that is not captured by the Immunization Record Information System (IRIS) databases available for the current analysis (22 of 36 across the province).

In this study, the completion of the vaccination series is unknown for girls who have moved into a public health region (or other province) where their immunization data were unavailable. As such, the estimates of adherence to the recommended schedule and series completion may be underestimated. Furthermore, if a girl moved out of the province, then information on outcomes from emergency, hospital or outpatient visits would be incomplete. However, as vaccination program completion was almost 90% for this population, the exposure risk period was relatively short for the safety analysis, and losses to follow-up in database studies are low and limited to persons who emigrate, the potential for loss to follow-up bias appears to be minimal.

Each qHPV vaccine dose administered is documented by the public health nurse who administers the vaccine, thereby capturing biological exposure to the qHPV vaccine. This manual immunization record is then transcribed into the IRIS database. When using databases, it is often assumed that the information contained therein is accurate, such as the date of HPV vaccination. Fortunately, a recent re-abstraction study of the KFL&A IRIS database demonstrated that this database is both valid and accurate in capturing individual’s HPV vaccination status with a sensitivity of 99.8% (95% CI, 99.3-99.9), a specificity of 97.7% (95% CI, 96.3-98.9), and a date accuracy of 98.6% for the
vaccination date.\textsuperscript{15} It may be argued that the accuracy of one IRIS database may not be
generalized to other IRIS databases in the province; however, as health units are legally
bound to track and record immunizations mandated under the \textit{Immunization of School
Pupils Act (1982)},\textsuperscript{16, 17} it is reasonable to assume that other IRIS databases across the
province would exhibit similar validity and accuracy to that of the KFL&A Public Health
IRIS database.

The etiologically relevant exposure risk period is not well-established for
neurological complications following immunization, in part because mechanistic studies
have not been carried out, and may have resulted in misclassification of the exposure
status of follow-up time. For example, if the risk period chosen was too narrow,
“exposed” events would have been misclassified as “unexposed”; the reverse would have
been true if this time window was too wide. However, the potential for misclassification
of exposure status of follow-up time was investigated in a series of sensitivity analyses
that clearly demonstrated that the choice of 0-30 days for the primary analysis was
appropriate since the observed risk of seizure was highest immediately following
vaccination, remained elevated up to day 30 and decreased thereafter. In addition, the
average time-to-seizure event following qHPV vaccination ranged from 2-3 weeks.

The use of National Ambulatory Care Reporting System (NACRS) for identifying
the outcomes may have been a source of misclassification as this database has been found
to have overall low agreement rates for International Classification of Diseases, 10\textsuperscript{th}-
Canadian Enhancement Code Revision (ICD-10CA) coding of the “Main Problem”.\textsuperscript{18}
However, ICD-10 coding for epilepsy in an equivalent database for emergency room
visits in Alberta was found to have high sensitivity.\textsuperscript{19} Moreover, few outcomes were
identified solely on the basis of NACRS. Should NACRS have introduced some misclassification of outcome status, it would have been non-differential because such errors would be unrelated to the assignment of exposed and unexposed person-time within any given individual in the self-matched analysis, particularly since the exposure risk windows were chosen a priori. As such, this may have biased the results towards the null and yielded underestimates of the associations studied; this potential source of outcome misclassification bias must be considered when interpreting the results of the safety analysis which demonstrated a small increased risk of seizures.

The primary outcome definition was a composite of the first occurrence convulsions, seizures and epilepsy; this was done to account for: (1) the likelihood that true epileptic seizures could be misdiagnosed as general convulsions or incorrectly interpreted by professional coders,19 (2) the likelihood that non-epileptic seizures could be mistaken for epileptic seizures,20,21 and (3) the possibility that tonic-clonic, seizure-like activity can accompany injection-related syncope; a now well established adverse event22. Thus, the use of a composite endpoint may have been an important limitation of the safety analysis. With this, the outcome misclassification from the use of Ontario Health Insurance Plan (OHIP) data also needs to be considered as the validity of OHIP coding for serious neurological conditions has not yet been validated. Neurological events captured in OHIP may not represent the true onset of the event because of the possibility of delayed physician visits. For example, it is likely that if a girl experienced a seizure at school, her guardian would be contacted and asked that she be taken to a physician for assessment and follow-up; such delays in presentation would have resulted in non-differential misclassification as the probability of these delays is unrelated to
person-time exposure status within any given individual in the self-matched analysis. Furthermore, the diagnostic code for “convulsions” in OHIP is truncated to the third position (OHIP code 780 versus ICD-9 code 780.3) which also included unrelated cases of ataxia, vertigo and headache (except for tension headache and migraine) and thus, misclassification. The use of this diagnostic code would also have resulted in non-differential misclassification, as non-convulsion cases were equally as likely to have occurred in an exposed or unexposed risk period, thereby biasing the results towards the null. Indeed, the impact of this source of misclassification was demonstrated in a sensitivity analysis that separated convulsions from seizure as the outcome definition. In this analysis, no risk was found for “convulsions” but a risk increase was observed for “seizures”. Since the vast majority of cases identified were OHIP-identified convulsions, this resulted in an inability to detect the risk increase for the analysis of the primary endpoint and is an important limitation of the use of a composite outcome definition. Of course, it was impossible to predict a priori the proportion of overall cases that would be OHIP-identified “convulsion”.

The self-controlled case series (SCCS) method was developed to address the problem of unmeasured and unknown confounders inherent in the post-marketing safety evaluation of vaccines. With this self-matched design, all time-independent confounders including genetic and environmental factors were fully controlled for, thereby eliminating the potential for confounding by unknown or unmeasured time-independent factors. The potentially confounding effects of age, an important time-dependent factor, were also controlled for by including the non-vaccinated cases in the analysis. Other time-dependent factors that have been known to confound vaccine
associations include influenza-like illness, upper respiratory infection, and the administration of other vaccines; however, as these were not known risk factors of convulsions, seizure or epilepsy, they were not believed to have confounding effects on the association between qHPV vaccination and neurological events.

The results of the usage and dose timing study may not be generalized to non-publicly funded, and/or non-school based HPV immunization programs. In Ontario, the publicly-funded nature of such a program removes, in principle, financial barriers for receiving the vaccine. In addition, the delivery of the HPV vaccine through school clinics by public health nurses means that the Health Units administering this program control, to a large extent, the timing of the doses. As such, the uptake and series completion rates reported in this thesis may not be generalized to other funding models. Similarly, the high rates of adherence with dose-timing recommendations observed in this study may be quite different from those of immunization programs delivery models.

Difficulty in generalizing the results of the usage and dose timing study may also pertain to health units within Ontario, as the IRIS databases of 14 of the province’s 36 public health units were not available at the time of the analysis, thereby excluding approximately 60% of the Ontario HPV vaccine-eligible population. The immunization records that were available represent a geographically diverse population including geographically large health units with low population density (e.g., Northwestern, Thunder Bay and Porcupine) as well as, geographically small health units with very high population densities (e.g., Peel and Durham). Nevertheless, if the health units that were not included in the analysis had different HPV vaccine uptake or series completion rates than those included, or faced particular difficulties delivering the vaccine doses on time,
then the results of the first thesis study would not be representative of the experience of the whole province. For example, it is possible that more populated health units may have had lower dose timing adherence because of the larger number of schools that needed to be visited. Conversely, it is also possible that a health unit of high population density would have considerably more staff, by virtue of servicing a larger population, that they may actually have had better adherence.

The results of the neurological safety analysis may not be easily generalized to younger or older female populations. In Ontario, the HPV immunization program is targeted at a Grade 8 (i.e., 12-13 years old) girl population, while the age-groups targeted by other provinces vary and are generally younger.\textsuperscript{24} As the baseline incidence of epilepsy is greater in younger age groups,\textsuperscript{25} the risk for vaccine-induced epileptic seizures may also differ with age. If vaccine-induced epileptic seizures are more common in younger individuals, the results of the neurological safety study may underestimate the risk for the younger population. Furthermore, if the risk is much lower in older persons, the results of the study may not be applicable to teenagers and young adults. Conversely, physiological (non-epileptic, anoxic) seizures are also known to be much more common in adolescent females;\textsuperscript{26} thus, study results may underestimate risk for vaccine-induced anoxic seizures in adolescent populations and may not be applicable to younger populations.

\textbf{6.4 Public Health Implications}

The results of this thesis may be used to improve health care policies and practices, as well as provide evidence that will allow informed decision-making by parents and health care providers in the delivery of the qHPV vaccine.
The low uptake rates in Ontario demonstrated by the first thesis study suggest the need for Ontario public health agencies to change their strategy in the promotion and provision of the vaccine. Perhaps it is the target age group that requires reconsideration, or it may simply be a matter of increasing the promotional efforts made by the public health agencies. Ontario should look to the practices of other provinces, such as Quebec or the Atlantic provinces which have >80% uptake of the vaccine, to improve its uptake rate. On the other hand, as parental concerns regarding the safety and long term effects of this vaccine has been identified as a major determinant of HPV vaccine uptake in a number of studies, facilitating the development of the necessary infrastructure to carry out post-marketing safety analyses, as done in the second thesis study, needs to be given serious consideration. Such infrastructure now exists for the post-marketing evaluation of drugs.

The first thesis study has also provided evidence for the need to improve immunization record keeping and information sharing practices. Current practices have allowed girls to receive more than the recommended number of doses, resulting in unnecessary costs. Extra-immunization in children has been found to often occur when multiple immunization providers are involved. Communication, including documentation, has been demonstrated as key factor for the occurrence of pediatric medication errors. Furthermore, parental recall for vaccinations requiring more than one dose has been observed to be poor. Improvements in immunization record keeping and information sharing will decrease errors in extra-immunization and ultimately reduce the amount of unnecessary spending.
As parental concerns regarding the safety of the qHPV vaccine have been shown to be an important determinant of vaccine uptake,\textsuperscript{1-4} the second thesis study attempted to determine the neurological safety of the qHPV vaccine. A risk for epileptic seizures was found, however, it was uncertain whether this risk is confined to those with predisposing risk factors for epilepsy. If the risk is limited to those with predisposing risk factors, health care providers may provide caution to parents of girls with predisposed risk, and simultaneously reassure other parents about the vaccine’s neurological safety. Nevertheless, the relative risk increase of post-vaccination seizures observed in this study corresponds to a number needed to harm (NNH) of 389, and must be weighed against the benefits of the qHPV vaccine.

6.5 Future Research

Studies conducted for this thesis have opened the gateway for future qHPV vaccine research. Future studies should investigate the determinants for the low vaccine uptake rates observed within Ontario. Additionally, as other provinces have experienced higher uptake of the vaccine, investigation and comparison of the different strategies across provinces could be beneficial to improving Ontario’s low uptake rate.

Most vaccine doses are received within appropriate time frames; however, this thesis found incidents where doses have been received too close together or too far apart. Future studies should investigate whether and how this may impact the effectiveness and safety of the qHPV vaccine.

Analysis for the neurological safety of the qHPV vaccine needs to be repeated to confirm the risk of epileptic seizures following its administration. As subgroup analyses for the composite endpoint indicated that the elevated risk may be confined to girls with a
history of epileptic seizures, cerebral palsy and Down syndrome, future studies are needed to determine whether the risk of epileptic seizure we observed is limited to those with predisposing risk factors. In addition, since anoxic seizures may be miscoded as epileptic seizures, future studies should attempt to delineate the type of seizures involved in such reactions as anoxic seizures represent injection-related reactions rather than vaccine-induced reactions.

Lastly, future studies to validate neurological diagnoses in the OHIP database are needed and would be ideal for future population database studies as neurological events are primarily captured in this database.

6.6 References


# Appendix A

## ICD-9, ICD-10CA and OHIP Diagnosis Codes

<table>
<thead>
<tr>
<th>Covariate/Outcome</th>
<th>ICD-9</th>
<th>ICD-10-CA</th>
<th>OHIP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epilepsy and Recurrent Seizures</strong></td>
<td>345 (excluding 345.6)</td>
<td>G40, G41</td>
<td>345</td>
</tr>
<tr>
<td>(including status epilepticus)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Convulsions (including febrile seizures)</strong></td>
<td>780.3</td>
<td>R56.0, R56.8</td>
<td>780</td>
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<tr>
<td><strong>Newborn Seizures/Convulsions</strong></td>
<td>779.0, 345.6</td>
<td>P90</td>
<td>779</td>
</tr>
<tr>
<td><strong>Cerebral Palsy</strong></td>
<td>343</td>
<td>G80</td>
<td>343</td>
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<tr>
<td><strong>Other Diseases of the Central Nervous System</strong></td>
<td>320-323.4, 323.6-339.9, 342, 344, 346-349</td>
<td>G01-G03.6, G03.9, G04.1, G04.2, G04.4-G34, G36.1-G36.9, G43-G47, G81-G99</td>
<td>320, 321, 330-332, 346-349</td>
</tr>
<tr>
<td><strong>Mental Retardation</strong></td>
<td>317-319</td>
<td>F70-F90</td>
<td>319</td>
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<tr>
<td><strong>Other Mental/Behavioral Disorders</strong></td>
<td>290-316</td>
<td>F00-F69, F80-F99</td>
<td>290-316</td>
</tr>
<tr>
<td><strong>Down Syndrome</strong></td>
<td>758.0</td>
<td>Q90</td>
<td>758</td>
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<tr>
<td><strong>Tuberous Sclerosis</strong></td>
<td>759.5</td>
<td>Q851</td>
<td>759</td>
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<td><strong>Other Congenital Anomalies</strong></td>
<td>740-757, 758.1-759.4, 759.6-759.9</td>
<td>Q00-Q85.0, Q85.2-Q89, Q91-Q99</td>
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<td><strong>Head Injury and Trauma</strong></td>
<td>850-854</td>
<td>S06</td>
<td>850, 854</td>
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<td><strong>Brain Neoplasm</strong></td>
<td>191</td>
<td>C71</td>
<td>191</td>
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<tr>
<td><strong>Other Neoplasm</strong></td>
<td>140-190, 192-239</td>
<td>C00-C70, C72-D48</td>
<td>140-190, 192-239</td>
</tr>
<tr>
<td><strong>Infections of the Central Nervous System</strong></td>
<td>036, 045-048, 049.0, 049.1, 049.8, 049.9, 062, 063, 071</td>
<td>A39, A80, A82-A89</td>
<td>036, 045, 047, 049, 062</td>
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<tr>
<td><strong>Sexually Transmitted Infections</strong></td>
<td>0541, 090-092, 097-099, 131</td>
<td>A50, A51, A53-A60, A63, A64</td>
<td>054, 097-099, 131</td>
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<td><strong>Human Immunodeficiency Virus</strong></td>
<td>042</td>
<td>B24</td>
<td>042-044</td>
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<td><strong>Other Infectious Diseases</strong></td>
<td>001-035, 037-041, 043-044, 049.2-049.7, 050-054.0, 054.2-058.1, 058.3-058.7, 000-035, 037-040, 052, 053, 055-057,</td>
<td>A00-A38, A40-A49, A52, A65-A79, A81, A90-99, B00-B09, B15-B19, B25-B99</td>
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<tr>
<td>Condition</td>
<td>Codes</td>
<td>Codes</td>
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<td>------------------------------------------------</td>
<td>--------------------------------------------</td>
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<tr>
<td>Asthma/Bronchitis/ Pneumonia – all types</td>
<td>466, 493, 490-491, 480-486</td>
<td>J12-J18, J20, J21, J40-J42, J44.8, J45</td>
<td>466, 491, 493, 486</td>
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<tr>
<td>Perinatal Complications (not including newborn febrile seizures)</td>
<td>760-778, 779.1-779.9</td>
<td>P00-P83, P91-P96</td>
<td>762-777</td>
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<tr>
<td>Autoimmune Disorders</td>
<td>232.6, 232.8, 240.9, 242, 244.9, 245, 246.9, 250, 283.0, 287.3, 323.5, 340, 341, 351, 357, 364, 3773, 710.0-710.4, 710.8, 710.9, 714</td>
<td>D69.3, D69.4, D47.3, D59, E01.2, E03.9, E04.9, E05, E06, E07.0, E10, G03.8, G04.0, G04.3, G35, G36.0, G37, G51, G61-G63, H20, H21, H46, M05, M06, M08, M12, M32, M33.2, M33.9, M34, M35.0, M35.5, M35.9</td>
<td>240, 242, 244, 245, 250, 283, 287, 323, 340, 351, 364, 377, 710, 714</td>
</tr>
<tr>
<td>Allergy (Anaphylaxis)</td>
<td>9950, 9951, 9952, 9953, 9956, 9957</td>
<td>T78</td>
<td>995</td>
</tr>
<tr>
<td>Syncope</td>
<td>780.2</td>
<td>R55</td>
<td>785</td>
</tr>
</tbody>
</table>
Appendix B
Research Ethics Approval

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD-DELEGATED REVIEW
November 15, 2011

Dr. Linda E Levesque
Department of Community Health and Epidemiology
Queen's University

Dear Dr. Levesque

Study Title: EPID-367-11 The Risk of Serious Neurological Complications Associated with the Use of the Quadrivalent Human Papillomavirus (HPV) Vaccine: The Ontario Grade 8 Cohort Study
File # 6006413
Co-Investigators: Ms. Wen-Ting Lim, Dr. Kim Sears

I am writing to acknowledge receipt of your recent ethics submission. We have examined the protocol for your project (as stated above) and consider it to be ethically acceptable. This approval is valid for one year from the date of the Chair's signature below. This approval will be reported to the Research Ethics Board. Please attend carefully to the following listing of ethics requirements you must fulfill over the course of your study:

- **Reporting of Amendments:** If there are any changes to your study (e.g. consent, protocol, study procedures, etc.), you must submit an amendment to the Research Ethics Board for approval. Please use event form: HSRB Multi-Use Amendment/Full Board Renewal Form associated with your post review file # 6006413 in your Researcher Portal (https://eservices.queensu.ca/romeo_researcher/)

- **Reporting of Serious Adverse Events:** Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other serious adverse events must be reported within 15 days after becoming aware of the information. Serious Adverse Event forms are located with your post-review file 6006413 in your Researcher Portal (https://eservices.queensu.ca/romeo_researcher/)

- **Reporting of Complaints:** Any complaints made by participants or persons acting on behalf of participants must be reported to the Research Ethics Board within 7 days of becoming aware of the complaint. Note: All documents supplied to participants must have the contact information for the Research Ethics Board.

- **Annual Renewal:** Prior to the expiration of your approval (which is one year from the date of the Chair's signature below), you will be reminded to submit your renewal form along with any new changes or amendments you wish to make to your study. If there have been no major changes to your protocol, your approval may be renewed for another year.

Yours sincerely,

[Signature]

Chair, Research Ethics Board
November 15, 2011

Investigators please note that if your trial is registered by the sponsor, you must take responsibility to ensure that the registration information is accurate and complete.
QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD

The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards as defined by the Tri-Council Policy Statement; Part C Division 5 of the Food and Drug Regulations, OHRP, and U.S DHHS Code of Federal Regulations Title 45, Part 46 and carries out its functions in a manner consistent with Good Clinical Practices.

Federalwide Assurance Number: #FWA00004184, #IRB00001173

Current 2011 membership of the Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board:

Dr. A.F. Clark, Emeritus Professor, Department of Biochemistry, Faculty of Health Sciences, Queen's University (Chair)

Dr. H. Abdollah, Professor, Department of Medicine, Queen's University

Dr. R. Britson, Professor, Department of Emergency Medicine, Queen's University

Dr. M. Evans, Community Member

Dr. S. Hogan, Manager, Program Evaluation & Health Services Development, Geriatric Psychiatry Service, Providence Care, Mental Health Services, Assistant Professor, Department of Psychiatry

Ms. J. Hudaee, Community Member

Dr. B.S. Kislevsky, Professor, School of Nursing, Department of Psychology and Obstetrics & Gynaecology, Queen's University

Ms. D. Morales, Community Member

Ms. P. Newman, Pharmacist, Clinical Care Specialist and Clinical Lead, Quality and Safety, Pharmacy Services, Kingston General Hospital

Dr. W. Race, Emeritus Professor, Department of Pharmacology & Toxicology, Queen's University

Ms. S. Rohland, Privacy Officer, ICES-Queen's Health Services Research Facility, Research Associate, Division of Cancer Care and Epidemiology, Queen's Cancer Research Institute

Dr. B. Simchison, Assistant Professor, Department of Anesthesiology, Queen's University

Dr. A.N. Singh, WHO Professor in Psychosomatic Medicine and Psychopharmacology
Professor of Psychiatry and Pharmacology, Chair and Head, Division of Psychopharmacology, Queen's University, Director & Chief of Psychiatry, Academic Unit, Quinte Health Care, Belleville General Hospital

Dr. E. Tsai, Associate Professor, Department of Paediatrics and Office of Bioethics, Queen's University

Rev. J. Warren, Community Member