QUADRIVALENT HPV VACCINE AND THE RISK OF TYPE 1 DIABETES MELLITUS IN GRADE 8 GIRLS: A POPULATION BASED COHORT STUDY

by

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A thesis submitted to the Department of Community Health and Epidemiology

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Abstract

Background

Vaccines have been hypothesized in the etiology of autoimmune diseases including type 1 diabetes. There are cases of diabetes reported in the Vaccine Adverse Event Reporting System (VAERS) following the administration of the human papillomavirus (HPV) vaccine, however this potential association has yet to be investigated. The objective of this thesis was to determine whether there is an association between immunization against HPV and the development of type 1 diabetes mellitus in grade 8 girls eligible for Ontario’s vaccination program.

Methods

A retrospective, population-based, cohort study of girls residing within an Ontario health unit and eligible for the province’s publicly funded school-based HPV vaccination program between 2007 and 2011 was executed using provincial administrative health databases and the Immunization Recording Information System (IRIS) database. To control for known, unknown and unmeasured time-independent confounders, a self-controlled case series analysis was conducted. The relative incidence and 95% confidence interval were estimated using conditional Poisson regression.

Results

The study cohort was comprised of 3465 girls with a mean age of 13.2 years at cohort entry (range 12.7 to 13.6 years). The mean duration of follow was 2.7 years and ranged from 1.6 to 3.6 years. The proportion of girls who received at least one dose of
the qHPV vaccine during the observation period was 58.3% (n=2020). During the study follow-up 15 cases of new onset type 1 diabetes were observed, six of which were classified as etiologically exposed to the qHPV vaccine. Using an indefinite risk window, immunization with the qHPV vaccine was not associated with an increased risk of developing type 1 diabetes (age and season-adjusted RI 0.15; 95% CI 0.02-1.32).

Conclusions

The results of this thesis regarding the risk of type 1 diabetes following immunization with the qHPV vaccine are inconclusive as a consequence of the small number of cases identified. However, the random distribution of cases across time and across exposure status suggests that there is no association. Before a definitive conclusion is reached the analysis must be re-conducted on a larger cohort.
Co-Authorship

This thesis is the work of Erica Walsh in collaboration with her supervisors, Dr. Linda Lévesque and Dr. Beatriz Alvarado. Erica Walsh completed data linkage and statistical analysis with assistance from Lindsey Colley (Biostatistician/Analyst at ICES-Queen’s). Some SAS program code used in parts of the analysis was adapted from the work of others and modified for the purpose of this study. The interpretation of the results of data analysis was done by Erica Walsh with guidance and advice from Dr. Linda Lévesque and Dr. Beatriz Alvarado. Other components of this thesis are the work of Erica Walsh with editorial feedback from Dr. Linda Lévesque and Dr. Beatriz Alvarado.
Acknowledgements

This thesis would not have been possible without the support and dedication of my supervisors Dr. Linda Lévesque and Dr. Beatriz Alvarado who provided an abundance of guidance, feedback and expertise. I am extremely grateful for all of their help and insight.

I would also like to thank my family and friends for their constant support and motivation.
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<th>Full Form</th>
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<tr>
<td>APC</td>
<td>Antigen-presenting cells</td>
</tr>
<tr>
<td>AS04</td>
<td>Aluminum hydroxide and 3-deacylated monophosphorul lipid A</td>
</tr>
<tr>
<td>BCG</td>
<td>Bacille Calmette-Guérin</td>
</tr>
<tr>
<td>CAEFI</td>
<td>Canadian Adverse Events Following Immunizations</td>
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<td>CAEFISS</td>
<td>Canadian Adverse Events Following Immunization Surveillance System</td>
</tr>
<tr>
<td>CDC</td>
<td>Centres for Disease Control</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CIHI</td>
<td>Canadian Institute for Health Information</td>
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<tr>
<td>CIN</td>
<td>Cervical intraepithelial neoplasia</td>
</tr>
<tr>
<td>CIRID</td>
<td>Centre for Immunization and Respiratory Infectious Diseases</td>
</tr>
<tr>
<td>DAD</td>
<td>Discharge Abstract Database</td>
</tr>
<tr>
<td>DPT</td>
<td>Diphtheria, pertussis and tetanus</td>
</tr>
<tr>
<td>DSA</td>
<td>Data Sharing Agreement</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>GAD65</td>
<td>Glutamate decarboxylase</td>
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<td>GBS</td>
<td>Guillain-Barré syndrome</td>
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<tr>
<td>HBV</td>
<td>Hepatitis B virus</td>
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<tr>
<td>HiB</td>
<td>Haemophilus influenza B</td>
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<tr>
<td>HLA</td>
<td>Centres for Disease Control</td>
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<td>HPV</td>
<td>Human papillomavirus</td>
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<tr>
<td>ICD-10</td>
<td>The International Statistical Classification of Diseases and Related Health Problems, 10th Revision</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>ICES</td>
<td>Institute of Clinical Evaluative Sciences</td>
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<tr>
<td>IKN</td>
<td>ICES key number</td>
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<tr>
<td>IMPACT</td>
<td>Immunization Monitoring Program ACTive</td>
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<td>IRIS</td>
<td>Immunization Recording Information System</td>
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<td>IRR</td>
<td>Incidence rate ratio</td>
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<tr>
<td>ITT</td>
<td>Intention to treat</td>
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<tr>
<td>MHC</td>
<td>Major histocompatibility complex</td>
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<td>MMR</td>
<td>Mumps, measles and rubella</td>
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<td>MOHLTC</td>
<td>Ministry of Health and Long Term Care</td>
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<td>NACRS</td>
<td>National Ambulatory Care Reporting System</td>
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<td>ODD</td>
<td>Ontario Diabetes Database</td>
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<td>OHIP</td>
<td>Ontario Health Insurance Plan</td>
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<td>PHAC</td>
<td>Public Health Agency of Canada</td>
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<td>qHPV</td>
<td>Quadrivalent human papillomavirus</td>
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<td>RCT</td>
<td>Randomized controlled trial</td>
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<td>RPDB</td>
<td>Registered Persons Database</td>
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<td>RI</td>
<td>Relative incidence</td>
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<td>RR</td>
<td>Relative risk</td>
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<td>SCCS</td>
<td>Self-controlled case series</td>
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<td>SDS</td>
<td>Same Day Surgery</td>
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<td>Type 1 diabetes</td>
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<td>The Environmental Determinants of Diabetes in the Young</td>
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Chapter 1

Introduction
1.1 Background and Rationale

Type 1 diabetes is an incurable, debilitating and lifelong illness that affects more than 300,000 Canadians.\(^1\) The estimated incidence and prevalence of the disease in Canadian children one to 19 years of age is 4.3 and 30.4 per 10,000, per year, respectively.\(^2\) The incidence rate of type 1 diabetes in Canada is rising with the greatest increase observed in children between five and nine years of age.\(^2\) Worldwide, Canada has the sixth highest incidence rate of diabetes in children under the age of 14.\(^1\)

Type 1 diabetes is an autoimmune disorder resulting from the destruction of insulin-producing beta cells of the pancreas.\(^3\) Without insulin the body is unable to absorb glucose from the blood stream into the cells of appropriate tissues including muscle, fat, and liver. At the time of diagnosis approximately 70-80\% of beta cells have already been destroyed, a process that occurs slowly, over months to years (Figure 1.1).\(^4\)

Once a sufficient number of beta cell are destroyed, the clinical manifestation of type 1 diabetes is often abrupt with symptoms at presentation including polyuria (frequent urination), polydipsia (excessive thirst), hunger, weight loss, lethargy, vision changes and loss of consciousness.\(^5\) To maintain and prolong survival, and to prevent complications, children diagnosed with type 1 diabetes must maintain a structured lifestyle focused on strict glycemic control. This is accomplished through regular monitoring of blood glucose and exogenous administration of insulin. Affected children face many issues that can negatively impact upon glycemic control including stress, hormonal changes, periods of growth, physical activity, medications, illness or infection, fatigue and compliance issues.
A diagnosis of type 1 diabetes is associated with a significant burden of disease at the level of the individual, their family, and society. Long-term complications of type 1 diabetes include kidney failure, adult blindness, stroke, heart attack, nerve damage and accompanying debilitating pain, and limb amputation. The life expectancy of a child diagnosed with the disease is reduced by a minimum of 10-15 years. Mortality rates among adults over the age of 20 with diabetes are twice as high as those without the disease. The use of health services is also influenced by diabetes. Children and adolescents with diabetes have 1.6 times more family physician visits, five times as many appointments with specialists and spend 11 times more days in hospital per year compared to those without the disease. Although the economic burden of type 1 diabetes has not been determined, the impact of all diabetes types and associated complications on the Canadian economy has been estimated at $17.4 billion per year. Consequently, even small increases in the risk of type 1 diabetes carries a significant burden and as such it is important to identify potentially modifiable risk factors of this disease.

The pathogenesis of type 1 diabetes is not completely understood. While genetic susceptibility is a prerequisite, research suggests that exogenous factors also play a key role by stimulating the immune system and triggering an autoimmune attack on insulin-producing pancreatic cells. Hypothesized triggers include, but are not limited to, infection, diet and vaccination. Much of the evidence suggesting a causal relationship between type 1 diabetes and vaccines is based on ecologic studies and is considered
weak. Further well-designed studies are required to evaluate the association between vaccination and type 1 diabetes and should be considered for any new vaccine.

In 2006, Health Canada issued approval of Gardasil®, a vaccine that provides protection against human papillomavirus (HPV). Gardasil® is a quadrivalent HPV (qHPV) vaccine indicated for females between 9 and 45 years of age to prevent infection caused by HPV types 6, 11, 16 and 18 and the diseases associated with the virus including cervical, vulvar and vaginal cancer, and pre-cancerous dysplasia as well as genital warts. Persistent high-risk HPV infection is the cause of virtually all cervical cancer and HPV 16 and 18 have been estimated to account for 70% of such cancers. In the fall of 2007, the government of Ontario introduced a publicly-funded, voluntary HPV vaccination program. The school-based program offers the recommended three doses of the qHPV vaccine free to all grade 8 girls. The estimated cost of the program when it was initiated was approximately $117 million over three years. Despite an anticipated 85% rate of uptake, in the first year of the program only 53% of eligible females received the first dose of the vaccine. Concerns surrounding the safety of this new vaccine are among the reasons for the observed low acceptance of the program. The purpose of this thesis is to examine the potential role of the HPV vaccine in the etiology of type 1 diabetes using real-world data from one public health unit within the province of Ontario. It is part of a team effort of public health units and researchers to address the safety of the HPV vaccine among grade 8 girls in Ontario. The results of this thesis will be of interest to parents, guardians, health-care providers and policy makers in Ontario as well as in
other provinces and territories in Canada, all of whom have implemented publicly funded HPV vaccination programs.\textsuperscript{18}

1.2 Study Objective

The primary objective of this thesis was to determine whether there is an association between immunization against HPV and the development of type 1 diabetes mellitus in grade 8 girls eligible for Ontario’s vaccination program.

1.3 Thesis Organization

This thesis is written in a traditional format and conforms to the guidelines set forth by the School of Graduate Studies at Queen’s University. Following this introduction, chapter two presents relevant background information on the qHPV vaccine and type 1 diabetes. Chapter three is a detailed description of the methodology of this thesis including the study design, data sources, and statistical analysis techniques. The fourth chapter delivers the results of this thesis. Lastly, chapter five contains a general discussion of the findings of the study, the strengths and limitations and areas for future research related to this topic.

1.4 Deviation from Thesis Proposal

During the proposal and planning of this thesis it was anticipated that up to date immunization data from public health units representing approximately 80% of the relevant population of the province of Ontario would be available. Due to unforeseeable circumstances these data did not come to fruition and as such, this thesis was modified such that the analysis was conducted using data from only one health unit in Ontario. The implications of this are discussed in chapter five.
1.5 References


11. Classen JB. Clustering of cases of IDDM 2-4 years after hepatitis B immunization is consistent with clustering after infections and progression to IDDM in autoantibody positive individuals. The Open Pediatric Medicine Journal 2008;2:1-6.


Figure 1.1 Diagrammatic representation of the onset of type 1 diabetes
Chapter 2

Literature Review
2.1 Vaccination

Vaccination is the administration, most often by injection, of a vaccine that contains attenuated or killed microorganisms or disease-specific antigens (foreign molecules) or parts of antigens. By weakening, killing or attenuating, the antigenic portion the vaccine does not cause the actual disease but instead stimulates the immune system to produce antibodies that offer protection against a particular disease.\(^1\) Most vaccines also contain an adjuvant, often in the form of an aluminum salt, which functions to boost the body’s immune response to the vaccine.\(^2\) Adjuvants function through a variety of methods including: (i) improved delivery of the antigen to lymph nodes, (ii) prolonged antigen exposure at the injection site, or (3) by binding to the immune-stimulating antigen. Besides adjuvants, vaccines may also contain preservatives and/or additives. Preservatives such as thimersol, phenol and 2-phenoxyethanol are added to multi-dose vaccines to prevent bacterial or fungal contamination. Additives such as human serum albumin, gelatin and bovine reagents are occasionally added to vaccines to support the growth and purification of immunogens, to inactivate toxins or to maintain product quality and stability.\(^2\)

Vaccination is acclaimed as one the greatest public health accomplishments of the 20\(^{th}\) century and is credited for saving more lives than any other healthcare intervention.\(^3\) The World Health Organization estimates that two to three million deaths are prevented annually due to vaccination. In 2008, approximately 1.7 million children worldwide under the age of five died as the result of vaccine-preventable diseases.\(^4\) Most of these deaths occurred in under-developed countries with poorly established vaccination
programs. In Canada where vaccination rates are high, the morbidity and mortality rates of vaccine-preventable diseases are low. As a result of the relatively low incidence of vaccine-preventable infections, the concern of the public and medical community has shifted more towards the safety of vaccines. Tolerance for adverse effects from vaccines is low as they are often administered to large populations of healthy persons, many of who are children.\(^5\)

### 2.2 Adverse Events Following Vaccination

As with many other health care interventions, vaccines are associated with adverse events.\(^6\) Any component of a vaccine, including the immunizing agent or antigen, adjuvant, antimicrobial, or preservative, may be responsible for inducing an adverse event following vaccination.\(^7,8\) However, the disease-specific antigen (immunizing agent) is the component most responsible for producing the immune response following vaccination and can be associated with serious adverse events. Following administration of a vaccine, the immune system recognizes the antigenic component as foreign and stimulates the immune system to produce T-lymphocytes and antibodies.\(^9\) As previously described, adjuvants are added to vaccines to make the antigen more immunogenic and heighten the body’s immune response. Since the antigen and adjuvant together stimulate immunity, they may additionally stimulate other pathways of the immune system leading to an adverse event.\(^10\) Some individuals are more sensitive to the immune-mediated effects of vaccines as a result of genetic predisposition, underlying medical conditions, age and other factors. Consequently, they
are more likely to experience an exaggerated immune response and ultimately a vaccine-induced adverse event.\textsuperscript{11}

Most reactions following vaccination are minor and acute, lasting a few hours to a few days. Examples of minor adverse events include local reactions at the injection site, low-grade fever, and flu-like symptoms. Minor systemic reactions include fever, irritability, nausea and drowsiness.\textsuperscript{7, 8} However, serious and life-threatening reactions have also been associated with vaccines, which can be either acute (i.e., anaphylaxis) or delayed (i.e., autoimmune disease such as type 1 diabetes). Examples of rare but serious systemic adverse events include seizures, anaphylaxis, encephalopathy, and autoimmune disorders.\textsuperscript{8, 12}

2.3 Vaccines and Autoimmunity

Autoimmune diseases occur when the immune system mistakenly attacks and destroys healthy body tissue.\textsuperscript{13} In developed countries, autoimmune diseases affect approximately five percent of the population and occur more commonly in women. Most often autoimmune diseases arise in individuals who are genetically predisposed and whose immune systems have been triggered by environmental factors such as infections, hormones, endocrine factors, drugs or vaccines.\textsuperscript{13, 14}

The incidence of autoimmune complications following vaccination is rare.\textsuperscript{15} As such, it can be difficult to establish a causal relationship between vaccines and autoimmunity, particularly when such assessments are based on case-reports from passive surveillance systems. The assessment of causality is further complicated by the delayed nature of such reactions. Moreover, much of the data either supporting or
refuting a relationship between a particular vaccine and an autoimmune disease is often based on weak evidence from case reports and case series (Table 2.1). When controlled studies are available they are often inadequately powered to detect such rare events. As a result, most vaccine-related autoimmune reactions are considered only temporally associated. Exceptions to this include the widely accepted causal relationship observed between swine-flu vaccine of 1976 and Guillain-Barré syndrome (GBS) as well as thrombocytopenia following the mumps/measles/rubella (MMR) vaccine.14

In the 1976-77 influenza vaccination campaign in the United States using the A/New Jersey/8/76 swine-flu vaccine a 7.6-fold increase in the baseline risk of GBS was observed in adults primarily concentrated within the five weeks following vaccination.16 The biological explanation for the association involves cross-reacting antibodies against peripheral nerve gangliosides.17 Upon consideration of the evidence, the Committee for the Immunization Safety Review concluded that the association between the vaccine and GBS was causal.17 The establishment of a causal relationship between MMR and thrombocytopenia was based on a review conducted by the Institute of Medicine of the National Academy of Sciences in Washington, DC. A committee consisting of 14 members spent 18 months reviewing and analyzing scientific and medical literature on the adverse reactions reported from a number of vaccines. From their review it was determined that the incidence of thrombocytopenia purpura occurring within two months of MMR vaccination was approximately six-fold higher than the incidence of thrombocytopenia for a two month period in children under the age 15 years who were not vaccinated. Their conclusions were based on data from uncontrolled studies and case
reports. It is clear from the above examples that when a relationship between vaccines and autoimmune diseases is noted, the magnitude of the association is relatively large. Further examples of this include the association between MMR and aseptic meningitis (relative incidence [RI] ranging from 14.3 to 31.4), oral rotavirus and intussusception (RI ranging from 21.7 to 29.4) and lastly, the intranasal flu vaccine and Bell’s palsy (RI ranging from 35.6 to 84).

Several mechanisms have been postulated to explain vaccine-induced autoimmunity. These include molecular mimicry, epitope spreading, bystander activation, and polyclonal activation. Molecular mimicry, which will be further discussed in the pathogenesis of type 1 diabetes, postulates that there is cross-reactivity between antigens present in the vaccine and self-antigens leading to an autoimmune response. Epitope spreading occurs after the immune system initially responds to the antigen resulting in a T-cell response. It is hypothesized that T-cells begin to respond to less dominant epitopes within an antigen as a consequence of the destruction of the initial pathogen thus revealing of additional epitopes. Bystander activation arises following the initial immune response to an antigen, which causes tissue damage and results in the release of sequestered antigens. These newly revealed antigens in turn activate auto-reactive T-cells. The self-immune attack is further propagated by the macrophages released as a result of the initial antigen that further stimulate pre-primed auto-reactive T-cells. Polyclonal activation occurs when there is a prolonged or constant activation of the immune system that leads to the production of a large number of antibodies some of which are self-reactive and cause damage to endogenous tissues.
Regardless of the mechanism, vaccine-induced autoimmunity is a serious adverse event with significant implications for those affected. As such, post-marketing phase IV studies should be conducted to assess safety with respect to serious adverse effects, and autoimmune diseases in particular, following the introduction of any new vaccine.

### 2.4 Vaccines and Type 1 Diabetes

Type 1 diabetes is an autoimmune disease that has been associated with a variety of childhood immunizations. There are published studies both supporting and refuting a relationship between vaccination and type 1 diabetes. The evidence supporting such an association is limited by a number of methodological flaws and all studies of this association originate from a single author (Table 2.2).

There are four ecologic studies published to date reporting a statistically significant rise in the incidence of type 1 diabetes primarily in young children in the two to four years following the institution of immunization programs with hepatitis B, pertussis, MMR, Bacille Calmette-Guérin (BCG), and hemophilus influenza B vaccines.\(^{20-23}\) These studies were flawed in many aspects including their design, analysis and reporting. With respect to design, the usefulness of ecologic studies is in general limited to hypothesis generation. They are low in terms of hierarchy of evidence and should not be the sole source of information when determining causation. The most significant limitation of this design is the “ecologic fallacy” whereby relationships observed at the population level do not necessarily accurately reflect what is occurring at the individual level. It is possible that the results observed by Classen suggesting a positive correlation between vaccination and the rising incidence of type 1 diabetes were
confounded by unknown or unmeasured factors. In addition, these studies did not provide a sufficient level of detail on the sources of information used for ascertaining the incidence of type 1 diabetes to determine their validity. If there were differences in how diabetes was reported or detected before and after the implementation of a change in immunization practices, this could explain the variability in the incidence of disease. Lastly, in all four studies, the incidence of type 1 diabetes was compared in the years before and after the implementation of a change in the vaccination practices of individual countries. In doing so, historical controls were used as the comparator group, which is a significant flaw given that the incidence of type 1 diabetes was increasing prior to the introduction of any change in immunization practices.  

Along with the issues relating to the design of the Classen papers, there were also limitations with the analyses. In general, there was no pre-defined hypothesis or rationale justifying the choice of two to four year risk windows for assessing the incidence of type 1 diabetes. For example, in the 2002 article, the authors arbitrarily chose a point in the curve of the diagram describing the cumulative incidence of type 1 diabetes in the vaccinated and unvaccinated groups and used that point for analysing the incidence of type 1 diabetes. As well, in the reporting of the results of this paper, the authors point out the statistical significance of certain results based on one-sided tests. The use of one-sided tests is inappropriate given that some studies suggest a protective effect.  

The aforementioned studies suggest a lag time of two to four years between exposure to a vaccine and the manifestation of type 1 diabetes in young children. However, it has also been postulated that the onset of type 1 diabetes could occur soon
after immunization in older age groups owing to the possibility of prior destruction of insulin-producing pancreatic cells. This hypothesis is supported by an observed increase of type 1 diabetes within ninety days following immunization against anthrax.\textsuperscript{22} Given the uncertainty regarding the etiologically relevant time window for the development of type 1 diabetes following vaccination, the use of an indefinite risk window following vaccine administration should be considered when assessing this association; the risk window is the time period during which an individual is considered at higher risk of developing the outcome of interest as a result of vaccination (i.e., the etiologically relevant exposure time-window).

While there exists a biologically plausible relationship between immunization and type 1 diabetes, the studies published to date have been of low quality and thus inconclusive. Well-designed studies are required to study the association between type 1 diabetes and newly marketed vaccines including the HPV vaccine.

2.5 HPV Vaccine and Type 1 Diabetes

2.5.1 Safety Evidence from Clinical Trials

The safety of the quadrivalent HPV (qHPV) vaccine was assessed prior to licensure through clinical trials conducted on more than 21,000 females.\textsuperscript{26} Four of the largest phase III randomized controlled trials (RCTs) enrolled females between the ages of nine and 45 (Table 2.3).\textsuperscript{27-30} All were multicentre, double-blinded studies funded by the vaccine manufacturer with a sample size ranging from 1,781 to 12,167 and a mean duration of follow up of 24 to 48 months. In three of the studies the comparator group received a placebo that contained the same adjuvant as the qHPV vaccine (amorphous...
aluminum hydroxyphosphate sulfate). In the fourth RCT, a saline placebo was used.

None of these trials reported an increased risk of type 1 diabetes. However, these trials had a number of important limitations with regards to assessing the safety of the qHPV vaccine. First, in many of these trials, safety was assessed using a short, 30 minute, post-vaccination observation period and in some cases, a vaccination report card which participants, parents or guardians were asked to complete for two weeks after the injection. Second, serious adverse events were typically reported only when they were considered by the investigator to be related to the vaccine. These methods of safety assessment can lead to reporting biases as a result of reliance on self-reporting and investigator selection of relevant adverse events. Third, randomized controlled trials published to date were not adequately powered to detect rare but serious adverse events such as type 1 diabetes. Indeed, these trials had less than 15% power to detect a doubling of the risk of any individual serious adverse event. Fourth, in three of the four phase III trials, patients randomized to the placebo arm received an aluminum-containing adjuvant. While the authors may argue that this was important for blinding, adjuvants on their own have the potential to cause adverse events including autoimmune diseases. Thus, comparing the vaccine to an adjuvanted placebo rather than saline may have lead to an underestimation of adverse events. Finally, the population studied in the clinical trials was not representative of the target age group for Ontario’s grade 8 HPV vaccination program. The mean age of study participants was approximately 20 years and girls under the age of 14 represented only about five percent of all trial participants thereby
suggesting that little is known about the safety of this vaccine in the grade 8 population. This may be particularly important given that there is evidence that adolescent girls have a heightened immune response to vaccines as a result of hormonal influences or other factors.\textsuperscript{32} In a study comparing the immunogenicity of the qHPV vaccine in young adult women (16-23 years of age) versus boys and girls (10-15 years of age), the immune response as measured through blood samples was 1.7 to 2.7 times higher in the latter group.\textsuperscript{33} This could translate into a higher incidence of adverse effects, in particular autoimmune reactions.

A systematic review and meta-analysis of the safety and efficacy of the HPV vaccine based on seven trials of a total of 44,142 females was recently published.\textsuperscript{34} Although the authors reported no overall increased risk of experiencing one or more serious adverse events for vaccinated compared to unvaccinated girls (relative risk (RR) of 1.0; 95% confidence interval [CI] 0.91-1.09) and a positive risk-to-benefit ratio, the efficacy analysis was based on both the per protocol and intention-to-treat (ITT) populations while the safety analysis was restricted to the ITT population. The latter may have resulted in an underestimation of the risks if adverse events occurred less frequently in those receiving fewer doses. Moreover, while the authors reported no statistically significant difference in the risk for vaccine-related serious adverse events between the vaccine and control groups (RR=1.82; 95%CI: 0.79-4.2) the possibility of a risk cannot be ruled out on the basis of the results. Despite the large number of girls included in this meta-analysis, there was still insufficient power for determining safety as evidenced by the upper limit of the confidence interval and the width of the confidence interval.
While few details on the specific types of serious adverse are provided in the aforementioned randomized controlled trials, the Gardasil® product monograph indicates that there have been reports of autoimmune-type reactions following the administration of this vaccine. In total, there were 307 reports of conditions potentially indicative of systemic autoimmune disorders among females between the ages of nine and 25 who received at least one dose of qHPV vaccine compared with 284 such events reported for those having received the placebo, primarily in adjuvanted form. However, the overall incidence of autoimmune-like reactions was the same between the vaccine and placebo groups (2.4% versus 2.5%) and included disorders such as rheumatoid arthritis, systemic lupus erythematosus, psoriasis, multiple sclerosis and autoimmune thyroiditis. Only four cases of type 1 diabetes were reported, two of which occurred in participants who received the qHPV vaccine.

2.5.2 Evidence from Post Marketing Surveillance Systems

As described above, prior to licensure in Canada vaccines are tested for immunogenicity, safety and efficacy. Unfortunately, during the three phases of pre-marketing clinical trials most often there are an insufficient number of subjects to detect rare but serious adverse effects. In addition, given the strict inclusion and exclusion criteria used in clinical trials the populations in whom the vaccine is eventually administered are often under-represented. Post-marketing surveillance and phase IV studies are critically important in addressing this safety evidence gap.

In Canada there are both passive and active post-marketing surveillance systems in place. Within the province of Ontario, the Health Promotion and Protection Act
requires by law that regulated health care professionals (i.e., physicians, nurses and pharmacists) who administer or care for recipients of vaccines report any adverse event following immunization to the medical officer of health of their local public health unit within seven days of recognizing the event. Any adverse event that is severe, unexpected, or of concern should be reported. Such reporting is also mandatory in Saskatchewan, Nova Scotia and Quebec whereas in the remaining provinces and territories, the reporting of adverse events following immunization is voluntary. After removal of personal identifiers, information pertaining to an adverse event is forwarded to the Vaccine Safety Unit of the Centre for Immunization and Respiratory Infectious Diseases (CIRID) at the Public Health Agency of Canada (PHAC) where it is stored in the Canadian Adverse Events Following Immunizations (CAEFI) database which is monitored by the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS). In addition to healthcare provider mandatory reporting, all vaccine manufactures are legally required to submit adverse event reports within 15 days of receiving notification. The Immunization Monitoring Program ACTive (IMPACT) is an active surveillance system for serious adverse events following immunization, vaccination failures and certain infectious diseases. The program is operated through the Canadian Pediatric Society and incorporates 12 major pediatric hospitals, which account for over 90% of all pediatric tertiary care hospital admissions in the country. Active surveillance occurs through regular review of admission records and collaboration between the admitting department, infection control personnel, neurology and infectious diseases staff as well as medical records technicians.
Regrettably, the public is not granted access to the CAEFI or IMPACT databases and as such, these sources of information could not be reviewed for this thesis project. However, the Vaccine Adverse Event Reporting System (VAERS) based in the United States is a well-known passive surveillance program for adverse events following immunization that can be accessed by the public and researchers. This national post-marketing safety surveillance program, co-sponsored by the Centres for Disease Control (CDC) and the Food and Drug Administration (FDA), collects information on potential adverse effects of vaccines from manufacturers, health care providers and the public. Each year, VAERS receives approximately 30,000 reports of which approximately 13% are classified as serious.

Post-marketing surveillance data suggest that the qHPV vaccine may increase the risk of adverse events including autoimmune diseases such as type 1 diabetes. A number of articles reviewing HPV vaccine safety data from post-marketing surveillance programs have been published. One such article, published in 2009, provides a summary and analysis of 12,424 reports of adverse events following HPV vaccination received by VAERS between June 1, 2006 and December 31, 2008. Included within the 772 reports of what were considered to be serious adverse events were cases of anaphylaxis, GBS, hypersensitivity reaction, transverse myelitis, pancreatitis, and autoimmune disorders. In total there were 51 reports of autoimmune disorders, 45 of which were temporally associated with the qHPV vaccine alone. Nineteen of the autoimmune disorders reported were considered serious adverse events. The types of autoimmune disorders reported following HPV vaccination include scleroderma (n=1), dermatomyositis (n=1), systemic
lupus erythematosus (n=18), rheumatoid arthritis (n=13), Sjogren syndrome (n=1) and mixed connective tissue disease (n=4). In addition to providing information on the number of cases the authors of the study also included reporting rates of adverse events following vaccination against HPV. Unfortunately, these rates were calculated based upon the number of vaccine doses sold rather than those administered and thus likely underestimated the actual incidence rate of the events.

An independent search of the VAERS database revealed a number of reports of diabetes following administration of the qHPV vaccine. There were 32 cases considered new onset diabetes occurring in females between six and 17 years of age. Figure 2.1 provides a diagrammatic representation of the VAERS data for the cases of type 1 diabetes occurring after the administration of the HPV vaccine. Most of the reported cases occurred within two months of vaccination. However, as previously stated, approximately 70-80% of pancreatic beta cells must be destroyed before the symptoms of type 1 diabetes become clinically apparent and a diagnosis is made; a process that occurs over a period of months to years. As such, the initial increase in the rate of reporting of type 1 diabetes observed in the VAERS database (i.e., first 60 days) could be the result of reporting or detection bias rather than true vaccine-induced disease. By and large, if one discounts the early increase as reporting bias, the timing of these reports provides no clear evidence for a specific risk window (i.e., period of etiologically relevant exposure) for the development of type 1 diabetes following HPV vaccination.

While post-marketing surveillance systems are essential tools for the early detection of potentially serious adverse effects of vaccines it is important to note that they
are not intended to establish causality but rather are signal generating and highlight the need for further investigation. The limitations of passive surveillance systems such as VAERS for assessing vaccine safety include: (i) the lack of an appropriate control or comparison group, (ii) reporting bias, (iii) the inability to determine the incidence of adverse events due to a lack of data regarding the number of vaccine doses that have been administered or the number of individuals vaccinated, and (iv) an insufficient level of detail about the cases. Reporting bias is particularly problematic and can be the result of underreporting or over reporting. Underreporting can be due to failing to recognize a symptom or disease as being associated with vaccination, failure to complete a report despite recognizing the potential association, or the belief that the adverse event is not related to the vaccine. On the other hand, over reporting can be caused by changes in reporting patterns due to public attention or awareness regarding a specific adverse event, as well as by the increased likelihood of reporting any adverse outcome occurring closest to the date of vaccination.

2.5.3 Safety Evidence from Epidemiologic Studies

Two large observational studies assessing the risk of systemic adverse events following the use of the qHPV vaccine have been published to date.\textsuperscript{45, 46} While neither study specifically addressed the risk of type 1 diabetes, both are relevant to the diabetes-HPV vaccine association as they provide evidence of this vaccine’s potential for causing serious, immune system mediated adverse events.

The first study used a school-based cohort of HPV vaccinated girls to identify cases of anaphylaxis and compared the incidence rate of this potentially life-threatening
adverse event to that observed in other school-based vaccination programs. There were 269,680 doses of the qHPV vaccine administered and seven cases of anaphylaxis identified for an estimated incidence rate of 2.6 per 100,000 doses (95% CI 1.0-5.3). In comparison, the observed incidence of anaphylaxis following immunization with other vaccines has been reported to be as low as 0.1 per 100,000 doses (95% CI 0.003 to 0.7). The authors concluded that the rate of anaphylaxis following qHPV vaccination was significantly higher than that of other school-based vaccines; the findings reflect the highly immunogenic nature of the qHPV vaccine.

The second study involved 189,629 females who received at least one dose of the qHPV vaccine between 2006 and 2008. This retrospective study used electronic medical records from two managed care organizations in California to identify new cases of 16 pre-specified autoimmune conditions (including type 1 diabetes) occurring within 180 days of vaccination. The background incidence rate of each autoimmune condition was estimated from an unvaccinated female population at one managed care organization and compared to the rate in vaccinated women. With the exception of Hashimoto’s disease (incidence rate ratio [IRR]=1.29, 95% CI 1.08-1.56), no statistically significantly elevated risks were observed for the autoimmune conditions studied. However, this study had a number of significant limitations that may have biased the results including the choice of comparator group, the lack of adjustment for important sources of confounding, and the duration of the risk window. The baseline incidence of autoimmune diseases was determined using unvaccinated women from only one of the managed care organizations. It is possible that results observed were due to differences
between vaccinated and unvaccinated women rather than the qHPV vaccine itself. Many autoimmune disorders are age-dependent and it is likely that the uptake of the vaccine differed by age yet, age was not controlled for in the design or analysis of this study. Indeed, there was no attempt made to compare vaccinated and unvaccinated women and control or adjust for differences in this ecologic analysis of individual-level data. Another important source of confounding in vaccine studies such as this one is the “healthy vaccine effect” whereby those who are able to be vaccinated are healthier. The fact that five of the associations studied reported a protective association, two of which were highly significant including that for type 1 diabetes (IRR 0.57, 95% CI: 0.47-0.73), provides evidence of confounding by “healthy vaccine effect” and highlights the dangers inherent in comparing vaccinated and unvaccinated individuals. In addition, the authors limited the post-vaccination follow up interval to 180 days. It is possible that this time frame was not long enough to identify cases of vaccine-induced type 1 diabetes given what is known of the pathogenesis of this disease. Additionally, given the likelihood that the average age of the subjects included in their study is significantly above 13, the generalizability of these study results to the population eligible for Ontario’s HPV vaccination program is limited. These aforementioned limitations need to be addressed in future safety studies.

2.6 The Pathogenesis and Determinants of Type 1 Diabetes

Prior to embarking on a study investigating the potential association between the HPV vaccine and type 1 diabetes an understanding of the disease is imperative. As such, this section will provide details on the pathophysiology and etiology of type 1 diabetes.
Type 1 diabetes occurs as a result of autoimmune destruction of the insulin producing beta cells of the pancreas. It is believed that the disease is triggered by environmental factors in genetically susceptible individuals. Genetic mapping has demonstrated a number of inherited quantitative trait loci related to the development of type 1 diabetes. Many of these regions contain human leukocyte antigen (HLA) genes that encode for major histocompatibility complex (MHC) proteins. These proteins produce antigens that the body recognizes as foreign thus stimulating an attack by the immune system. The first step in the initiation of the destruction of pancreatic cells is the presentation of beta-cell specific autoantigens by antigen-presenting cells (APC), also known as macrophages and dendritic cells, to CD4+ T helper cells in combination with MHC class II molecules. Macrophages and CD4+ T cells then secrete cytokines that further stimulate the immune system and induce the migration of CD8+ cytotoxic T cells that are fatal to beta cells.

Factors responsible for initiating the autoimmune response that results in the destruction of pancreatic beta cells have yet to be conclusively established. Potential environmental triggers include vaccines, diet, socioeconomics (more specifically hygienic conditions), infection and season. Evidence to support diet, socioeconomics, infection, and season as determinants of type 1 diabetes will be discussed in this section whereas the role of vaccines has previously been reviewed in section 2.4.

With respect to diet, vitamin D deficiency has been postulated as a trigger of type 1 diabetes. This theory is supported by the established role of vitamin D in modulating immune cell function as well as by the epidemiology of type 1 diabetes. The highest
The incidence of type 1 diabetes in the world is in Finland where long winters limit skin exposure to ultraviolet B radiation, which is required for vitamin D synthesis. In addition, several observational studies have demonstrated that vitamin D supplementation is associated with a lower risk of type 1 diabetes. Other potential but unproven dietary triggers include exposure to cow’s milk, exposure to gluten-containing cereals, length of breastfeeding, and food additives.

The “hygiene hypothesis” has been used to describe the hypothesized relationship between socioeconomics and the incidence of type 1 diabetes. It has been proposed that improvements in hygiene and living conditions is associated with a lower incidence of childhood infections and altered maturation of the immune system thus making children more susceptible to autoimmune and allergic diseases. The biological basis for this hypothesis is founded on the observation that non-obese diabetic mice have demonstrated a higher incidence of type 1 diabetes when raised in a sterile environment. Although there are some epidemiologic studies to support this hypothesis, data are conflicting and further research is required.

The most convincing evidence of the role of infection in the etiology of type 1 diabetes implicates viruses. Although a causal relationship has yet to be conclusively established, many studies have suggested an association between specific viruses and the onset of type 1 diabetes, with up to 13 different viruses implicated to date. The most extensive, albeit conflicting, data supporting this hypothesis involves enteroviruses such as coxsackie, echoviruses, and rubella. Other viruses less commonly associated with diabetes include cytomegalovirus, Epstein-Barr, mumps, retrovirus, and rotavirus.
rationale for this association is multi-factorial and includes\textsuperscript{56}: (i) the ability of viruses to induce a strong immune response, (ii) the season of the onset of type 1 diabetes especially when the diagnosis is preceded by an infection\textsuperscript{57, 58}, (iii) reports of viruses being isolated from the pancreases of deceased patients with newly diagnosed type 1 diabetes and, (iv) the detection of virus-specific IgM antibodies and viral RNA in a small number of newly diagnosed patients.\textsuperscript{56, 59}

The two most common mechanisms by which viruses have been proposed to cause type 1 diabetes are molecular mimicry and bystander activation (section 2.6). The best evidence to support molecular mimicry as an explanation for the virus-type 1 diabetes association involves Coxsackie B virus. Research has demonstrated similarities in the amino acid sequences of glutamate decarboxylase (GAD65), an enzyme located in the pancreas of humans, and P2-C, an enzyme involved in the replication of Coxsackie B virus.\textsuperscript{60} Bystander activation occurs when the immune system is non-specifically stimulated by a virus resulting in activation of autoimmunity. More specifically, infection with a virus results in activation of antigen presenting cells that are able to then stimulate preprimed autoreactive T cells which in turn results in autoimmune destruction of pancreatic beta cells.\textsuperscript{61}

As in the case of vaccines, the timing of the onset of type 1 diabetes following viral infection is a source of controversy.\textsuperscript{48} Traces of the enterovirus have been detected in individuals with recent onset type 1 diabetes suggesting a short exposure window. On the other hand, in utero exposure to enteroviruses and rubella is considered a risk factor
for childhood type 1 diabetes suggesting that the time frame for onset of diabetes following exposure to viruses is years in length.\textsuperscript{48, 55}

The results of studies investigating the role of season in the onset of type 1 diabetes are conflicting.\textsuperscript{57} This association has been most often observed in older children and in males. In general, the reported incidence of type 1 diabetes peaks in colder months and is at its lowest in warmer months. This seasonal pattern has been observed in 42 of 53 countries studied.\textsuperscript{57} In Canada, the observed peak in the incidence of type 1 diabetes occurred in the months of December to March and the trough from June to September. A number of hypotheses have been proposed to explain this seasonal variation.\textsuperscript{62} The most common of these include a potential link between viral infection and season, whereby a higher incidence of viral infections in colder months contributes to the higher incidence of type 1 diabetes observed during this time period, and decreased sunlight exposure in colder months resulting in a reduction in vitamin D synthesis, a proposed risk factor for the disease.

Establishing and proving which environmental factors are responsible for triggering type 1 diabetes has proven difficult. The National Institutes of Health has completed enrolment for “The Environmental Determinants of Diabetes in the Young (TEDDY)” study that aims to address this gap in knowledge.\textsuperscript{63} This large, multicentre, prospective cohort study initiated in 2003 was designed to identify environmental factors that either protect or predispose children to the development of type 1 diabetes. Participants will be followed from birth until the age of 15 and will include over 7,000 newborns without a family history of diabetes but, who have a genetic predisposition for
the disease. A number of the factors previously described will be examined in this study as potential triggers of the disease, including vaccines. Until the environmental determinants of type 1 diabetes are better understood researchers must rely on the information currently available.

2.7 The HPV Vaccine and Ontario’s Vaccination Program

At the centre of this thesis is the qHPV vaccine and Ontario’s grade 8 HPV vaccination program. This section aims to provide information on both of these topics.

In 2006, Health Canada granted approval for the first of two vaccines prophylactic against HPV infection.64 Gardasil® is a recombinant, quadrivalent vaccine offering protection against HPV types 6, 11, 16 and 18.35 It was approved for use in females nine to 45 years of age for the prevention of HPV infection and its associated disease including: (i) cervical, vulvar and vaginal cancer (HPV 16/18), (ii) genital warts (HPV 6/11), and (iii) precancerous or dysplastic lesions (HPV 6/11/16/18) including cervical adenocarcinoma (in situ), cervical intraepithelial neoplasia (grade 1/2/3), vulvar intraepithelial neoplasia (grade 2/3) and vaginal intraepithelial neoplasia (grade 2/3). In addition, the qHPV vaccine was recently approved for use in males and females nine to 26 years of age for the prevention of anal cancer (HPV 16/18), anal intraepithelial neoplasia (HPV 6/11/16/18) grades 1-3 and genital warts in males (HPV 6/11).35 Cervarix®, marketed in Canada in 2010, is a recombinant bivalent vaccine that protects against infection from HPV types 16 and 18. This vaccine was approved for use in females 10-25 years of age.65 Both Gardasil® and Cervarix® are prepared from highly purified virus-like particles of the recombinant major capsid L1 protein of the human
papillomavirus and contain an aluminum-based adjuvant, which is responsible for augmenting the body’s immune response to the vaccine. The adjuvant deployed in Gardasil® is an aluminum hydroxyphosphate system (amorphous aluminum hydroxyphosphate sulfate) while Cervarix® contains aluminum hydroxide and 3-deacylated monophosphorul lipid A (AS04), a novel agent. Gardasil vaccine is administered intramuscularly as three separate doses at zero, two and six months, whereas the recommended dosing schedule of Cervarix is zero, one and six months.35,65

Both HPV vaccines have demonstrated efficacy in preventing HPV-16/18 induced cervical intraepithelial neoplasias (CIN).66 In per protocol analyses, the efficacy of Gardasil® in preventing HPV16/18-related CIN grade two or higher in previously uninfected females aged 15-26 years was 97.96% (95% CI: 76-100%).67 It is important to note that these analyses were restricted to study participants who: (i) had not been previously infected with HPV 16 or 18, (ii) did not develop such an infection up to one month following the administration of the third dose, (iii) received all three doses within one year, and (iv) had no protocol violations (i.e., attended five to six clinic visits for Pap testing and taking of anogenital swabs). The reported efficacy decreased to 44% (95% CI: 26-58%) in the modified intention-to-treat analysis that included study participants regardless of baseline serologic and HPV DNA status who received at least one dose of the vaccine.66 Long-term follow up of women vaccinated with Gardasil® has demonstrated vaccine efficacy for a minimum of five years.68

In the fall of 2007, the government of Ontario introduced a voluntary school-based HPV vaccination program. At that time, only the quadrivalent vaccine (qHPV)
was approved for use in Canada and therefore offered through publicly funded programs. The quadrivalent vaccine continues to be the only HPV vaccine publicly funded. In Ontario, each of the province’s 36 local public health agencies are responsible for implementing the school-based program which offers the recommended three doses of the qHPV vaccine (Gardasil®) free to all grade 8 girls at a cost of approximately $117 million over three years.\textsuperscript{69} The three doses of HPV vaccine are typically administered in schools by public health nurses in September/October, November/December and March/April of each academic year. Girls eligible for the program are also able to receive the vaccine at no charge from their local public health agency (health unit) or family physician, who must obtain the vaccine from the health unit. Information pertaining to all doses of the qHPV vaccine administered under Ontario’s HPV vaccination program is documented in the electronic Immunization Recording Information System (IRIS) database of the respective health unit. Each of Ontario’s 36 public health units is responsible for maintaining their own individual IRIS database. However, an exchange of data facilitated by the Ministry of Health’s central immunization database does occur when a child moves within the Province.\textsuperscript{70} To qualify for the publicly funded program, girls have until the end of August of their grade 8 school year to start their dosing regimen. A catch-up program is offered to grade 9 girls who failed to complete their vaccine series in their grade 8 year provided the first dose was administered while in grade 8. Individuals not eligible under the Ontario HPV vaccination program may receive the vaccine from a physician or nurse at a cost of approximately $170 per dose. In general, this information is not recorded in IRIS. A
detailed description of the IRIS database, including strengths and limitations is provided in chapter three.

Despite an anticipated 85% rate of uptake, in the first year of the program only 53% of eligible girls in Ontario received the first dose of the vaccine.\textsuperscript{71} Adherence to the recommended three-dose vaccination schedule was also an issue as not all girls who received the first dose of vaccine went on to receive the remaining two doses.\textsuperscript{72} Concerns surrounding the safety of the vaccine are among the reasons for the observed low acceptance and compliance with the program.\textsuperscript{73} Additional research is required to address lingering safety concerns particularly because of the limitations of the safety data available as well as the fact that the Ontario HPV vaccination program is targeting a younger population than that studied in clinical trials that may be more susceptible to serious adverse effects of vaccination, including autoimmune diseases such as type 1 diabetes.\textsuperscript{31} The potential increase in the risk of adverse effects is the result of age-related hormonal influences and the heightened immune response to the HPV vaccine observed in adolescents.\textsuperscript{32, 33}

2.8 Conclusions

The safety profile of the HPV vaccine is a valid concern for recipients of the vaccine, parents, guardians, and health care providers. The decision to vaccinate must weigh the benefits of the vaccine against the potential harms including the possibility of developing an incurable autoimmune disease such as type 1 diabetes. Yet, the current safety evidence base has significant limitations particularly with respect to validity, power and generalizability. Population-based, observational studies such as this thesis
are required to assess whether there is an association between exposure to the HPV vaccine and the onset of type 1 diabetes.
2.9 References


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Table 2.1 Autoimmune diseases temporally associated with vaccination\textsuperscript{15}

<table>
<thead>
<tr>
<th>Autoimmune Disorder</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
<td>HBV, tetanus toxoid, anthrax</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>HBV, tetanus toxoid, typhoid/paratyphoid, MMR</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>HBV, swine-flu</td>
</tr>
<tr>
<td>Reactive arthritis</td>
<td>BCG, DPT, MMR, HPV, influenza</td>
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<td>BCG, smallpox, diphtheria, DPT</td>
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<td>Polyarteritis nodosa</td>
<td>Influenza, pertussis, HBV</td>
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<tr>
<td>Guillain-Barré syndrome</td>
<td>Influenza, oral polio vaccine, tetanus, rabies, meningococcal (MCV4)</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>HiB, mumps</td>
</tr>
<tr>
<td>Idiopathic thrombocytopenia</td>
<td>MMR, HBV, hepatitis A virus</td>
</tr>
</tbody>
</table>

Hepatitis B virus (HBV), mumps/measles/rubella (MMR), Bacillus Calmette-Guerin (BCG), diphtheria-pertussis-tetanus (DPT), Haemophilus influenza B (HiB)
Table 2.2 Summary of research supporting an association between vaccination and type 1 diabetes

<table>
<thead>
<tr>
<th>Reference</th>
<th>Purpose</th>
<th>Population</th>
<th>Methods</th>
<th>Results/Conclusions</th>
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| Classen 2003    | To determine whether there is a clustering of cases of type 1 diabetes (T1D) 2-4 years after vaccination with vaccines other than hemophilus vaccine. | Young children in Finland, the United Kingdom and Denmark                  | Medline search to determine the incidence of T1D in children 0-14 years of age in industrialized Western nations (limits: articles containing incidence data from 1975 to 2003 and at least 100 patients with T1D.) Following identification of articles, a subsequent search was performed to determine if there were any changes to immunization practices in the respective countries during the same time frame. | - 52% increase in risk of type 1 diabetes in the 2-3 years after addition of more potent pertussis vaccine in Finnish children 1-4 years of age [RR 1.52 (1.3-1.73)]  
- Decrease in the incidence of type 1 diabetes in children aged 0 to 4 years in the 3-4 years after the rate of immunization with pertussis dropped from 77% to 31% (RR 1.46, p=0.0082)  
- Increase in the risk of type 1 diabetes in Finnish children aged 1-4 years in the 2-4 years after measles vaccine was replaced with MMR [RR 1.4 (1.25-1.57)]  
- In the UK, in the 4 years following replacement of the measles vaccine with MMR, an increase in the average incidence of T1D in children 0-4 years from 10 cases per year to 15 cases per year. (RR=1.48, range 1.09 to 2)  
- Following discontinuation of the BCG vaccination program in Denmark, the incidence of type 1 diabetes declined over the following 4 years (RR 1.6 to 2.7) |
| Classen 2002    | To determine if the Hemophilus influenza B (HiB) vaccine is associated with an increase in the risk of T1D by detecting clusters of cases of diabetes from a clinical trial. | Children born in Finland between October 1st, 1985 and August 31st, 1987 (n=116,000). Historical controls were unvaccinated children born in the 24 months prior to the original study (n=128,500). | Follow up on a previously conducted clinical trial designed to test the efficacy of the polysaccharide-protein conjugated form of the HiB vaccine administered as 4 doses (3, 4, 6 and 18 months of age) compared to the control group which received a single dose of the vaccine at 24 months of age. Children were quasi-randomized to receive either 1 dose of the HiB vaccine at 24 months of age or 4 doses starting at 3 months of life (3, 4, 6, 18 months of age). | - After 10 years, the difference in the incidence of type 1 diabetes between those receiving 4 doses compared to 0 doses was non-significant at 58 cases per 100,000 (p=0.058) with a relative risk of 1.17. The difference in cumulative incidence of disease comparing those receiving any dose to zero doses was also non-significant (47 cases per 100,000, p=0.056) with a relative risk of 1.14.  
- The authors noted a statistically significant difference in incidence of type 1 diabetes after 7 years of follow up and a relative risk increase of 1.2 (1.02-1.42).  
- Most of the extra cases of type 1 diabetes were noted by the authors to be occurring at 38 months after the vaccine with the peak lasting about 6 months.  
- The authors concluded that exposure to HiB vaccine is associated with an increased risk of T1D. |
<table>
<thead>
<tr>
<th>Reference</th>
<th>Purpose</th>
<th>Population</th>
<th>Methods</th>
<th>Results/Conclusions</th>
</tr>
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</table>
| Classen 2008 22 | To determine if clustering of cases of T1D occur after immunization with hepatitis B vaccine. | Birth cohorts: (i) Italy (ages 1-5) 1988 to 1990 (unvaccinated; n=150,000) and 1991-1993 (vaccinated; n=150,000) (ii) France (ages 0-4;10-14) 1988 to 1994 (unvaccinated) and 1997 (vaccinated) (iii) New Zealand (ages 0-14; 0-19) from 1980-1989 (unvaccinated) and 1990-1999 (vaccinated) | The authors used disease registries from each country to determine the cumulative incidence of T1D before and after implementation of a hepatitis B immunization program | Italy  
- RR 1.24 (p=0.2) for children under 6  
- Subsequent analysis on children born between 1978 and 1984, 12 years of age in 1991 of later, RR=2.22 (p=0.036)  
France  
- In the 0-4 year old age group, incidence of T1D in 1997 compared to 1988-1994 - RR=1.61 (1.11<RR<2.33; p=0.01)  
- In the 10-14 year old age group, incidence of T1D in 1997 compared to 1988-1994 - RR=1.31 (1.04<RR<1.65; p=0.02)  
- Incidence was stable in the 15-19 year old group and no analysis done on the 5-9 year old group  
New Zealand  
- In the 0-14 year old age group, the incidence of T1D between 1980-1989 compared to 1990-1999 indicated a RR=1.48 (1.17<RR<1.86; p=0.008)  
- In the 0-19 year old age group, the incidence of T1D between 1980-1989 compared to 1990-1999 indicated a RR=1.35 (1.1<RR<1.66; p=0.004)  
Authors concluded that the findings of a 2-3 year delay between hepatitis B vaccination and the rising incidence of T1D is consistent with a causal relationship  
| Classen 1997 23 | Children of varying ages (0-19) from a large number of countries | The authors used a number of sources including but not limited diabetes registries, drug registries for prescription data, hospital records to ascertain the risk of type 1 diabetes prior to significant changes in vaccination practices | - A decrease of 48.64 cases per 100,000 (p=0.0057) observed in children aged 4-15 years from Sweden 2 years after discontinuation of the BCG vaccine program in 1975  
- A 64% (p<0.0001) rise in the incidence of type 1 diabetes observed in 0-4 year olds in the 2 years following changes to the immunization program in Finland  
- In New Zealand, the incidence of type 1 diabetes in children 0-19 years of age increased by 6.9 per 100,000 (p=0.0008) in the years following the introduction of hepatitis B vaccination.  
- Authors conclusions: Timing of pediatric immunizations can impact upon the development of T1D |
### Table 2.3 Summary of safety evidence of HPV vaccine from randomized controlled trials

<table>
<thead>
<tr>
<th>Reference</th>
<th>Description</th>
<th>Population</th>
<th>Intervention</th>
<th>Endpoint/Analysis/Safety Assessment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Munoz 2009(^7)</td>
<td>Phase III Multicentre Randomized Double-blind Placebo-controlled Allocation concealment Manufacturer sponsored Duration of follow up: approx. 4 years</td>
<td>N=3819 Females 24-45 year of age Exclusion criteria: pregnancy, history of genital warts, present or past cervical disease, immunocompromised</td>
<td>Stratification (age ≤ 34 and age ≥ 35) then random assignment (1 to 1) to receive 3 doses at 0, 2 and 6 months: (i) Quadrivalent HPV vaccine, or (ii) Aluminum-containing placebo</td>
<td>1° - Combined incidence of 6-month persistent infection, CIN1-3, VIN1-3, VaIN1-3, AIS, cervical, vulvar or vaginal cancer, and genital warts associated with HPV 6, 11, 16 or 18, or with HPV 16 or 18 alone. 2° - Combined incidence of 6-month persistent infection, CIN1-3, VIN1-3, VaIN1-3, AIS, cervical, vulvar or vaginal cancer, or genital warts associated with HPV 6 or 11</td>
<td>Safety assessment: General questioning at study visits and with a vaccine report card that was provided at every visit. Per protocol analysis for efficacy endpoints (HPV seronegative on day 1, and PCR negative day 1-month 7, received all 3 doses and have one or more follow up visits after 7 months)</td>
</tr>
<tr>
<td>Reisinger 2007(^8)</td>
<td>Randomized Double-blind Placebo-controlled Multi-centre Manufacturer Sponsored Mean follow-up: 2 years</td>
<td>N=1781 Sexually naïve males and females</td>
<td>Stratified by age (2:1 ratio; 9-12 and 13-15 year olds) and gender (1:1) to receive at 0, 2 and 6 months: (i) Quadrivalent HPV vaccine, or (ii) Placebo without aluminum adjuvant or HPV virus-like particles</td>
<td>1° - Tolerability of the 3 dose regimen. All participants receiving at least one dose of the vaccine were included in the analysis 2° - Non-inferiority of immune response to the vaccine in preadolescent and adolescent boys compared to girls, as measured by anti-HPV geometric mean titres (GMTs) and seroconversion rates one month post dose 3 (per-protocol)</td>
<td>Safety assessment: A 30 minutes post vaccination monitoring period. Oral</td>
</tr>
<tr>
<td>Reference</td>
<td>Description</td>
<td>Population</td>
<td>Intervention</td>
<td>Endpoint/Analysis/Safety Assessment</td>
<td>Results</td>
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<tr>
<td>Reisinger 2007</td>
<td>continued</td>
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<td>temperatures were recorded for 5 days after vaccination. All AEs were collected for 14 days following vaccination on a report card. Interview to assess general safety during follow-up visits at 2, 6, 7, 12 and 18 months. Reporting of all deaths and serious AEs considered by the investigator to be vaccine-related during the study period.</td>
<td>Serious systemic AE: 0.4% vaccine, 0% placebo</td>
</tr>
<tr>
<td>Garland 2007</td>
<td>Phase III Double-blind Placebo-controlled Randomized Manufacturer sponsored Multi-centre</td>
<td>N=5455 Females 16-24 years of age Inclusion criteria: Healthy women, not pregnant and no history of genital warts or abnormal results on cervical cytologic testing and a lifetime number of no more than 4 sexual partners</td>
<td>Randomized (1:1) within each study centre to receive: (i) Quadrivalent HPV vaccine or, (ii) Aluminum-containing placebo at 0, 2 and 6 months</td>
<td>1° - Coprimary composite endpoint of incidence of genital warts, vulvar or vaginal intraepithelial neoplasia, or cancer and the incidence of cervical intraepithelial neoplasia, adenocarcinoma in situ or cancer associated with HPV types 6, 11, 16 or 18 using the per-protocol population Safety assessment: A 30 minute observation period following vaccination and by use of a vaccine report card whereby women were asked to record oral temperature 4 hours after the vaccine and daily for 4 days. Adverse effects were recorded with a report card for 15 days after vaccination</td>
<td>Vaccine efficacy was 100% (95% CI: 94-100%) for external anogenital, vaginal and cervical lesions using per protocol analysis. Efficacy dropped to 73% (95% CI: 58-83%) in per-protocol analysis for external anogenital and vaginal lesions and 55% (95% CI: 40-66%) for cervical lesions. The proportions of subjects with ≥ 1 AEs was higher in the vaccine group compared to the placebo. The risk difference for systemic events was 1.6 (95%CI: -1.0-4.2). The incidence of serious events was the same in both groups; risk difference of 0.1 (95%CI: -0.6-0.8) One endocrine disorder reported in the vaccine group and none in the placebo. There were 17 (0.6%) cases of immune disorders in the vaccine group and 18 (0.7%) in the vaccine group with a risk difference of 0 (95% CI: -0.5-0.4).</td>
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<tr>
<td>Reference</td>
<td>Description</td>
<td>Population</td>
<td>Intervention</td>
<td>Endpoint/Analysis/Safety Assessment</td>
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</table>
| Future II Study Group 2007 | Randomized Phase III Double blind Placebo controlled Multi-centre Manufacturer sponsored Mean follow up: 3 years | N=12,167 | Randomly assigned to receive: (i) Quadrivalent HPV vaccine, or (ii) Aluminum-containing placebo at 0, 2 and 6 months | 1° - CIN 2 or 3, AIS or invasive carcinoma of the cervix with detection of HPV-16 or 18, or both using per protocol analysis<br>2° - Persistent infection, CIN1-3 and AIS associated with HPV 31, 33, 45, 52, 58<br>

Safety assessment: A 30 minute post vaccination observation period and self-reporting of any serious adverse event occurring 1-15 days after each injection. All subjects were asked to record all serious and non-serious adverse events occurring 1-15 days after each vaccination. During the trial, all serious adverse events potentially related to the vaccine, all deaths and all pregnancies were reported. | 1° endpoint: Efficacy of the vaccine for the prevention of the primary composite outcome was 98% (95% CI: 86-100) in the per protocol analysis and 44% (95% CI: 26-58%) in the intention-to-treat analysis. 2° endpoint: Efficacy of the vaccine in preventing secondary outcome in the intention-to-treat population was 17% (95%CI: 1-31) Subjects who experienced 1 or more systemic events: 61.4% in vaccine group, 60% in placebo group Subjects who experienced any serious event: 0.7% in vaccine group, 0.9% in placebo group The reported incidence of immune system disorders was 2.2% (n=10) in the vaccine group and 0.4% (n=2) in the control group. Risk difference = 1.8 (95% CI 0.3-3.7) |
Figure 2.1 Distribution of occurrence of type 1 diabetes in females ages 6-17 years following administration of the HPV vaccine from VAERS query (n = 21)\textsuperscript{43}
Chapter 3

Methodological Considerations
3.1 Empirical Objective

The primary objective of this thesis was to determine whether there is an association between immunization against HPV and the development of type 1 diabetes mellitus in grade 8 girls eligible for Ontario’s vaccination program.

3.2 Overview of Study

To investigate the potential association between the qHPV vaccine and the onset of type 1 diabetes, a retrospective, population-based cohort study was conducted. The study cohort consisted of all girls residing within one Ontario health unit who were eligible to participate in the province’s grade 8 HPV vaccination program during the 2007/08 to 2009/10 school years. The vaccination status of individual cohort members was ascertained from the Immunization Recording Information System (IRIS) database. Information pertaining to the diagnosis of type 1 diabetes was obtained by record linkage with Ontario’s administrative health databases. For statistical analysis, a self-controlled case series approach was undertaken to control for all time-independent confounders (Figure 3.1). Using this analysis method the incidence rates for type 1 diabetes were compared within an individual during exposed and unexposed time periods or risk windows. The duration of the etiologically exposed person-time risk window following vaccination was based on the pathogenesis of type 1 diabetes, the biological model for vaccine induced autoimmune reactions, and the time to onset of type 1 diabetes obtained from the VAERS database.
3.3 Sources and Quality of Data

Data pertaining to qHPV vaccination status and vaccine history were acquired from the IRIS database. This database was developed in 1993 for public health units in the province of Ontario to assist them with tracking of immunization status for school-aged children. The IRIS database records all mandatory childhood vaccines under the Immunization of School Pupils Act (1982) and the Amended Act (1984) as well as government funded vaccines administered by a public health unit representative. Each of Ontario’s 36 public health units is responsible for maintaining their own individual IRIS database. However, an exchange of data facilitated by the Ministry of Health’s central immunization database does occur when a child moves within the province. In addition to containing the qHPV vaccination history of girls who received the vaccine through Ontario’s publicly funded program, the IRIS database also holds the immunization history of females who received the vaccine at a physician’s office since the vaccine must be obtained from the health unit to be free. Variables contained within the IRIS database include a unique encrypted identifier, referred to as the ICES key number (IKN), the type of vaccine administered, the number of vaccine doses, the dates of vaccine administration, and the health region where vaccines were administered. The accuracy and precision of HPV immunization data within the IRIS database has previously been quantified for one Ontario public health unit with a sensitivity of 99.8% (95% CI, 99.3-99.9) and specificity of 97.7% (95% CI, 96.3-98.7) for immunization status and a sensitivity of 98.6% for dates of vaccination. In addition, 95.6% of eligible girls were successfully linked to Ontario’s administrative health databases.
All other data required for this study were contained within Ontario’s Ministry of Health and Long-Term Care administrative health databases. Copies of these databases are housed at ICES-Central and were accessed at Queen’s University via ICES’s satellite unit. The following databases were accessed for the purpose of completing this thesis: (1) the Registered Persons Database (RPDB), (2) the Ontario Diabetes Database (ODD), (3) the Ontario Health Insurance Plan (OHIP), (4) the Discharge Abstract Database (DAD) from the Canadian Institute for Health Information (CIHI), and (5) the National Ambulatory Care Reporting System (NACRS). These databases were used to ascertain information related to socio-demographics, physician services, emergency department visits, and hospitalizations as well as for determining the occurrence type 1 diabetes within the cohort. A summary of the databases accessed for this study is provided in Table 3.1.

The Registered Persons Database (RPDB) contains the IKN as well as demographic information, including the sex, date of birth, and postal codes for all residents eligible for Ontario’s health insurance coverage.² For this thesis, the RPDB was used to identify the study cohort and to obtain socio-demographic information. Unlike other administrative databases, the socio-demographic information contained in the RPDB may not be up to date because individuals are not forced to notify the Ministry of Health of address changes within or outside of the province.⁴ To overcome this limitation and to ensure more accurate demographic information, ICES enriches the database with geographic, contact and death information from other ICES administrative data holdings.
The ODD contains all identified individuals diagnosed with diabetes, excluding gestational diabetes, since 1991. Relevant data elements within the database include the IKN, date of diagnosis, age at diagnosis and the source of diagnosis. The ODD is cumulative and is re-created on a yearly basis using updated data from the OHIP, CIHI, Same Day Surgery (SDS), and RPDB databases. Since 2008, the criterion for identifying individuals under the age of 19 with diabetes is four physician OHIP claims containing a diabetes diagnosis code (OHIP dxcode 250), or one OHIP diabetes fee claim within two years. Diabetes fee claims include diabetes management incentive (Q040), insulin therapy support (K029) and diabetes management assessment (K030). This definition is associated with 83% sensitivity and 99% specificity. Given the time-frame of the study and the two year delay required to fulfill the diagnostic algorithm, not all cases of diabetes observed in the cohort were captured within the ODD. As such, the OHIP, DAD and NACRS databases were also accessed to ascertain the outcome of interest.

The OHIP database contains most claims for eligible health services rendered in the province of Ontario by a physician at a private practice, emergency department or hospital. The main data elements contained within with database include encrypted unique patient (IKN) and physician identifiers, the code and date of the service provided, the associated diagnosis and the fee paid. ICES receives OHIP claim data on a monthly basis, directly from the Ministry of Health and Long-Term Care (MOHLTC). There are limitations to the accuracy and completeness of the available data including missing or late data due to lack of or delays in billing, incorrect service dates, and differences in codes used by OHIP and CIHI to identify institutions. As described above, physician
billing claims from the OHIP database are used in the creation of the ODD. A study validating the case definition of pediatric diabetes in Ontario demonstrated that one physician billing claim in a one year period was associated with 96.6% sensitivity and 97.1% specificity. Given the aforementioned limitations of the ODD, this definition was used to identify cases of type 1 diabetes from the OHIP database.

The DAD (CIHI) database contains the IKN as well as demographic (sex, date of birth, postal code, county and residence code), administrative (institution/hospital number), and clinical (diagnoses, procedures, physicians) data for all hospital admissions and discharges including inpatient, day surgery, chronic and rehabilitation stays. A jointly conducted reabstraction study reviewing clinical coding practices in Ontario hospitals found an 81% sensitivity and 88% specificity when the most responsible diagnosis was type 1 diabetes. The study also found that in general, demographic, procedures, and the ‘most responsible diagnosis’ were well coded with high sensitivity and specificity. On the contrary, the coding of comorbid diagnoses, including those occurring prior to admission and during hospital stay was often very poor. For this reason, the usefulness of the DAD (CIHI) database is limited in terms of employing it to confirm the diagnosis of type 1 diabetes when it is not the most responsible diagnosis (i.e., when it is present as a comorbidity), but is a reliable source of information for identifying new cases of type 1 diabetes admitted to hospital.

The NACRS database contains demographic, clinical, administrative, and financial data on all hospital and community based ambulatory care visits including surgical care, outpatient clinics and emergency departments. Between 2004 and 2005,
charts at 15 health care facilities in Ontario were reviewed as part of a reabstraction study conducted to evaluate the quality of emergency department data submitted to NACRS. The accuracy of demographic, financial, institutional, visit and assessment data was considered very high. The authors did however note a problem of under-reporting of health problems for patients seen in emergency departments, particularly with patients presenting with multiple conditions or co-morbidities and with under-reporting of interventions performed. There were high agreement rates when determining a patient’s main problem (85.5%) but low agreement rates in the diagnosis code used to describe the problem (68.8%).

Regardless of the limitations of abovementioned databases, they contain a wealth of information and are useful tools for conducting clinical research, benchmarking and health care planning. The databases served as a reasonable source of information for identifying cases of type 1 diabetes and had a low likelihood of missing cases, particularly when used in combination.

3.4 Data Access

Access to Ontario’s administrative health databases held by ICES was acquired through Dr. Linda Lévesque who is an appointed ICES Scientist. The Medical Officer of Health of individual health units is the legal custodian of the IRIS database under the province’s Personal Health Information Protection Act (PHIPA, 2004). As part of the larger study from which this thesis project is based, access to the IRIS dataset had previously been obtained through a Data Sharing Agreement (DSA) between the Medical Officers of Health of the public health unit and ICES-Central. The transfer of the IRIS
dataset to ICES-Central was executed via high encryption, dedicated secured portals according to ICES’s standardized procedures. Experience to date has demonstrated that over 95% of girls in IRIS can be record linked with the province’s administrative health databases. The vast majority of record linkages were deterministic (81.42%), that is based upon individuals’ health card number and IKN. When this was not feasible matching was probabilistic (14.20%) using a girl’s first and last name, sex and date of birth.

Ethics approval for this thesis was obtained from the Queen’s University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board. (Appendix I)

3.5 Study Cohort

The study population comprised of grade 8 girls eligible for the province’s HPV immunization program between 2007 and 2010. A cohort was created using both the RPDB and the IRIS database. All girls born between 1994 and 1996, residing in Ontario between September 2007 and 2010, respectively were identified through the RPDB. The rationale for using birth year rather than school grade was that the latter information is not available within the IRIS database. Since a girl must be 13 years of age before December 31st of her grade 8 year, most girls in grade 8 in 2007 would have been born in 1994. A recent re-abstraction study has demonstrated that the use of birth cohorts correctly identified 96.4% of eligible grade 8 girls (L.Lévesque, personal communication, April 3, 2012). For inclusion in the cohort, girls also had to be identifiable within the IRIS database. By record linking the IRIS and RPDB databases, a cohort of eligible grade 8 girls residing within the health unit were identified. Cohort entry was defined as
the September 1st of their grade 8 year. More specifically, girls born in 1994, 1995, and 1996, who were living in the health unit entered the cohort on September 1st, 2007, 2008, and 2009, respectively. A diagnosis of type 1 diabetes preceding cohort entry or a death date before the start of the observation period (i.e., t0) excluded girls from the cohort; this was ascertained from the administrative health databases. To be included in the cohort girls had to have an active and up-to-date vaccination record, or alternatively, the date in which the vaccination record was last updated had to be greater than or equal the date of cohort entry. Cohort members were followed from the beginning of their grade 8 school year until their date of death, or the end of the study period, defined as March 31st, 2011, whichever came first.

3.6 Ascertainment and Classification of Exposure

The IRIS database was used to identify all doses of the qHPV vaccine administered during study follow-up. The time following administration of the first dose of the qHPV vaccine until the end of the study was considered etiologically exposed person-time (Figure 3.2). This indefinite risk window represented the follow up time during which a girl was considered exposed to the vaccine’s effect (i.e., etiologically relevant risk period for developing type 1 diabetes). All time prior to administration of the first dose of the qHPV vaccine (i.e., from cohort entry until immediately preceding the first dose of vaccine) was considered unexposed person-time. The choice of an indefinite frame for identifying etiologically exposed person-time post vaccination was based on the pathogenesis of type 1 diabetes (i.e., not acute), data from the VAERS database and other studies investigating vaccine-induced autoimmune diseases, including
type 1 diabetes. Data from the VAERS database indicated that there could be an increased risk of type 1 diabetes in the first few months following vaccination. As previously described, this early risk is believed to be due to reporting bias. However, this cannot be definitively established and as such the exposure risk window for the primary analysis included this time frame. In addition to the VAERS data suggesting an early onset of type 1 diabetes following vaccination, many studies investigating vaccine-induced autoimmune disease have examined a narrow time frame post vaccination (months), albeit no association was found. Despite the limited evidence suggesting a short time frame for the onset of type 1 diabetes following vaccination, the pathogenesis of the disease indicates a more delayed onset. This late-onset time frame is further supported by the ecological studies presented in section 2.4 and by a cohort study that investigated the occurrence of the type 1 diabetes following vaccination against Haemophilus influenzae type B. The latter indicated a two to three year delay following immunization before the diagnosis of type 1 diabetes. Given the uncertainty regarding the onset of diabetes following vaccination, an indefinite risk window post-qHPV administration (i.e., risk any time following vaccination) was used in this thesis. The use of an infinite exposure risk window has been successfully studied with other vaccines using the same analytical method applied in the current study.

3.7 Ascertainment and Classification of Outcome

The primary outcome of the study was a new diagnosis of type 1 diabetes occurring any time after cohort entry as identified through the ODD, OHIP, DAD (CIHI) and NACRS databases. A list and description of the codes used for identifying cases of
type 1 diabetes from the individual databases is provided in Table 3.2. As previously discussed in section 3.3, although the ODD is considered a reliable source of information for ascertaining the diagnosis of type 1 diabetes, up to 17% of cases may be missed and the two-year delay imposed by its diagnostic algorithm means that it is possible that cases occurring towards the end of the study period would not be identifiable from the ODD. Thus, the OHIP, DAD (CIHI) and NACRS databases were also used to identify cases of type 1 diabetes. The outcome of a new case of type 1 diabetes was met if any of the following conditions were satisfied during the study period, but after the date of cohort entry:

1. Identifiable within the ODD with a date of diagnosis after cohort entry.
2. One hospital discharge associated with a diagnosis of type 1 diabetes as ascertained through the DAD (CIHI). Diagnosis codes for type 1 diabetes in the first three positions were considered. Questionable, pre-admission and comorbidity diagnoses of type 1 diabetes were excluded.
3. One fee claim for the management of diabetes as ascertained through the OHIP database.
4. One physician claim associated with a diagnosis of diabetes as ascertained through the OHIP database.
5. An emergency department or ambulatory care visit associated with a diagnosis of type 1 diabetes as ascertained through NACRS. Diagnosis codes for type 1 diabetes in the first three positions were considered. Questionable or suspected diagnoses of type 1 diabetes were excluded.
3.8 Statistical Analyses

Vaccine safety studies are most commonly executed using cohort or case-control designs. However, confounding by variables such as genetics, race, ethnicity, socioeconomic status and underlying health states related to both vaccination and the outcome of interest can bias study results.\textsuperscript{12, 23} In the case of type 1 diabetes, the most important predictor of disease is genetic susceptibility. Besides genetics, little is definitively known about the factors responsible for initiating or precipitating the onset of disease in children and as such there is no way to measure or control for these. As such, this thesis is designed as a retrospective cohort study however, the \textit{analysis} is executed using the self-controlled case series (SCCS) method which implicitly controlled for all time-independent (time-fixed) confounders as girls were compared to themselves over time (i.e., self-matched).

3.8.1 The Self-Controlled Case Series Method

The self-controlled case series (SCCS) method was introduced in 1995 to study the relationship between vaccines and adverse events.\textsuperscript{24} Since then it has been used extensively in vaccine safety analyses and in other areas of pharmacoepidemiology.\textsuperscript{1} Based on the cohort design, the SCCS estimates the relative incidence of an event in an \textit{a priori} chosen period of time following exposure (i.e., exposure risk window). With this method, a study time frame (i.e., observation period) is defined and then individuals who experience the event of interest within this period are identified as cases. It is assumed that cases arise within individuals in a non-homogenous (i.e., random), age-dependent fashion following a Poisson distribution.\textsuperscript{25} After cases are identified, the vaccination
history is ascertained and it is determined whether the cases occurred during an exposed or unexposed risk period (person time). An exposed risk period is any time following exposure during which a case is at a hypothetical higher risk of developing the outcome of interest as a result of vaccination. In an SCCS, each case with the outcome of interest serves as its own control. The incidence rates during periods of exposed follow-up (person-time) and unexposed follow-up are then compared.\textsuperscript{23} In an SCCS analysis the number of events that an individual experiences within the observation period is fixed; this is referred to as conditioning on the number of events. Given this, the only unknown parameter is the time frame in which a subject experiences the event (i.e., during an exposed or unexposed risk period). Of note, non-cases do not contribute information for the IRR and therefore, are not included in the analysis unless there is concern regarding residual confounding by age.

There are three main advantages of the SCCS method compared to a cohort or case-control analysis.\textsuperscript{1} The most significant of these is that all individual-level confounders (whether measured or not) independent of time are controlled for as a consequence of self-matching.\textsuperscript{23, 26} Other advantages of this method are that it allows for age or temporal variation in the baseline incidence of the outcome and it is usually as statistically efficient as the cohort design it is modelled after. As with any method certain assumptions must be met. The underlying assumptions of the SCCS method include: (1) the probability of the exposure cannot be affected by the occurrence of the outcome event, (2) there is variability in the time or age at which events occur (i.e. events arise in a non-homogeneous Poisson manner), and (3) the event is rare if one is studying non-
recurring events. For the purpose of this thesis, assumptions two and three were met by design; however the first assumption had to be tested. To demonstrate that a diagnosis of type 1 diabetes did not influence upon the receipt of subsequent doses of the qHPV vaccine, cross-tabulations of the number of vaccine doses received prior to diagnosis to the total number administered were examined. Despite the advantages of the SCCS method, there are potentially important limitations such as the inability to calculate the absolute incidence of the outcome of interest as only cases are considered in the analysis. This however can be overcome when the SCCS is used to analyze cohort data from which crude incidence rates can be derived.

3.8.2 Assessment of Potential Confounding Variables

As previously discussed, the SCCS method inherently controls for all sources of confounding from time-fixed or time-independent factors including those that are unknown, unmeasured, or difficult to quantify such as race/ethnicity, genetic susceptibility, and parental beliefs. However, factors that vary over time (i.e., time-dependent) are not implicitly controlled for and may introduce residual confounding if not properly accounted for in the SCCS analysis.

The time-dependent covariates that were hypothesized to be potential confounders in this study included age, season, and a history of viral illness. As previously discussed in section 2.6, these covariates have been identified as possible risk factors for the development of type 1 diabetes; however, they may also be associated with the probability of being immunized with the qHPV vaccine. Age is strongly associated with the probability of qHPV vaccination because Ontario’s HPV vaccination program is only
offered free of charge to girls in grade 8 (approximately 13 years of age). The timing of qHPV vaccine administration is directly correlated with season. For the majority of girls who receive the vaccine through Ontario’s grade 8 HPV vaccination program the first dose is administered in the fall with subsequent doses administered in the winter and spring seasons. While the relationship between viral illness and the HPV vaccine is less well established, it is conceivable that a recent viral illness could delay or omit the administration of the qHPV vaccine as a result of absenteeism from school or parental concern regarding immunizing an “unwell” child thereby introducing confounding.

The SCCS analysis used in this study was prone to confounding by age because of the use of a long or indefinite risk period. To address this source of residual confounding (age effect), the unvaccinated cases were also included in the analysis. This approach has been tested in simulation studies and shown to be an effective method to adjust for the effects of age.24 In addition, girls were stratified into two age categories (≤ 14.9 and > 14.9 years of age at diagnosis). Ideally, a greater number of finer age categories would have been used to address the potentially confounding effects of age, however, the unexpectedly small number of cases observed during the study period did not permit further stratification. Consequently, to assess the potential magnitude of residual confounding by age, the strength of the association between age and the diagnosis of type 1 diabetes was assessed among unvaccinated girls using a time-matched, univariate, case-control approach. In this analysis, the date of diagnosis of type 1 diabetes served as the index date for cases while the controls were assigned a random date during their follow up. Since age is a time-dependent covariate, the analysis was conducted using age at the
The association between age at index and the probability of type 1 diabetes was estimated using logistic regression.

To test for the potentially confounding effect of season, the SCCS analysis was stratified accordingly. Any diagnosis of type 1 diabetes between December 1st and March 31st was classified as occurring during ‘high’ season while all other events were classified as occurring during ‘low’ season. Similarly to that described above, the small number of cases prevented further stratification. As such, the strength of the association between season and a diagnosis of type 1 diabetes was tested using the same approach as described with age.

Due to the unexpectedly small number of cases observed during the study period it was not possible to test viral illness as a potential confounder in the SCCS analysis. As described above with respect to age and season, it was planned to test the relationship between viral illness and the outcome of interest, type 1 diabetes through univariate analyses in the group of girls who did not receive the HPV vaccine. In this case, the administrative health databases were searched for viral illnesses occurring at any time between cohort entry and the index date. Cases and controls were considered “exposed” to a recent viral illness if they had such a diagnosis within six months of the index date. As no cases of type 1 diabetes were “exposed” to a viral illness in this time frame, the potentially confounding effects of a recent viral illness could not be assessed.

3.8.3 Primary Analysis

A diagram depicting the SCCS analysis is provided in Figure 3.1. As previously
described, the time frame for the study was from September 1\textsuperscript{st}, 2007 until March 31\textsuperscript{st}, 2011. For the primary analysis, all follow-up time (i.e., person-time) following the administration of the first dose of the qHPV vaccine was categorized as etiologically \textit{exposed} and the person-time preceding the first dose was categorized as \textit{unexposed}. For the SCCS analysis, each case of type 1 diabetes identified during follow-up was classified as having occurred during an exposed or unexposed time period. These exposure risk windows were defined \textit{a priori} and are depicted in Figure 3.2. The exposed risk period corresponded to person-time of follow-up after vaccination during which an individual was considered to be at a higher risk of developing the outcome of interest based on the pathogenesis of vaccine-induced type 1 diabetes and the timing of cases reported in the VAERS database. The unexposed risk period reflected the person-time during which a diagnosis of type 1 diabetes was not attributed to the vaccine. The incidence rate ratio of type 1 diabetes and 95% confidence intervals were estimated using conditional Poisson regression to account for the self-matched nature of the data. All statistical analyses were conducted using SAS 9.2 software.

\textbf{3.8.4 Sensitivity Analysis}

To test the robustness of the study’s results a planned sensitivity analysis was conducted. Given the uncertainty associated with the timing of the onset of type 1 diabetes following vaccination, a sensitivity analysis was done to examine the impact of varying the exposure risk window on the relative incidence of type 1 diabetes. In particular, the data were re-analyzed assuming an exposure risk window of 0 to 60 days following vaccination, greater than 60 days post vaccination, and two to three years post
vaccination. Data from the VAERS database suggested a potential increased risk of type 1 diabetes in the first 60 days post HPV vaccination however this could be the result of reporting bias hence the reason for the sensitivity analysis using 0 to 60 days and greater than 60 days post vaccination.\textsuperscript{9} The rationale for testing the two to three year post-vaccination exposure window is based on ecological studies previously presented that suggest the diagnosis of type 1 diabetes is delayed until years after immunization.\textsuperscript{15-19}
3.9 References


4. ICES Data Holdings [Internet]; c2011 [cited 2011/08/10]. Available from: https://outside.ices.on.ca.


16. Classen JB. Clustering of cases of IDDM 2-4 years after hepatitis B immunization is consistent with clustering after infections and progression to IDDM in autoantibody positive individuals. The Open Pediatric Medicine Journal 2008;2:1-6.

17. Classen JB, Classen DC. Clustering of cases of type 1 diabetes mellitus occurring 2-4 years after vaccination is consistent with clustering after infections and progression of type 1 diabetes in autoantibody positive individuals. Journal of Pediatric Endocrinology & Metabolism 2003;16:495-508

18. Classen JB, Classen DC. Clustering of cases of insulin dependent diabetes (IDDM) occurring three years after hemophilus influenza B (HiB) immunization support causal relationship between immunization and IDDM. Autoimmunity 2002;35(4):247-53


23. Glanz JM, McClure DL, Xu S, Hambidge SJ, Lee M, Kolczak MS, Kleinman K, Mullooly JP, France EK. Four different study designs to evaluate vaccine safety were equally validated with contrasting limitations. Journal of Clinical Epidemiology 2006;59:808-18.


Figure 3.1 Description of self-matched case controlled series analysis technique

1. Study time window selected and exposure window defined

2. Identify cases

3. Vaccination history ascertained and defined as having either occurred during exposed or unexposed period
Table 3.1 Description of databases

<table>
<thead>
<tr>
<th>Database</th>
<th>Description</th>
<th>Data Source</th>
<th>Years Available</th>
<th>Update Frequency</th>
<th>Main Data Elements</th>
<th>Use and Time Frame</th>
<th>Coding System</th>
</tr>
</thead>
</table>
| IRIS     | Record of immunization history of school-aged children                       | Local public health units | 1990 to present  | continuous       | • Demographic information  
• Vaccine type  
• Vaccine date of administration  
• Vaccine location of administration (i.e. health unit)                                                                                                                                                  | • Identification of study cohort through data linkage with RPDB using IKN  
• Vaccination history  
• Dates of administration of HPV vaccine for determining study exposure 1994 – 2011                                                                                                   | n/a            |
| RPDB     | Record of all persons ever issued an Ontario health card number              | MOH, ICES             | April 1990 to May 2011 | Every even month | • Demographic information  
• Date of last contact  
• Date of death (when available)                                                                                                                                                                               | • Identification of study cohort through record linkage with IRIS using IKN  
• Demographic information  
• 1994 - 2011                                                                                                                                    | n/a            |
| ODD      | Record of all identified persons diagnosed with diabetes                     | ICES                  | 1991 to August 2011 | Yearly in the Fall | • Diagnosis date  
• Age at diagnosis  
• Source of diagnosis  
• Incident in fiscal year  
• Prevalent in fiscal year  
• Fiscal year of diagnosis                                                                                                                                                                                  | • Identification of cases of pre-existing type 1 diabetes (exclusion criteria)  
• ODD 2010 (includes all incident cases from 1991 until August 2011)                                                                                                                                   | n/a            |
<table>
<thead>
<tr>
<th>Database</th>
<th>Description</th>
<th>Data Source</th>
<th>Years Available</th>
<th>Update Frequency</th>
<th>• Main Data Elements</th>
<th>• Use and Time Frame</th>
<th>Coding System</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAD (CIHI)</td>
<td>Record of all hospital stays</td>
<td>CIHI</td>
<td>April 1988 to March 2011</td>
<td>Annually in September</td>
<td>• Demographics&lt;br&gt;• Clinical data&lt;br&gt;• Administrative data&lt;br&gt;• Other information</td>
<td>• Dates and diagnosis of type 1 diabetes occurring in hospital for ascertaining study outcome&lt;br&gt;2003 to 2011</td>
<td>Starting in 2002: &lt;br&gt;• ICD10-CCI codes&lt;br&gt;• Up to 25 diagnosis per visit&lt;br&gt;Each diagnosis code associated with diagnosis type</td>
</tr>
<tr>
<td>OHIP</td>
<td>Record of claims from eligible health care professionals providing services</td>
<td>MOH</td>
<td>July 1991 to June 2011</td>
<td>Every odd month</td>
<td>• Patient and physician identifiers&lt;br&gt;• Code for service provided, date or service and associated diagnosis&lt;br&gt;• Fee paid</td>
<td>• Date and type of service provided (as reflected in the diagnosis and fee code) by physicians who are paid on a fee for service basis&lt;br&gt;• To used to determining study outcome&lt;br&gt;2003 to 2011</td>
<td>• 3-digit ICD-9 based diagnosis code&lt;br&gt;• 1 diagnosis per visit&lt;br&gt;OHIP fee code</td>
</tr>
<tr>
<td>NACRS</td>
<td>Record of ambulatory care visits to outpatient clinics, emergency departments and for day surgery</td>
<td>ICES</td>
<td>July 2000 to March 2011</td>
<td>Annually in September</td>
<td>• Demographics&lt;br&gt;• Clinical data&lt;br&gt;• Administrative data&lt;br&gt;• Financial data&lt;br&gt;• Service-specific data elements for day surgery and emergency</td>
<td>• Date and diagnoses in emergency departments related to the outcome of interest</td>
<td>• ICD 9 and 10&lt;br&gt;• 1-10 diagnoses per consultation</td>
</tr>
</tbody>
</table>
Figure 3.2 Description of study time frames

(a) Girls born in 1994

(b) Girls born in 1995

(c) Girls born in 1996

Non-exposed person time (unexposed risk window)

Exposed person time (exposed risk window)
Table 3.2 Classification of study Outcomes

<table>
<thead>
<tr>
<th>Coding System</th>
<th>DAD (CIHI)</th>
<th>NACRS</th>
<th>OHIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD-10 CA code</td>
<td>E10 – Type 1 diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Including the following subdivisions:</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Type 1 diabetes with -</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E10.0: coma</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E10.1+: acidosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E10.2+: kidney complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E10.3+: ophthalmic complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E10.4+: neurological complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E10.5+: circulatory complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E10.6+: other specific complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E10.7+: multiple complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E10.9: without mention of complication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OHIP dxcode</td>
<td></td>
<td>250</td>
<td>Diabetes mellitus including complications</td>
</tr>
<tr>
<td>OHIP feecode</td>
<td></td>
<td>K029</td>
<td>Insulin therapy support</td>
</tr>
<tr>
<td></td>
<td></td>
<td>K030</td>
<td>Diabetes management assessment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>K045</td>
<td>Diabetes management by a specialist</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q040</td>
<td>diabetes incentive management</td>
</tr>
</tbody>
</table>
Chapter 4

Results
4.1 Description of Cohort

The study cohort comprised of 3465 girls (Figure 4.1). The numbers and proportions of girls entering the cohort on September 1st of a particular year were as follows: 1302 (37.58%) in 2007, 1179 (34.03%) in 2008 and 984 (28.4%) in 2009. No deaths occurred during the observation period and as such, all girls were followed until March 31, 2011. The mean duration of follow-up was 2.7 years and ranged from 1.6 to 3.6 years. At cohort entry, the mean age was 13.2 years and ranged from 12.7 to 13.6 years. The proportion of girls who received at least one dose of the qHPV vaccine during the observation period was 58.3% (n=2020) (Table 4.1).

4.2 Description of Cases

During study follow up 15 cases of new onset type 1 diabetes were identified. While four administrative health databases (ODD, OHIP, CIHI, NACRS) were initially used for detecting new onset type 1 diabetes, all cases were identified from the OHIP database. No other database detected cases that were not captured by the OHIP database. With respect to HPV vaccination status eight cases did not receive any doses of the qHPV vaccine during the study period and were therefore classified as unvaccinated, whereas the remaining seven cases received at least one dose of the vaccine (Table 4.2). When a case occurred during the etiologically exposed time window, the mean duration of time from administration of the first dose of qHPV vaccine to diagnosis was 625 days (20.5 months) and ranged from 73 days (2.4 months) to 1194 days (39.2 months) (Figure 4.3).
4.3 Analysis of Potential Confounding Variables

While executing this thesis, unforeseen circumstances arose involving data availability which resulted in an unexpectedly low number of cases being available for the analysis. Though the effects of potential confounders that were time-dependent could be assessed through the SCCS analysis (age and season), others could not or could not be accounted for as tightly as needed. Consequently, the potential confounding effects of age, season, and a history of viral illness on the hypothesized relationship between the qHPV vaccine and type 1 diabetes were also assessed through univariate analyses. The associations between each of the potential confounders and type 1 diabetes were tested on the group of unvaccinated girls (n=1445), thus removing the effects of the qHPV vaccine on this association.

The mean age of the unvaccinated cases and controls at cohort entry was 14.4 and 14.6, respectively. No association was observed between age or season and type 1 diabetes as demonstrated by the odds ratios presented in Table 4.3.

4.4 Primary Analysis

Immunization with the quadrivalent HPV vaccine was not associated with an increased risk of developing type 1 diabetes (RI 0.18; 95% CI 0.02-1.55) (Table 4.4). This was determined based upon an SCCS analysis of seven cases of type 1 diabetes occurring over a span of three and a half years in girls from one health unit. For the primary analysis, an indefinite exposure window was tested whereby a girl was considered etiologically exposed to the qHPV vaccine from the date of administration of her first dose of qHPV vaccine until the end of the study period. Adjusting for age and
season did not change the results materially as evidenced by the following relative incidences: age-adjusted (RI 0.16; 95% CI 0.02-1.41), season-adjusted (RI 0.18; 95% CI 0.02-1.48), age and season-adjusted (RI 0.15; 95% CI 0.02-1.32). All of the effect estimates were very imprecise as evidenced by the width of the confidence intervals and the associated confidence limit ratios (Table 4.5). The confidence limit ratio (CLR) is the ratio of the upper to lower 95% confidence intervals and serves as a means of quantifying the precision of the result of the study. A ratio rather than the difference between the upper and lower confidence intervals is used when estimating effect size on a relative scale.

4.5 Sensitivity Analysis

The planned sensitivity analysis testing the 0 to 60 day exposure window could not be conducted as no cases arose during this time frame. Consistent with the primary analysis, in the 61-day to indefinite and two to three year exposure windows, immunization with the qHPV vaccine was not associated with an increased risk of developing type 1 diabetes as evidenced by the relative incidence and/or the width of the confidence intervals. However, the results of the primary analysis did change somewhat with the various sensitivity analyses (Table 4.4). For example, the risk estimates were closer to the null in the 61-day to indefinite exposure window regardless of adjustments made (unadjusted relative incidence was 0.61 [95% CI 0.07-5.12] compared to 0.18 [95% CI 0.02-1.55] in the primary analysis where the risk window was indefinite). The change was even more pronounced when the risk window was restricted to two to three years following vaccination (unadjusted relative incidence 1.60 [95% CI 0.29-8.83]). For each
of the exposure risk windows (61-day to indefinite and two to three years), age and season adjusted relatives incidences were calculated. The results were as follows: (i) 61-day to indefinite exposure window: age-adjusted RI 0.54 (95% CI 0.06-4.81), season-adjusted RI 0.57 (95% CI 0.07-4.82), age and season-adjusted RI 0.49 (95% CI 0.05-4.39), (ii) two to three year exposure window: age-adjusted RI 1.44 (95% CI 0.20-10.15), season-adjusted RI 1.56 (95% CI 0.28-8.58), age and season-adjusted RI 1.30 (95% CI 0.18-9.46) (Table 4.4). The latter demonstrated that age, and possibly season of diagnosis, did result in residual confounding.
Figure 4.1 Cohort flow diagram

Ontario birth cohort
N = 748,542

female birth cohort
N = 363,958

female birth cohort; without type 1 diabetes prior to t0 and alive at t0
N = 356,132

female birth cohort; without type 1 diabetes prior to t0; alive at t0 and recorded in IRIS database
N = 5,526

Study Cohort: female birth cohort; without type 1 diabetes prior to t0; alive at t0 and recorded and active in IRIS database
N = 3,465

Boys
N = 384,958

Type 1 diabetes prior to t0
N = 5,309

Date of death before t0
N = 2,517

Girls not found in IRIS database
N = 350,606

Girls not active in IRIS database during study period
N = 2,601
Table 4.1 Vaccination status of study cohort

<table>
<thead>
<tr>
<th>Number of qHPV doses</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1445</td>
<td>41.7</td>
</tr>
<tr>
<td>1</td>
<td>96</td>
<td>2.77</td>
</tr>
<tr>
<td>2</td>
<td>717</td>
<td>20.69</td>
</tr>
<tr>
<td>≥3</td>
<td>1207</td>
<td>34.83</td>
</tr>
</tbody>
</table>

* less than 0.5% of cohort received 4 doses of vaccine
Table 4.2 Distribution of number of doses of HPV vaccine administered to cases

<table>
<thead>
<tr>
<th>Number of HPV doses administered prior to diagnosis of type 1 diabetes</th>
<th>Total number of HPV doses administered</th>
<th>Number of cases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>0</td>
<td>3</td>
<td>≤ 5</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>≤ 5</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>≤ 5</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>≤ 5</td>
</tr>
</tbody>
</table>

*cell sizes less than five suppressed due to privacy and confidentiality of personal health information as per privacy agreement with ICES
Figure 4.2 Boxplot representation of time from cohort entry to diagnosis of type 1 diabetes among vaccinated and unvaccinated grade 8 girls
Figure 4.3 Chart representation of time from cohort entry to diagnosis of type 1 diabetes among vaccinated and unvaccinated grade 8 girls

Figure redacted due to privacy and confidentiality of personal health information as per privacy agreement with ICES.
Figure 4.4 Diagrammatic representation of distribution of cases of type 1 diabetes among vaccinated and unvaccinated grade 8 girls

Figure redacted due to privacy and confidentiality of personal health information as per privacy agreement with ICES
Table 4.3 Description of relationship between potential confounding variables in unvaccinated girls and type 1 diabetes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases</th>
<th>Controls</th>
<th>Odds ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years at cohort entry (SD)</td>
<td>14.4</td>
<td>14.6</td>
<td>0.85 (0.41-1.77)</td>
</tr>
<tr>
<td>Season</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High[^]</td>
<td>---γ</td>
<td>553</td>
<td>1.60 (0.40-6.42)</td>
</tr>
<tr>
<td>Low[~]</td>
<td>---γ</td>
<td>884</td>
<td></td>
</tr>
<tr>
<td>Viral illness[^#]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>---γ</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>---γ</td>
<td>1370</td>
<td></td>
</tr>
</tbody>
</table>

NR – not reported  SD – standard deviation
[^]  High season = December 1st to March 31st
[~]  Low season = April 1st to November 30th
[^#]  Viral illness occurring within six months of index date
[*]  Odds ratio for viral illness not reported as there were no documented viral illnesses in the unvaccinated cases
[γ]  Cell contents suppressed due to privacy and confidentiality of personal health information as per privacy agreement with ICES
<table>
<thead>
<tr>
<th>Risk Window</th>
<th>Unadjusted RI (95% CI)</th>
<th>Age-adjusted RI* (95% CI)</th>
<th>Season-adjusted RI (95% CI)</th>
<th>Age and season-adjusted RI* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indefinite</td>
<td>0.18 (0.02-1.55)</td>
<td>0.16 (0.02-1.41)</td>
<td>0.18 (0.02-1.48)</td>
<td>0.15 (0.02-1.32)</td>
</tr>
<tr>
<td>0-60 days</td>
<td>–γ</td>
<td>–γ</td>
<td>–γ</td>
<td>–γ</td>
</tr>
<tr>
<td>61 days-indefinite</td>
<td>0.61 (0.07-5.12)</td>
<td>0.54 (0.06-4.81)</td>
<td>0.57 (0.07-4.82)</td>
<td>0.49 (0.05-4.39)</td>
</tr>
<tr>
<td>2-3 years</td>
<td>1.60 (0.29-8.83)</td>
<td>1.44 (0.20-10.15)</td>
<td>1.56 (0.28-8.58)</td>
<td>1.30 (0.18-9.46)</td>
</tr>
</tbody>
</table>

RI = Relative Incidence; CI= Confidence Interval

* Adjusted for age (<14.9 years, >14.9 years)
† RI inestimable because no cases observed during time frame
Table 4.5 Confidence limit ratios (CLR) for the associated 95% confidence interval of the relative incidence of type 1 diabetes following qHPV vaccination

<table>
<thead>
<tr>
<th>Risk Window</th>
<th>Unadjusted RI CLR</th>
<th>Age-adjusted RI* CLR</th>
<th>Season-adjusted RI CLR</th>
<th>Age and season-adjusted RI* CLR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indefinite</td>
<td>78</td>
<td>71</td>
<td>74</td>
<td>66</td>
</tr>
<tr>
<td>0-60 days</td>
<td>--(^\gamma)</td>
<td>--(^\gamma)</td>
<td>--(^\gamma)</td>
<td>--(^\gamma)</td>
</tr>
<tr>
<td>61 days–indefinite</td>
<td>73</td>
<td>80</td>
<td>69</td>
<td>88</td>
</tr>
<tr>
<td>2-3 years</td>
<td>30</td>
<td>51</td>
<td>31</td>
<td>53</td>
</tr>
</tbody>
</table>

RI = Relative Incidence; CI = Confidence Interval
Indefinite = day of first qHPV vaccine administration until study end
61 days – indefinite = 61 days after first qHPV vaccine administration until study end

* Adjusted for age (<14.9 years, >14.9 years)
\(^\gamma\) RI inestimable because no cases observed during time frame
Chapter 5

Discussion and Conclusions
5.1 Introduction

Post-marketing surveillance is fundamental in identifying rare adverse effects post vaccination. By identifying important side effects early, it can minimize the potential harmful effects of vaccines. In addition, post-marketing surveillance is essential for sustaining public confidence in immunization and adherence to vaccination programs. Database studies are recognized as an essential form of post-marketing research as they can accommodate the large sample size required for detecting rare but serious adverse effects following vaccination. This retrospective cohort database study is the first post-marketing study specifically designed to examine the potential role of the qHPV vaccine in the onset of type 1 diabetes using a self-controlled case series analysis. Although type 1 diabetes is a rare disease, the devastating effects of this chronic progressive disease are indisputable. On an individual level, this lifelong illness can negatively impact upon survival and diminish quality of life. At a societal level, the cost of managing the disease and associated complications is substantial. As such, the significance of preventing the onset of type 1 diabetes should not be underestimated. This study sought to determine whether there was an association between the HPV vaccine and incident type 1 diabetes. While no association was observed, the difficulties encountered during the execution of the study limit the conclusions that can be drawn from it.

5.2 Summary of Results and Interpretation of Findings

Parental concern regarding the safety of the HPV vaccine has been cited as one of the main reasons for poor compliance with Ontario’s HPV vaccination program. While
many parents do not have an appreciable understanding of the mechanisms of immunization and the plethora of potential adverse effects following HPV vaccination, their uneasiness is nonetheless appropriate. The qHPV vaccine is relatively new and all possible adverse effects are yet to be recognized and/or understood. In addition to this lack of knowledge and understanding of the entire adverse effect profile of the qHPV vaccine, Ontario’s HPV vaccination program targets an otherwise generally healthy population that may be particularly susceptible to autoimmune-induced adverse effects following vaccination owing to the young age of the target population.²,³

The objective of this thesis was to determine whether there is an association between immunization against HPV and the development of type 1 diabetes mellitus in grade 8 girls eligible for Ontario’s vaccination program. Despite evidence from case reports suggesting a possible link between the qHPV vaccine and type 1 diabetes this was not observed in this study. In the primary analysis, the relative incidence and 95% confidence interval represent an indeterminate result that lacks statistical significance. While the relative incidence of 0.18 suggests that HPV vaccination may offer protection against type 1 diabetes, this finding was statistically non-significant given the small number of cases identified and the upper limit of the confidence interval fails to rule out the possibility of a risk increase. In addition, there is no scientific evidence or biological basis for a protective effect of HPV vaccination on the onset of type 1 diabetes. Furthermore, the results of the sensitivity analyses indicate that considering follow up time immediately after vaccination as etiologically exposed may have introduced misclassification. This interpretation is based on the observation that the relative
incidence of type 1 diabetes moved closer to the null after removing the first 60 days post-vaccination from the exposure window. Moreover, the point estimate crossed the null when the etiologically relevant risk window was restricted to two to three years post-vaccination suggesting that the qHPV vaccine may be associated with an increased risk of type 1 diabetes. Nevertheless, this result is also very imprecise and not statistically significant. In addition, the relative incidence observed for this analysis is very small compared to the effect sizes commonly observed in studies of vaccine-induced adverse effects. For example, aseptic meningitis following administration of the MMR vaccine was associated with a RI of 30.4 (95% CI 11.5-80.8), intussusception after oral rotavirus RI=29.4 (95% CI 16.1-53.6), and Bell’s palsy subsequent to the intranasal flu vaccine RI=35.6 (95% CI 14.1-89.8). Considering these large effect sizes in comparison to the relative incidence observed in the two to three year post-vaccination exposure window sensitivity analysis of this thesis, it is unlikely that there is a real association between the qHPV vaccine and type 1 diabetes. Moreover, the distribution of cases, depicted in Figures 4.2, 4.3 and 4.4 indicates that events occurred somewhat randomly across exposure status suggesting no association between HPV vaccination and type 1 diabetes. Caution must be exercised when comparing vaccinated and unvaccinated girls due to the potential for confounding, however based on the case distribution depicted in these figures this does not appear to have been an issue. If an association did exist between HPV vaccination and type 1 diabetes a clustering of cases would have been observed. To confirm or exclude the possibility of a relationship between the qHPV vaccine and type 1 diabetes, the current study will need to be repeated in a larger sample size.
Given the uncertainty and inconclusiveness of the results of this thesis, the clinical and public health significance of the current research is limited. However, in an attempt to convey the importance of studying this topic consideration is given to the three possible conclusions that could be drawn from the observed results. The unadjusted relative incidence of 0.18 in the primary analysis suggests that the qHPV vaccine may offer protection against the development of type 1 diabetes. However, it is prudent to consider this finding unproven until such time as the analysis is repeated in a larger cohort as there is no biological or scientific basis for this observation; it is likely that this association will be disproven once the analysis is repeated on a larger sample size. Alternatively, if repeat analyses using a larger sample size were to confirm that the qHPV vaccine was associated with the onset of type 1 diabetes as indicated by the upper limit of the confidence interval in the primary analysis and by the point estimate observed in the two to three year exposure window sensitivity analysis, the impact could be significant. With such an association greater consideration would need to be given to the magnitude of the effect size. If the true association between vaccination and type 1 diabetes were small (i.e., in the range of 1.5 to 2), the corresponding absolute increase would also be small and the clinical significance less pronounced especially when one considers the potential benefits of vaccination. Ultimately the decision to vaccinate is a personal choice based upon an individual’s beliefs as well as the perceived harms of the vaccine compared to its benefits with regards to preventing HPV-related disease, possibly including cervical cancer. What is interesting to note is that the HPV vaccine has been promoted as a means of preventing cervical cancer. This claim is currently not supported.
by the available scientific evidence; in fact it will take decades before it can be established whether the vaccine decreases the incidence of cervical cancer and cervical cancer related mortality and morbidity. As a final scenario to consider, if subsequent analysis using a larger sample size were to confirm that there is no relationship between the qHPV vaccine and type 1 diabetes, as is suspected, this information could be used to reassure parents, health care professionals and policy makers that the vaccine is not associated with at least one type of autoimmune disease.

5.3 Strengths, Areas of Uncertainty and Limitations

A major strength of this study is the approach chosen for the analysis. As previously described, an SCCS analysis inherently controls for both known and unknown time-independent confounding variables through self-matching. In other words, girls are compared to themselves over time. Because of this one can be confident that factors that remain constant over time such as race/ethnicity and genetics did not bias the study results. Time-dependent variables on the contrary are not inherently controlled for in the SCCS method and therefore need to be addressed. For this reason, consideration was given to time-dependent variables that could potentially confound the relationship under study and an attempt was made to either control or test for these factors (i.e., age, season, and viral illness). Another important strength of this study is the data source accessed for ascertaining exposure to the qHPV vaccine. In the majority of cases information within the IRIS database pertaining to exposure to the qHPV vaccine followed the vaccine being physically administered by a public health nurse who recorded this information in a legal
document. As such, the vaccination data contained in IRIS represents biological exposure and would have introduced minimal misclassification. Lastly, the use of IRIS and the Ministry of Health databases for conducting this study limits the potential for many important sources of bias common to field studies including recall bias, interviewer bias, participation bias and reporting bias.

When interpreting the results of any research it is important to consider alternative explanations for the observations including the role of chance, bias and confounding. This is particularly important with this thesis given the unexpectedly small sample size, the limited number of cases observed and the corresponding wide confidence intervals. Each of these will be elaborated upon below.

5.3.1 Random Error

Random error results in divergence from the true measure of association by chance alone. It is often a consequence of sampling variability and is reflected as poor precision in the point estimate. The ratio of the upper to lower 95% confidence intervals, referred to as the (CLR), is a way of quantifying the precision of a study result. In the primary analysis of this thesis, the CLRs ranged from 66 to 78; whereas a desirable CLR is less than five. CLRs of the magnitude observed in this study suggest that the results are highly influenced by random error and are more likely due to chance rather than a reflection of the true relationship between the qHPV vaccine and type 1 diabetes. The explanation for the poor precision observed in this study is the unexpectedly low sample size. During the planning of this thesis, it was anticipated that
the IRIS databases from 24 of 36 health units, representing approximately 75% of the province’s population of girls eligible for Ontario’s Grade 8 HPV vaccination program, would be record linked to the province’s administrative health databases and made available for use. The anticipated cohort size was originally around 240,000 girls. However, during the execution of the study unforeseeable circumstances arose such that record linkage did not occur at ICES-Central within the anticipated time frame. As a result, this thesis was conducted using the IRIS database from one health unit. In addition, IRIS data was only available from the 2007/08 to 2009/10 school years, one year less than expected. As a consequence of the small sample size the analysis was underpowered and the resulting point estimates were very imprecise.

In addition to the small sample size affecting the power of the study, changes had to be made to the planned analyses. For example it was not possible to test for the potential confounding effects of viral illness within the SCCS analysis due to the small number of cases. As well, it was not possible to conduct a sensitivity analysis to test the 0-60 day post vaccination exposure window as no cases arose during this time period. Lastly, a sensitivity analysis could not be conducted on the data sources for the diagnosis of type 1 diabetes.

5.3.2 Systematic Error

Systematic error or bias, also results in deviations from the true value of the effect estimate. It is attributable to either how subjects are selected for inclusion into the study, the measurement of exposure and/or outcome, or important differences between the
groups being compared. A discussion of the selection biases and sources of measurement error encountered in this thesis follows, whereas confounding will be addressed in a separate section.

Selection Bias

Selection bias can be a major threat to the validity of a traditional cohort analysis due to the potential for loss to follow-up and participation or volunteer bias. However, this population-based administrative health database study captured information on all insured residents of Ontario thus minimizing the potential for selection bias. On the other hand, the study cohort was based on birth year rather than school grade as the latter information was not available in the databases used. As a result there is the possibility that some girls who were enrolled in grade 8 between 2007 and 2009 were excluded from the cohort from which cases of type 1 diabetes were identified. This may have arisen if for example a grade was skipped or a student was held back a year in school. This could have introduced selection bias if these girls were more or less likely to have been vaccinated. However, the frequency at which this is likely to have occurred is low and as such, would be unlikely to have negatively impacted upon the internal validity of the study. Moreover, a recent reabstraction study carried out in an Ontario health unit demonstrated that the birth cohort definition correctly identified 96.4% of eligible girls, and that the percentage missing was similar among the vaccinated and unvaccinated girls (L.Lévesque, personal communication, April 3, 2012). Consequently, the potential for selection bias is minimal to non-existent in this thesis.
Measurement Error

Measurement error leading to misclassification of exposure and/or outcome occurs commonly in database studies and arises from the procedures or methods implemented in the measurement of exposure and/or outcome status. Any ensuing misclassification is either non-differential, occurring equally in the groups being compared, or differential if the errors are disproportionate in one group.

In this thesis, it is possible that errors related to the measurement of exposure may have lead to an individual being inaccurately identified as either vaccinated or unvaccinated. For example, it is possible that an individual was identified within the IRIS database but had an inaccurate measurement of exposure as the result of HPV vaccine being administered by external source such as a family physician who did not notify the health unit. Regardless, since this source of exposure misclassification is independent of a future diagnosis of type 1 diabetes, it is expected to be non-differential and bias the results towards the null. In addition, very few girls receive their vaccination from the physician’s office. Lastly, the validity of the IRIS database of one Ontario health unit has previously been evaluated and found to have a sensitivity of 99.8% (95% CI 99.3-99.9) and specificity of 97.7% (95% CI, 96.3-98.7) for HPV vaccination status and a sensitivity of 98.6% for dates of HPV vaccination.¹

A final consideration with respect to misclassification of exposure is the choice of the exposure risk windows, particularly the use of an indefinite exposure window post-vaccination for the primary analysis. The rationale for choosing an indefinite risk
window has previously been described in chapter three. While it was contemplated that the information from the VAERS database indicating a potential increased risk of type 1 diabetes in the first 60 days post HPV vaccination was the result of reporting bias this could not be definitively determined. As such, the 60 days post qHPV vaccination was included in the exposure window despite the pathophysiology of type 1 diabetes indicating that it may take months to years following triggering of autoimmune destruction of the pancreatic cells before a diagnosis is made. As the exposure window in this thesis is narrowed from (1) indefinite (i.e., from date of first vaccine administration until study end) to (2) 61-days post-vaccination to study end then eventually (3) two to three years post vaccination, the relative incidence of type 1 diabetes increases. In this case, falsely categorizing the first 60 days or more as exposed person-time could have contributed to the vaccine appearing protective against the onset of type 1 diabetes.

Errors related to the measurement of the outcome resulting in misclassification may also have occurred in this thesis. Examples of outcome measurement error that may have occurred include missed cases of types 1 diabetes, or cases identified as type 1 diabetes when in fact the diagnosis was type 2 diabetes (not an autoimmune disease) or perhaps another diagnosis. It was originally anticipated that most cases of type 1 diabetes would be identified through the ODD, which has been validated. As previously described, in the pediatric population the definition for inclusion in the ODD is four diabetes-related physician claims over a two year period. This definition is associated with a sensitivity and specificity of 83% and 99% respectively. In the current study, only a small number of cases of type 1 diabetes (<50%) were identifiable within the ODD.
The majority of cases of type 1 diabetes were identified through the OHIP database with the definition for inclusion being one physician claim for diabetes or one diabetes associated fee claim. In the ODD validation study, identification of a case of pediatric diabetes using the definition of one physician claim in one year was associated with 96.6% sensitivity and 97.1% specificity. While using this definition does increase the probability of falsely classifying a child as having diabetes it also results in the identification of more cases of diabetes. Given the sensitivity and specificity for identifying cases of diabetes using physician claims from the OHIP database, the likelihood of misclassification of outcome status is low. Of note, the OHIP database and physician claims do not differentiate between the types of diabetes. In Canada, the incidence of childhood and adolescent type 2 diabetes is rising with the most pronounced increase observed in the Aboriginal population. With respect to this thesis, this may mean cases of type 2 diabetes occurring during adolescence were incorrectly classified as type 1 diabetes. The extent of this type of misclassification is likely very low and independent of the choice exposure risk window (i.e., exposure status), thereby biasing the results towards the null.

One of the sensitivity analyses planned a priori to test for misclassification bias was to examine the association between HPV vaccination and type 1 diabetes according to the various sources of diagnosis. Since the ODD-based case definition is the only one that has been validated the plan was to repeat the analysis using only cases identified from this database. If the relative incidence differed significantly from the primary analysis, this may have indicated misclassification of outcome. Unfortunately due to the
small sample size and limited number of cases, it was not possible to conduct this analysis.

Another type of error related to the measurement of outcome involves the detection of cases. The risk of detection bias resulting in errors in outcome measurement is more pronounced when the exposure occurs in close proximity to the outcome. From Figures 4.2-4.4 it is evident that the majority of cases of type 1 diabetes occurring during exposed person time arose more than one year after administration of the first dose of the qHPV vaccine. Furthermore, type 1 diabetes is a potentially life-threatening condition that will ultimately be detected regardless of vaccine exposure history. As well, by studying an indefinite exposure risk window, the influence of this potential source of bias would be mitigated. For these reasons in this study the risk of measurement error resulting from detection bias is minimal.

In addition to misclassification of exposure and outcome it is also important to consider misclassification of other important variables, in particular potential confounders. This will be discussed in the next section.

5.3.3 Confounding

As mentioned above, the potential effects of confounding by time-independent variables including age at diagnosis, season and viral illness were controlled for in the analysis. The rationale for considering these variables as potential confounders was previously described in the methods chapter. Age as a confounding variable was tested for in the SCCS analysis. From Table 4.4 it is evident that only a small change (i.e., 10%
or less) in the relative incidence occurred between the crude and the age-adjusted values. This was consistent throughout the sensitivity analyses testing the various exposure windows. This led to the conclusion that age did not materially confound the relationship between vaccination against HPV and type 1 diabetes and is consistent with the analysis showing no association between age and the risk of type 1 diabetes in this study given the relatively short duration of follow up (Table 4.3). By ruling out an association between age at diagnosis and type 1 diabetes it was confirmed that age does not confound the relationship between the qHPV vaccine and type 1 diabetes. The variable season was tested as a potential confounder in the same way as age. As for age, season was not associated with the risk of type 1 diabetes and therefore did not confound the relationship between the qHPV vaccine and type 1 diabetes as shown in the SCCS analysis. With respect to viral illness it was not possible to test this variable in either the SCCS analysis or in the time-matched case-control analysis. This is because there were no viral illnesses observed during exposed person time (SCCS analysis) as well as no viral illnesses observed in the cases (case-control analysis). While viral illnesses may be relatively common in the population studied it is possible that some episodes of viral illness were not captured by the databases used as only individuals with severe symptoms would have come into contact with the health care system. Based on the analyses conducted, the time-dependent variables age and season were unlikely to have confounded the study results. However it is possible that another unknown and unmeasured time-dependent variable could have confounded the study and contributed to the unexpected results.
Before testing a variable as a potential confounder, it is important to consider how the variable was measured and whether misclassification may have resulted. In measuring age at index in the unvaccinated girls, any misclassification that may have occurred would result in residual confounding. An example of when misclassification of age at index could have occurred relates to the multiple databases accessed for ascertaining outcome. For cases of type 1 diabetes detected in more than one database, the index date chosen was the earliest date of diagnosis. This may not be the most accurate diagnosis date. Based on this, it is possible that the true age at index was underestimated for some cases and overestimated for others. Misclassification of the variable season may have occurred in this thesis for the same reason as with age (i.e., if a case were identified in more than one database, the earliest date of was considered the index date). Any misclassification of season would have been non-differential with regards to outcome status and thus have biased the measured association between season and type 1 diabetes towards the null. With respect to viral illness, as mentioned it was not possible to test for an association with type 1 diabetes as no viral illnesses occurred in the cases.

A final source of confounding to consider is the “healthy vaccinee effect”. It is based on the fact that girls who are unhealthy are more likely to be absent from school on the day that the qHPV vaccine is administered and thus will either not receive the dose or have the administration of the vaccine delayed to a time when they are healthy enough to be exposed. If vaccine administration were delayed as a consequence of the “healthy vaccine effect” this could explain why the relative incidence in the two to three year risk
window sensitivity analysis was higher as the time period preceding vaccination (i.e., unexposed time) would represent a period of lower baseline risk of the outcome. At the same time, if only healthy girls received the vaccine, the results of the study would be biased towards the null if a real risk existed or may have made vaccine appear protective if in actuality there was no increased risk. This may explain the relative incidence of 0.18 observed in the primary analysis.

5.4 External Validity

This study was designed to test for an association between the qHPV vaccine and type 1 diabetes in grade 8 girls from Ontario. Although it seems unlikely it is possible that girls from the one health unit for which data were available are not representative of the target population. Any impact this limitation may have had will be overcome when the analysis is repeated using a larger sample size containing girls from across the province.

5.5 Future Research

As previously mentioned, it is essential that the association tested for in this thesis be repeated using a larger sample size to obtain more definitive results. Given the small number of cases observed in the current study, few conclusions can be drawn from the results. When the analysis is repeated, it will be important to further address the issue of confounding by time-dependent factors. In addition to including unvaccinated cases in the SCCS analysis, age should be further stratified into smaller sub-groups. As well,
exposure to viral illness should be tested in the SCCS analysis as a potential time-dependent confounder.

In addition to improving upon the strategies used in the current study to further control for confounding by time-dependent variables, effect modification by other vaccines will be considered in future analyses. The HBV vaccine is an optional, publicly-funded vaccine offered in the seventh grade through a school-based immunization program. It has been previously demonstrated that girls who receive the qHPV vaccine are two to three times more likely to be vaccinated against HBV compared with girls who did not receive with qHPV vaccine.\(^1\) By stratifying on previous HBV vaccine exposure and repeating the SCCS analysis it will be possible to assess whether effect modification is present and discern the independent contribution of the HBV vaccine versus qHPV vaccine on the risk of type 1 diabetes. If vaccines act as a trigger of type 1 diabetes and the effect is delayed by two to three years after vaccination then it is possible, given the indefinite exposure window studied, that HBV vaccine would also contribute to the risk of developing type 1 diabetes. The effect of other vaccines could also be considered however, HBV vaccine is the most frequently administered vaccine given in close proximity to qHPV.

Other issues to consider in future studies of the qHPV-type 1 diabetes association include adjusting the exposure time frame, investigating the possibility of a dose-response relationship, conducting a sensitivity analysis on the source of diagnosis and testing for the “healthy vaccine effect”. Given the evidence from this study suggesting the possibility of misclassification of exposure with the use of an indefinite risk window,
future studies should focus on identifying a more accurate and precise exposure time window. The possibility of a dose-response relationship was not tested in this thesis because of the small number of cases observed, however, this will be an important factor to consider in future studies. To test for a relationship between the number of doses of qHPV administered and the risk of type 1 diabetes, a stratified analysis could be performed. Given that the ODD is the only validated data source for identifying cases of diabetes, a sensitivity analysis should be conducted to determine whether the relationship between the qHPV vaccine and risk of type 1 diabetes varies as a function of the database from which the diagnosis originated. Lastly, the “healthy vaccine effect” may have biased the study results and contributed to the apparent protective effect observed in the primary analysis. One way of exploring this possibility would be to conduct an analysis looking at the rate of emergency room visits (NACRS) or physician visits (OHIP) in the time period immediately preceding vaccination in a larger sample size. If there were a decrease in the rate during this time and then a return to baseline following vaccination, this would indicate that the study results could be biased due to the “healthy vaccine effect”.

Finally while this thesis attempted to address the potential association between the qHPV vaccine and type 1 diabetes, there are many other hypothesized vaccine-induced autoimmune disorders. As such, further research should be conducted to address the safety of the HPV vaccine as it pertains to illnesses such as GBS, systemic lupus erythematosus, Grave’s disease, multiple sclerosis, and others.
5.6 Conclusions

While the results regarding the risk of type 1 diabetes following HPV vaccination are inconclusive due to the small number of cases identified, the random distribution of cases across time and across exposure status suggests no association. However, before a definitive conclusion can be reached the result must be confirmed in a larger cohort. Policy makers and health care providers have a moral and ethical obligation to continue researching and disseminating real world safety information pertaining to the qHPV vaccine that will allow parents and guardians to make informed decisions regarding vaccination.
5.7 References


Appendices
Appendix I Ethics Approval

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD-DELEGATED REVIEW
October 27, 2011

Dr. Linda E Levesque
Department of Community Health and Epidemiology
Curuthers Hall

Dear Dr. Levesque

Study Title: EPID-365-11 Quadrivalent HPV vaccine and the risk of type I diabetes mellitus in grade 8 girls: a population-based cohort study
File # 6006551

Co-Investigators: Ms. E. Walsh

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: HSREB Multi-Use Amendment/Full Board Renewal Form associated with your post review file no 6006551 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 6006351 in your Researcher Portal (https://services.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,

Chair, Research Ethics Board
October 27, 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