The use and safety of the quadrivalent HPV vaccine in Grade 8 girls in KFL&A

by

Leah Marie Smith

A thesis submitted to the Department of Community Health and Epidemiology
in conformity with the requirements for
the degree of Master of Science

Queen’s University
Kingston, Ontario, Canada
September 2010

Copyright © Leah Marie Smith, 2010
ABSTRACT

Use of the quadrivalent human papillomavirus (HPV) vaccine through Ontario’s $117 million program has been low, reaching only half of the eligible population. Safety concerns have been identified as a major barrier to vaccine uptake. In order to maximize the cost-effectiveness and health benefits of this program, it is necessary to understand factors associated with vaccine use and address parental safety concerns.

We conducted a population-based, retrospective cohort study of girls eligible for Ontario’s Grade 8 HPV vaccination program in 2007 and 2008 residing in the Kingston, Frontenac, Lennox and Addington (KFL&A) health region. Using data from the province’s administrative databases, we described the patterns of use of the quadrivalent HPV vaccine, identified factors associated with this use, and assessed the vaccine’s safety with respect to the risk of autoimmune diseases. To assess vaccine use, cross-tabulations were used to determine the vaccination and adherence status of girls according to socio-demographic and clinical characteristics. Logistic regression was used to estimate the strength of these associations. To assess the risk of autoimmune diseases, we identified all new cases of selected autoimmune diseases diagnosed during study follow-up. Juvenile arthritis was the only condition for which there were sufficient cases to permit further analysis. Rate ratios for juvenile arthritis were estimated using a self-matched analysis.

We identified a cohort of 2519 girls eligible for publicly funded HPV vaccination in KFL&A, 56.6% of whom received at least one dose of the HPV vaccine and 48.2% of whom received all three doses. Vaccinated and unvaccinated girls differed only on the basis of vaccination history, whereas adherers and non-adherers differed on the basis of
socio-demographics. The risk of juvenile arthritis was more than four times higher in the 60 days following HPV vaccination than in other time periods (RR 4.33, 95% CI 1.36-13.73). This risk appeared to vary across time.

The results of this thesis provide new evidence of an increased risk of juvenile arthritis following quadrivalent HPV vaccination in girls aged approximately 13-15 years. Moreover, it demonstrates important differences between vaccinated and unvaccinated girls, as well as adherers and non-adherers that have potential policy implications.
CO-AUTHORSHIP

This thesis presents the results of research that I initiated and developed. I wrote the thesis protocol, which was later expanded and funded by the Canadian Institutes for Health Research and the Ministry of Health and Long-Term Care Drug Innovation Fund. I also assisted with acquiring access to data from the Institute of Clinical Evaluative Sciences and with the transfer of the Kingston, Frontenac, Lennox and Addington (KFL&A) Immunization Recording Information Systems (IRIS) to ICES. I used these data to identify and verify the study cohort and identify baseline characteristics, exposure statuses, and study outcomes. I conducted all of the statistical analyses required for the execution of the first study, including data verifications. I was also responsible for creating the dataset for the case series analysis of the second study. The case series analysis was carried out under the guidance of Drs. Linda Lévesque and Heather Whitaker (UK). I wrote the two thesis manuscripts, which were reviewed by the co-authors. Throughout the execution of this project, Dr. Linda Lévesque provided me with methodological and clinical advice.
ACKNOWLEDGMENTS

A number of individuals and organizations helped bring this thesis into fruition. The following deserve special recognition for their contribution:

First, Linda for her unbelievable support and kindness. You have made this the most challenging, stimulating, and inspirational experience imaginable. I am so excited to continue this wonderful collaboration in September.

Dr. Paul Brassard for his great advice and insight.

The Department of Community Health and Epidemiology for its academic and administrative support.

KFL&A Public Health and the Ontario Graduate Scholarship Program for their financial support.

Finally, my parents who, despite the distance, managed to spoil me with as much love and encouragement as ever. This would not have been possible without you.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSTRACT</td>
<td>ii</td>
</tr>
<tr>
<td>CO-AUTHORSHIP</td>
<td>iv</td>
</tr>
<tr>
<td>ACKNOWLEDGMENTS</td>
<td>v</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>vi</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>ix</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>x</td>
</tr>
<tr>
<td>LIST OF ACRONYMS</td>
<td>xi</td>
</tr>
<tr>
<td>CHAPTER 1: GENERAL INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>1.1 HPV Vaccine in Canada</td>
<td>2</td>
</tr>
<tr>
<td>1.2 References</td>
<td>4</td>
</tr>
<tr>
<td>CHAPTER 2: REVIEW OF THE LITERATURE</td>
<td>6</td>
</tr>
<tr>
<td>2.1 Adverse Events Following Immunization (AEFIs)</td>
<td>7</td>
</tr>
<tr>
<td>2.1.1 Autoimmune Diseases</td>
<td>9</td>
</tr>
<tr>
<td>2.1.1.1 Guillain-Barré Syndrome</td>
<td>10</td>
</tr>
<tr>
<td>2.1.1.2 Multiple Sclerosis</td>
<td>11</td>
</tr>
<tr>
<td>2.1.1.3 Juvenile Arthritis</td>
<td>12</td>
</tr>
<tr>
<td>2.1.1.4 Systemic Lupus Erythematous</td>
<td>13</td>
</tr>
<tr>
<td>2.1.1.5 Type 1 Diabetes</td>
<td>15</td>
</tr>
<tr>
<td>2.1.1.6 Bell’s Palsy</td>
<td>16</td>
</tr>
<tr>
<td>2.1.1.7 Conclusion</td>
<td>17</td>
</tr>
<tr>
<td>2.2 The Quadrivalent HPV Vaccine and Program</td>
<td>17</td>
</tr>
<tr>
<td>2.3 Adverse Events Following HPV Immunization</td>
<td>19</td>
</tr>
<tr>
<td>2.3.1 Experimental Evidence</td>
<td>20</td>
</tr>
<tr>
<td>2.3.2 Epidemiologic Evidence</td>
<td>21</td>
</tr>
<tr>
<td>2.3.3 Passive Surveillance Evidence</td>
<td>22</td>
</tr>
<tr>
<td>2.4 Determinants of Adverse Events Following Immunization</td>
<td>24</td>
</tr>
<tr>
<td>2.5 References</td>
<td>27</td>
</tr>
<tr>
<td>CHAPTER 3: METHODOLOGICAL CONSIDERATIONS</td>
<td>34</td>
</tr>
<tr>
<td>3.1 Empirical Objectives</td>
<td>35</td>
</tr>
<tr>
<td>3.2 Overview of Study Design</td>
<td>35</td>
</tr>
</tbody>
</table>
3.3 Data Sources and Quality........................................................................................................36
3.4 Data Access, Linkages, and Management ..............................................................................39
3.5 Cohort Formation....................................................................................................................40
3.6 Ascertainment and Classification of Exposure .........................................................................41
3.7 Ascertainment and Classification of Outcomes .......................................................................41
3.8 Ascertainment and Classification of Baseline Characteristics ...............................................43
3.9 Statistical Analyses.................................................................................................................45
  3.9.1 Patterns of Use Analysis ..................................................................................................45
  3.9.2 Safety Analysis ..............................................................................................................45
    3.9.2.1 The Self-Controlled Case-Series ...........................................................................46
    3.9.2.2 Statistical Analysis .................................................................................................47
    3.9.2.3 Sensitivity Analysis .................................................................................................48
3.10 References...............................................................................................................................50

CHAPTER 4: PATTERNS OF USE OF THE HPV VACCINE .......................................................54
  4.1 Preface to the manuscript ......................................................................................................55
  4.2 Factors associated with HPV vaccine uptake and adherence in an Ontario cohort of Grade 8 girls ........................................................................................................56
  4.3 References...............................................................................................................................77

CHAPTER 5: THE RISK OF AUTOIMMUNE DISEASES FOLLOWING HPV VACCINATION .................................................................................................................................80
  5.1 Preface to the manuscript ......................................................................................................81
  5.2 The risk of juvenile arthritis following quadrivalent HPV vaccination in Grade 8 girls: a population-based cohort study ......................................................................................82
  5.2 References...............................................................................................................................99

CHAPTER 6: SUMMARY AND CONCLUSION .............................................................................104
  6.1 General Discussion ..............................................................................................................105
  6.2 References..............................................................................................................................117

BIBLIOGRAPHY ..........................................................................................................................119

APPENDICES ..............................................................................................................................131
  Appendix I Ethics Approval ......................................................................................................132
Appendix II  Diagnoses and corresponding diagnostic codes for baseline medical history
LIST OF TABLES

Table 3.1 Description, use, and time windows for data sources ..................................52
Table 3.2 Records linkage of all KFL&A IRIS records ..................................................40
Table 3.3 Outcomes and corresponding ICD-10-CA and OHIP diagnostic codes…….42
Table 3.4 Exposure risk periods (days) .................................................................48
Table 4.1 Patterns of use of the quadrivalent HPV vaccine according to campaign
year.......................................................................................................................67
Table 4.2 Baseline characteristics of girls vaccinated and unvaccinated with the
quadrivalent HPV vaccine .................................................................68
Table 4.3 Baseline characteristics of girls immunized with the HPV vaccine according
to their adherence with the three-dose regimen .................................70
Table 5.1 Rate ratio for juvenile arthritis following HPV vaccination ...............91
## LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 3.1</td>
<td>Depiction of self-controlled case series method</td>
<td>47</td>
</tr>
<tr>
<td>Figure 4.1</td>
<td>Cohort Flow Diagram</td>
<td>65</td>
</tr>
<tr>
<td>Figure 4.2</td>
<td>Patterns of use of the quadrivalent HPV vaccine</td>
<td>66</td>
</tr>
<tr>
<td>Figure 5.1</td>
<td>Schematic of the frequency and timing of events relative to study follow-up</td>
<td>92</td>
</tr>
</tbody>
</table>
**LIST OF ACRONYMS**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEFI</td>
<td>adverse effects following immunization</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CIHI</td>
<td>Canadian Institute for Health Information</td>
</tr>
<tr>
<td>DAD</td>
<td>Discharge Abstract Database</td>
</tr>
<tr>
<td>GBS</td>
<td>Guillain-Barré syndrome</td>
</tr>
<tr>
<td>HCN</td>
<td>health card number</td>
</tr>
<tr>
<td>HPV</td>
<td>human papillomavirus</td>
</tr>
<tr>
<td>ICD-9</td>
<td>International Classification of Diseases diagnosis codes – version 9</td>
</tr>
<tr>
<td>ICD-10</td>
<td>International Classification of Diseases diagnosis codes – version 10</td>
</tr>
<tr>
<td>ICES</td>
<td>Institute for Clinical Evaluative Sciences</td>
</tr>
<tr>
<td>IKN</td>
<td>ICES Key Number</td>
</tr>
<tr>
<td>IRIS</td>
<td>Immunization Recording Information System</td>
</tr>
<tr>
<td>JA</td>
<td>juvenile arthritis</td>
</tr>
<tr>
<td>KFL&amp;A</td>
<td>Kingston, Frontenac, Lennox and Addington</td>
</tr>
<tr>
<td>LHIN</td>
<td>local health integration network</td>
</tr>
<tr>
<td>LPHA</td>
<td>local public health agency</td>
</tr>
<tr>
<td>MMR</td>
<td>measles, mumps, rubella</td>
</tr>
<tr>
<td>MOHLTC</td>
<td>Ministry of Health and Long-Term Care</td>
</tr>
<tr>
<td>MS</td>
<td>multiple sclerosis</td>
</tr>
<tr>
<td>NACRS</td>
<td>National Ambulatory Care Reporting System</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>OHIP</td>
<td>Ontario Health Insurance Plan</td>
</tr>
<tr>
<td>PSTLYEAR</td>
<td>Best Yearly Postal Code for Eligible RPDB Persons</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized control trial</td>
</tr>
<tr>
<td>RI</td>
<td>relative incidence</td>
</tr>
<tr>
<td>RPDB</td>
<td>Registered Persons Database</td>
</tr>
<tr>
<td>RR</td>
<td>rate ratio</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>SCCS</td>
<td>self-controlled case series</td>
</tr>
<tr>
<td>SLE</td>
<td>systemic lupus erythematosus</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>VAERS</td>
<td>Vaccine Adverse Events Reporting System</td>
</tr>
</tbody>
</table>
CHAPTER 1: GENERAL INTRODUCTION
1.1 HPV Vaccine in Canada

Cervical cancer is the second most common cancer and the fifth leading cause of cancer mortality among women worldwide.\(^1\) This burden primarily affects developing nations, where Papanicolaou (Pap) tests are not yet commonplace. Nevertheless, every year in Ontario approximately 500 women are diagnosed with cervical cancer and 140 women die from the disease.\(^2\)

The human papillomavirus (HPV) is considered a necessary, although not sufficient, precursor to cervical cancer.\(^3\) While over 100 strains of HPV have been identified, it is estimated that types 16 and 18 are present in 70% of cervical cancers.\(^4,5\) In addition, HPV infections are associated with anogenital condylomas, better known as genital warts, and it is estimated that HPV types 6 and 11 are present in 90% of these cases.\(^6\) While cervical cancer and genital warts inflict the greatest HPV-related burden on Canadians, additional illnesses, such as recurrent respiratory papillomatosis\(^7\) and certain anogenital cancers,\(^8\) also contribute to this problem. Overall, HPV types 6, 11, 16, and 18 are estimated to cost the Canadian healthcare system $33 million annually.\(^9\)

In July 2006, Health Canada approved a quadrivalent HPV vaccine (Gardasil\(^\text{®}\)) for prophylactic use against HPV types 6, 11, 16, and 18 in females aged 9-26 years.\(^10\) Soon after, the Ontario government implemented a three-year, $117 million program to provide free HPV vaccinations to all Grade 8 girls through school-based clinics.\(^11,12\) Although it was expected that vaccine uptake would exceed 80%, the initiative prompted a great deal of controversy and less than 50% of eligible girls availed of the vaccination program.\(^13\) Moreover, not all girls who received the first injection proceeded to obtain all three
required doses. At such low levels of uptake, it is unlikely that Ontario’s HPV vaccination program will significantly reduce the burden of HPV-related diseases or be cost-effective.

Low uptake and adherence of the HPV vaccine has been largely attributed to safety concerns among parents who felt they had inadequate information about the effects of the vaccine, particularly with respect to the school program’s young target age group. Indeed, even individuals who agree with HPV vaccination have expressed safety as an important concern. Such apprehension is supported by evidence that randomized controlled trials (RCTs) published to date have been limited in their ability (i.e., <80% power) to detect serious adverse events putatively associated with the HPV vaccine. In addition, less than 5% of girls in these trials were under the age of 16, indicating there is limited information available about the safety of this vaccine in Grade 8 girls. Given concerns about the safety of the HPV vaccine, the resulting low uptake, and the limited information available about the effects of this vaccine in Grade 8 girls, it is important to assess the quadrivalent HPV vaccine within the Ontario’s program using a population-based approach. The purpose of this thesis was to provide real-world evidence about the safety and usage of the quadrivalent HPV vaccine among Grade 8 girls in one of Ontario’s health regions.
1.2 References


CHAPTER 2: REVIEW OF THE LITERATURE
2.1 Adverse Events Following Immunization (AEFIs)

Prophylactic vaccines, like the human papillomavirus (HPV) vaccine, are designed to protect individuals against future rather than existing infections. However, they are not without risk. Since vaccines are generally given to healthy individuals and vaccine-preventable diseases are practically non-existent in developed nations, the public has become increasingly concerned with adverse events following immunization (AEFIs). Consequently, it is important to understand the risks as well as the benefits of a vaccine in order to make informed decisions about immunization.

The main component of a vaccine is its infectious disease antigen (i.e., immunizing agent), which induces specific and active immunity against that antigen by stimulating the immune system to produce specific immunoglobulin G (IgG) antibodies and T-lymphocytes. However, in individuals who are especially sensitive to this process (e.g., due to a genetic predisposition), the immune response may be exaggerated and result in a vaccine-induced adverse event (e.g., autoimmune reaction). Moreover, since the antigen stimulates immunity, it may unintentionally stimulate other mechanisms of the immune system, such as the production of IgE, which may also lead to an adverse event (e.g., allergic reaction). In some cases, an adverse event reflects a pharmacological reaction caused by a component of the vaccine other than its immunizing agent. For example, vaccines may also contain preservatives, antibiotics, stabilizers, culture contaminants, and, importantly, adjuvants. An adjuvant is any substance that, when combined with an antigen, augments the body’s immune response. Therefore, in the same way the immunizing antigen may unintentionally lead to an adverse event through hyperactivation of the immune system, adjuvants also have the potential to cause such
reactions. In particular, aluminum-containing adjuvants, like that contained in the HPV vaccine, have the potential to cause local and systemic adverse events and have even been implicated in the development of autoimmune diseases.

AEFIs can be local or systemic and have immediate or delayed onset. Certain injection-site (e.g., pain, swelling), systemic (e.g., headaches, nausea), and other allergic (e.g., hives, bronchospasm) reactions are common to most vaccines and usually occur within 24 hours following immunization. Since these reactions tend to be mild to moderate in severity and usually resolve without clinical sequelae, it is generally accepted that the benefits afforded by the vaccine outweigh these risks. In some instances, however, vaccine-induced reactions may be serious and even life-threatening.

The United States Food and Drug Administration (FDA) defines a serious adverse event (SAE) as any event following use of a medical product that (1) results in death, (2) is life-threatening, (3) requires inpatient hospitalization or prolongation of existing hospitalization, (4) results in significant, persistent, or permanent disability, (5) requires intervention to prevent permanent impairment or damage, or (6) results in a congenital anomaly. Although SAEs to vaccines are uncommon, they are understandably of concern. For example, vaccines are known to cause acute, potentially life-threatening anaphylactic shock, a severe type of allergic reaction that occurs as a result of an inappropriate immunologic response to a normally harmless antigen. Since the reaction occurs almost immediately following exposure to a foreign protein, it is fairly easy to determine causality. Establishing a causal link for other SAEs, however, is not as straightforward. This is especially true when the reaction is delayed, as is the case with autoimmune diseases.
2.1.1 Autoimmune Diseases

Autoimmune diseases are the result of an exaggerated and aberrant immune response against endogenous antigens that causes damage to and ultimately dysfunction of the target organ(s). The category is comprised of multiple diseases, which range from organ-specific (e.g., type 1 diabetes) to systemic (e.g., systemic lupus erythematosus). This wide spectrum of diseases has thus been referred to as the “mosaic” of immune diseases and, not surprisingly, no single hypothesis or mechanism has been able to adequately explain their pathogeneses. It is known, however, that certain predisposing genetic, hormonal, immunological, and environmental factors are associated with most autoimmune diseases.\(^\text{11, 12}\)

It is also generally accepted that some vaccines are causally linked to certain autoimmune diseases. Although the mechanism by which this reaction occurs has yet to be fully elucidated, it has been postulated that a process known as “molecular mimicry” may help explain the development of vaccine-induced autoimmune responses. Molecular mimicry implies that a component of the vaccine is sufficiently similar in structure to an endogenous antigen to trigger an autoimmune reaction in susceptible individuals.\(^\text{13}\) Since autoimmune diseases tend to develop gradually and may not be diagnosed until a few weeks to months following onset, the role of vaccines in the development of autoimmune diseases remains somewhat controversial. Nevertheless, it is plausible that exposure to vaccines is causally associated with a number of autoimmune diseases, including Guillain-Barré syndrome, multiple sclerosis, juvenile arthritis, systemic lupus erythematosus, type 1 diabetes, and Bell’s palsy.
2.1.1.1 Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) is a serious neurologic disorder involving inflammatory demyelination of the peripheral nerves.\(^{14}\) It is characterized by sudden, unexpected pain, numbness, paraesthesia, or weakness in the extremities that spreads proximally. The disease usually peaks within 2 to 4 weeks of onset and is followed by a plateau phase that lasts weeks to months. Although most individuals affected eventually make a full recovery, up to 20% are left with a chronic disability (e.g., residual weakness or fatigue) and, in the most severe cases, pulmonary complications (e.g., respiratory failure) and/or autonomic nervous system problems (e.g., cardiac arrhythmias) lead to death.

The diagnosis of GBS is based on well established and accepted criteria\(^{15}\) and poses no difficulty for the neurologist. For the general practitioner, on the other hand, diagnosing GBS can be challenging. This is true not only because they so rarely see cases, but also because the early signs and symptoms of GBS are indicative of a vast number of other illnesses that need to be ruled out first (e.g., poliomyelitis, botulism, neuropathic lesions).\(^{14}\) As a result, there is sometimes a time lag between the onset of disease symptoms and the date of diagnosis.

While GBS is one of the most common causes of acute neuromuscular paralysis, it is nonetheless a rare condition with an estimated annual incidence ranging from less than 1 per 100,000 person-years in those younger than 30 years of age to over 4 per 100,000 person-years in the elderly.\(^{14,16}\) Although its aetiology remains largely unknown, up to two-thirds of individuals diagnosed with GBS have had an infection, often manifested as a flu-like illness, within 6 to 8 weeks prior to disease onset. In addition to the influenza
virus, the *cytomegalovirus* and Epstein-Barr virus, as well as some bacteria (e.g., *Campylobacter jejuni* and *Mycoplasma pneumomiae*) have been identified as common antecedent pathogens for GBS. These pathogens trigger the production of T-lymphocytes and antibodies that are believed to lead to neuronal inflammatory demyelination through a variety of complex mechanisms. Vaccines are believed to induce a similar autoimmune response in susceptible individuals. Indeed, GBS has been causally related to the oral polio, tetanus-diphtheria toxoid and influenza vaccines. For example, studies of the 1976 swine influenza vaccine reported a 4- to 8-fold increase in risk of GBS six weeks following immunization, and a more recent study reported a 45% relative increase in the risk of GBS (RR 1.45, 95% CI 1.05-1.99) two to seven weeks following administration of the influenza vaccine.

### 2.1.1.2 Multiple Sclerosis

Multiple sclerosis (MS) is an inflammatory disorder of the brain and spinal cord characterized by demyelination of the central nervous system (CNS). The progress, severity, and specific symptoms of MS vary between individuals but include cognitive impairment, numbness, paralysis, tremors, and loss of vision. The clinical course of the disease usually evolves over decades, beginning with episodes of neurological dysfunction that usually recover, and progressing to extensive and chronic neurodegeneration. In children, the disease tends to take longer to reach states of irreversible disability. The prevalence of MS in Canada is among the highest in the world, with estimates around 90 per 100,000 persons in the 1990s. Like other autoimmune diseases, the pathogenesis of MS is complex, involving interplay of environmental exposure and genetic susceptibility. While exposures like
climate, stress, diet, and hormones have been studied as potential risk factors, infection is most often publicized as a putative causal agent.\textsuperscript{22} In particular, rhinoviruses, responsible for most cases of the common cold and upper respiratory infections, are suspected to be linked with the onset of MS.\textsuperscript{23} In addition, measles, mumps, rubella, varicella, Epstein-Barr virus, and \textit{Chlamydia pneumonia} have been associated with MS, although the evidence remains inconclusive.\textsuperscript{19, 22} Epidemiologic studies also suggest that viral infections in general are associated with a threefold increase in the risk of MS exacerbation.\textsuperscript{24} The link between exposure to vaccine and the risk of MS has also been studied. For example, MS has been temporally and biologically associated with the hepatitis B vaccine.\textsuperscript{25} In fact, a magnetic resonance imaging (MRI) study documented demyelination of the CNS within days to weeks after Hepatitis B vaccination in some individuals.\textsuperscript{26}

\textit{2.1.1.3 Juvenile Arthritis}

Juvenile arthritis (JA) comprises a group of conditions characterized by chronic inflammation in one or more joints in children less than 16 years of age at disease onset.\textsuperscript{27} Initial symptoms of JA include joint stiffness, pain, and swelling, as well as rash, weight loss, tiredness, irritability, and blurred vision. Since these symptoms are also associated with other conditions and because there is no specific test for JA, diagnosis can be difficult and is usually made only after a number of other conditions have been ruled out.\textsuperscript{28} If not treated early and aggressively enough, this condition can have devastating effects that last a lifetime. Potential consequences include growth disturbances, deformities, and significant delays in gross and fine motor skills, as well as pericarditis, osteopoenia, and inflammatory eye disease. In addition to drug therapy, proper
management of this disease requires a multidisciplinary team that may include rheumatology specialists, physical and occupational therapists, and social workers.\textsuperscript{28}

JA is the most common rheumatic condition in children, with a reported annual incidence of 0.8 to 22.6 per 100,000 person-years.\textsuperscript{29, 30} Despite the important burden posed by this disease, it has not been as well studied as other autoimmune diseases.\textsuperscript{27} Nevertheless, predisposing genes are being identified and there is increased attention directed at identifying possible environmental influences. For instance, although evidence remains inconclusive, breastfeeding, vitamin D exposure, and socio-economic status have all been investigated as possible risk factors of JA.\textsuperscript{27} In addition, arthritis is a relatively common sequelae to a number of infections, including \textit{cytomegalovirus}, hepatitis B virus, Epstein-Barr virus, and parvovirus B19.\textsuperscript{31} Research also indicates that JA may be triggered by certain vaccines. For example, one study assessing the incidence of joint manifestations (arthralgia or arthritis) following vaccination with the measles-mumps-rubella (MMR) vaccine found an increased risk (RR=1.6; 95% CI 1.2-2.1) of new episodes within six weeks following immunization.\textsuperscript{32}

2.1.1.4 Systemic Lupus Erythematosus

Systemic lupus erythematosis (SLE) is a chronic, multisystem autoimmune disease characterized by inflammation of the body’s tissues.\textsuperscript{33} Initially, children may present with prolonged malaise, joint pain, and a malar (“butterfly”) rash across the nose and cheeks. Because SLE can affect any part of the body, a number of other explanations for the presenting symptoms and laboratory findings must be ruled out before a diagnosis can be made.\textsuperscript{34} In addition, of the eleven established classification criteria, four are sufficient for diagnosis, but these may not be clinically apparent for months following
initial presentation. Clinical features of the disease in children include arthritis, facial erythema, hypertension, thrombocytopenia, pericarditis, restrictive lung disease, and cognitive impairment. Over the course of one’s lifetime, these symptoms generally fluctuate from mild to extreme, and can cause the body’s organs a great amount of damage. Although presentation and clinical features of SLE are similar in both adult and paediatric populations, juvenile-onset SLE tends to be more severe at onset, more aggressive, and have higher rates of organ involvement.

Incidence rates of SLE worldwide are reported to be between 1-5 per 100,000 person-years. It is estimated that approximately 15-20% of all prevalent SLE cases are diagnosed in childhood. The incidence of this diagnosis peaks between 11 and 15 years of age and is particularly dominant among females.

The biological factors related to SLE are becoming increasingly understood in terms of novel gene mutations, cytokine alterations, and hormonal and reproductive factors. On the other hand, relatively little is known about the potential effects of occupational and environmental exposures on the risk of SLE. Factors like silica dust, smoking, and ultraviolet light exposure have been studied in relations to SLE, but these associations remain weak. In contrast, a dominating hypothesis is that SLE may result from an aberrant response to a relatively common infectious agent. In particular, mounting biologic and epidemiologic evidence suggests that the Epstein-Barr virus is a causal pathogen of SLE. For example, in a study of children and young adults, 99% (116/117) of SLE patients were seropositive for Epstein-Barr virus, compared to only 70% (107/153) of controls (OR=49.9; 95% CI 9.3-1025).
To date, over 25 drugs have been studied as potential causes of SLE. The majority of confirmed cases of drug-induced SLE involve hydralazine (an antihypertensive) or procainamide (an antiarrhythmic), but vaccines have also been the focus of such research. For example, in a case-series of ten patients with SLE, the mean latency between hepatitis B vaccination and onset of autoimmune symptoms was 56.3 days. In another report, symptoms were observed within 15 days of first dose of the hepatitis B vaccine. Currently, evidence on the possible relationship between immunization and SLE is purely temporal and based primarily on case reports.

2.1.1.5 Type 1 Diabetes

Type I diabetes, formally known as “insulin dependent diabetes mellitus” or “juvenile onset diabetes”, is a chronic metabolic disorder characterized by the body’s inability to produce endogenous insulin secondary to the autoimmune destruction of the insulin-producing cells of the pancreas. As a result, persons with this disease require regular injections of insulin in order to survive. Type 1 diabetes is the most common chronic disease of children and young adults and presents at a rate of approximately 24 per 100,000 person-years in Canada. Initial signs and symptoms of the disease include excessive thirst, weight loss, weakness, and fatigue, but the diagnosis is based mainly on a test of blood glucose levels.

While the influence of genetics on the risk of type 1 diabetes is indisputable, less than 10% of genetically pre-disposed individuals progress to clinical diabetes. Consequently, it is evident that environmental factors have a modulating role. For example, it has been hypothesized that early consumption of cow’s milk in susceptible infants might trigger type 1 diabetes. In addition, maternal and early childhood stress
have been identified as potential risk factors, independent of family history.\textsuperscript{47}

Observational studies also suggest that infectious pathogens, particularly viruses, can induce type 1 diabetes. In particular, studies demonstrate that the Coxsackie C viruses, the Epstein-Barr virus, mumps, \textit{cytomegalovirus}, and rubella are connected with processes that lead to destruction of the pancreatic cells.\textsuperscript{46} The association between diabetes and immunization has been widely studied and, although there is currently no conclusive evidence of a harmful association,\textsuperscript{48} researchers recommend that additional studies be undertaken following the introduction of new vaccines.\textsuperscript{49}

2.1.1.6 Bell’s Palsy

Bell’s palsy is a neurologic disorder characterized by peripheral facial paralysis. While it is much more common in adults, it is estimated that the average annual incidence of Bell’s palsy in children aged 0-14 years is 6.6 per 100,000 person-years.\textsuperscript{50} The clinical course of Bell’s palsy is generally marked by an acute onset and rapid progression, whereby muscle weakness peaks within 48 hours.\textsuperscript{51} During the course of the disease, patients often experience tearing, pain, and altered sensation of taste.\textsuperscript{52} Nevertheless, Bell’s palsy tends to be self-limiting and non-life threatening. In the vast majority of cases (96%), the palsy recovers without clinical sequelae within 11 weeks of onset.\textsuperscript{52}

While the cause of Bell’s palsy remains unclear, it has been postulated that genetic, vascular, infective, and immunological factors contribute to its onset. In the paediatric population, its aetiology is largely suspected to be viral in origin. This is evidenced by the fact that 60% of cases of Bell’s palsy in children are preceded by a viral illness occurring 1-4 weeks before disease onset.\textsuperscript{53} In particular, the varicella-zoster virus is believed to be an important cause of peripheral facial paralysis in children aged 6-15
years. In addition, herpes simplex virus type 1 has been identified as a probable cause of most cases of Bell’s palsy. Forty-six cases of Bell’s palsy were also recorded among people who had received the newly licensed intranasal influenza vaccine in Switzerland in 2002. An ensuing case-control study found that, compared with parenteral vaccines, the intranasal vaccine significantly increased the risk of Bell's palsy (OR 84.0; 95% CI, 20.1 to 351.9), and that this risk was especially high 31-60 days following vaccination. Associations between Bell’s palsy and other vaccines (e.g., hepatitis B and influenza vaccines) are also currently under study, but results remain inconclusive.

2.1.1.7 Conclusion

Autoimmune diseases are rare and complicated; consequently, it is a challenge to study them observationally. Because their risk factors remain largely unknown, it is difficult to fully control for potential confounding bias using standard epidemiologic methods (i.e., stratification, restriction, and modelling). In addition, it is important to recognize and account for the potential of delayed diagnoses relative to disease onset. Despite such challenges, the autoimmune diseases described here are serious conditions that, based on biological plausibility and previous vaccine research, are potential adverse events following immunization with the HPV vaccine that need to be investigated.

2.2 The Quadrivalent HPV Vaccine and Program

To date, two competing vaccines have been developed and marketed to prevent HPV infections. One, a bivalent vaccine (Cervarix®) by GlaxoSmithKline, is indicated for the prevention of infections with HPV types 16 and 18. The other, a quadrivalent vaccine (Gardasil®) by Merck Frosst, is indicated for the prevention of infections with HPV types
6, 11, 16, and 18. In addition, second-generation HPV vaccines, aimed at increasing the cost-effectiveness of immunization by providing protection against a greater number of HPV strains, are currently being tested.\textsuperscript{59, 60} In July 2006, Health Canada approved the quadrivalent HPV vaccine for use in girls and women aged 9 to 26 years. Since it remains the only HPV vaccine that falls under Canada’s publicly funded healthcare program, the following review is limited to this product.

The antigen in the quadrivalent HPV vaccine is derived from highly purified inactive proteins (L1 major capsid proteins) that come from HPV types 6, 11, 16, and 18.\textsuperscript{61} Using recombinant DNA technology, the L1 proteins self-assemble into non-infectious vaccine-like particles (VLPs). Since these VLPs do not contain viral DNA, they cannot reproduce or infect cells. The manufacturer currently recommends that the quadrivalent vaccine be administered intramuscularly as three separate 0.5-mL doses at 0, 2, and 6 months. Each 0.5-mL dose contains 20 μg of HPV 6 L1 protein, 40 μg of HPV 11 L1 protein, 40 μg of HPV 16 L1 protein, 20 μg of HPV 18 L1 protein, and 225 μg of amorphous aluminum hydroxyphosphate sulphate (AAHS) as an adjuvant. The vaccine also contains sodium chloride, L-histidine, polysorbate 80, sodium borate, and water for injection.

In September 2007, the Ontario Ministry of Health and Long-Term Care (MOHLTC) implemented a three-year, $117 million program to offer free HPV vaccinations to all Grade 8 girls in the province.\textsuperscript{62} Ontario’s HPV vaccination program is delivered by each of the 36 local public health agencies (LPHAs) as a school-based initiative and funds all three required doses. These doses are generally administered by public health nurses in September/October, November/December, and March/April of
each school year. Eligible girls are also able to obtain the vaccines at their LPHA or through their family physician; they have until the end of August of their Grade 8 year to start their dosing regimen. For girls who fail to receive their second and/or third dose(s) in Grade 8, catch-up programs are offered, providing them with the opportunity to complete their immunization schedule in Grade 9.

Information on all doses administered under the province’s free HPV immunization program are entered into the Immunization Recording Information System (IRIS) electronic databases of individual LPHAs. Girls and women not eligible for the province’s program may obtain the vaccine from their physician or nurse at a cost of approximately $130 per dose; unless a girl is subsequently eligible for the publicly funded program, these doses are not recorded in the IRIS database.

2.3 Adverse Events Following HPV Immunization

Although the Ontario government expected vaccine uptake through the Grade 8 program to exceed 80%, the initiative prompted a great deal of controversy and only 53% of eligible girls received the first dose of the vaccine. Moreover, not all girls who received the first injection proceeded to obtain all three required doses. In large part, the low uptake and adherence has been attributed to safety concerns among parents who felt they had inadequate information about the effects of this vaccine, particularly with respect to the program’s young target age group. Indeed, even individuals who support HPV vaccination have expressed concerns about the vaccine’s safety. Given the potential negative impact of this uncertainty, it is important to evaluate the evidence based on the safety of the quadrivalent HPV vaccine.
2.3.1 Experimental Evidence

The results of three phase III randomized control trials on the quadrivalent HPV vaccine have been published to date. The largest trial randomized 12,167 women aged 15-26 years to receive either the quadrivalent HPV vaccine or the amorphous aluminum hydroxyphosphate sulphate (AAHS) adjuvant. The next largest trial randomized 5455 women aged 15-24 years to receive either the vaccine or an aluminum-containing adjuvant. The smallest of the trials randomized 1781 boys and girls aged 9-15 years to either the vaccine or saline. Participants in each of these trials were followed for up to 30-48 months. These trials were all funded by the vaccine’s manufacturer, Merck Frosst.

For the evaluation of safety in the aforementioned trials, participants were monitored for 30 minutes immediately following vaccination and were asked to report adverse events experienced during the ensuing two weeks. In addition, information on adverse events was solicited from trial participants at each follow-up visit. The most commonly reported reactions were injection-site pain, redness, and swelling. Frequently reported reactions also included muscle pain and fatigue, as well mild, transient fevers and headaches. Other adverse reactions that researchers considered to be possibly related to the vaccine included bronchospasm, gastroenteritis, and hypertension. Although these studies reported that the vaccine was generally well tolerated, they were powered to evaluate the efficacy of the HPV vaccine. As such, they were underpowered to detect clinically meaningful increases in the risk of rare but serious adverse events putatively associated with the vaccine. Indeed, a systematic review of the literature found that the largest of these trials had less than 15% power to detect a
doubling of the risk (HR = 2.0) of any individual SAE.\textsuperscript{71} Moreover, the incidence and types of adverse events detected in these studies were likely underestimated because the comparator groups in the two largest trials were given an aluminum-based adjuvant rather than an inert placebo. In addition, only adverse events deemed relevant by the investigators were reported and included in the analyses, meaning published results were based on selective reporting.

Another important limitation of these trials is that they did not adequately represent the population eligible for Ontario’s Grade 8 HPV vaccination program. To illustrate, less than 5% of participants was under the age of 16 and their mean age was 20 years.\textsuperscript{71} Since this is considerably older than the 13 and 14 year olds targeted by Ontario’s school-based program, the safety results of these studies may not be generalizable to Grade 8 girls. This age discrepancy is especially disconcerting given that pubescent girls may be more likely than their older counterparts to experience an exaggerated immune response to vaccination (see section 2.4).

2.3.2 Epidemiologic Evidence

Because the vaccine is relatively new, few observational studies have been published to date on its safety. In one study, however, a cohort of 114,000 women over the age of 14 was used to evaluate Australia’s school-based publicly funded quadrivalent HPV vaccination program. Based on the number of confirmed cases of anaphylaxis, researchers estimated that the rate of anaphylaxis following administration of the HPV vaccine was 2.6 per 100,000 doses.\textsuperscript{75} Since the estimated incidence of anaphylaxis following administration of other vaccines generally ranges from 0.1 to 1.0 per 100,000 doses,\textsuperscript{76} these results indicate that the incidence of anaphylaxis following administration
of the HPV vaccine was significantly higher than the incidence identified in comparable school-based vaccination programs. This suggests that the HPV vaccine may be more immunogenic than other vaccines and may therefore have a higher propensity to cause immune-mediated adverse effects.

Apart from the cohort study, some case reports have been published describing adverse events following immunization against HPV. For example, Sutton et al.\textsuperscript{77} described four cases of acute demyelinating syndromes (including multiple sclerosis) that presented in girls ages 16-25 years within 1 to 21 days following the second or third dose of the HPV vaccine. Although such cases only provide evidence of temporality, it is important to further investigate these associations using comparative studies before causality can be ruled out.

2.3.3 Passive Surveillance Evidence

The Vaccine Adverse Events Reporting System (VAERS) is a passive surveillance program designed to detect possible signals of adverse events associated with vaccines licensed in the United States (US). Using this online system, individuals (e.g., patients, physicians, parents) can voluntarily report information about adverse events experienced following immunization.

Between June 1, 2006 and December 31, 2008, there were 12,424 VAERS reports of adverse events following HPV vaccination in the US.\textsuperscript{78,79} This represents a rate of 53.9 reports per 100,000 doses distributed. However, since each individual may receive up to three doses, this could represent an event rate as high as 161.7 reports per 100,000 persons. Of the 12,424 VAERS reports, 11,652 (93.8\%) were considered non-serious
adverse events and 772 (6.2%) were classified as serious. Non-serious events included syncope (i.e., fainting), pain at the injection site, headache, nausea, and fever.

A 2009 review of VAERS reports and associated medical charts found that 30-40% of fainting reports depicted signs of seizure-like activity (e.g., jerking) and 20% of these resulted in a traumatic injury (e.g., concussion). Gardasil’s® product monograph has since been updated to emphasize the risk of fainting following its administration.80

Other serious adverse events (SAEs) reported in VAERS include syncope with and without trauma; neurologic complications, including seizures and convulsions; Guillain-Barré syndrome; and venous thromboembolic disorders, including deep vein thrombosis, acute myocardial infarction, and ischemic stroke.78,79 In 2008 alone, 142 of HPV vaccine SAEs reported to VAERS were considered life-threatening and 28 resulted in death.81 To date, causal links between these SAEs and the HPV vaccine have not been established and the evidence remains inconclusive.

It is important to recognize the limitations of VAERS database for assessing vaccine safety. As a passive surveillance system, VAERS was designed to generate, not test, hypotheses regarding vaccine safety.82 This is because, without a comparator, it is impossible to determine whether reported events are truly associated with vaccine use or are merely coincidental. In addition, since reporting to VAERS is completely voluntary, it is believed that only a small fraction of all adverse events are actually reported. Moreover, among cases that are reported, insufficient clinical information is collected to assess causality. As such, temporal associations reported to VAERS cannot be regarded as causal and must be subjected to subsequent clinical or epidemiologic studies.
2.4 Determinants of Adverse Events Following Immunization

The factors that predispose an individual to an AEFI are as varied as the diseases that are implicated. For instance, for autoimmune disorders, there is considerable evidence suggesting that environmental factors may trigger the onset or progression of autoimmune diseases. In particular, certain infections, pharmaceutical agents, and psychosocial stressors have been identified as risk factors. Other immune-mediated conditions, such as allergies and asthma, are largely influenced by family history. Environmental and lifestyle factors also appear to increase the risk of SAEs, but their role is not yet well understood. While a great deal of information about the development of immune-mediated conditions has yet to be elucidated, it is known that factors like sex, race, and genetics are important determinants of most AEFIs. Age is also an important factor that influences the risk of an AEFI.

The immune system undergoes considerable development in cell number and function throughout life, resulting in an age-dependent immune function. As a result, there are qualitative and quantitative differences in immune function and response between adolescents and adults, which may be particularly pronounced in young women. Because immunogenicity differs between adolescents and adults, it is not surprising that the safety and efficacy of vaccines may also differ between these groups. Consequently, with respect to the study HPV vaccine, age at vaccination may be an important determinant of the risk of immune-mediated adverse events. This also suggests that the safety profile of the HPV vaccine observed in RCTs of women with a mean age of 20 may not be representative of the effects of this vaccine on Grade 8 girls.
2.5 Determinants of Vaccine Exposure

Given that the HPV vaccine is offered to all Grade 8 girls in Ontario through a publicly funded, school-based program, usual concerns about prescribing behaviours as a source of confounding in observational studies of vaccine effects (e.g., selective prescribing, confounding by indication) are not an issue. At the same time, because the vaccine is not mandatory, the decision of whether or not to avail of the program is left to the parents and guardians of Grade 8 girls. Thus, the voluntary nature of this vaccination program introduces the need for careful consideration of the determinants of vaccine uptake as important source of confounding bias.

Since the program’s launch in September 2007, approximately 50% of eligible girls in Ontario have received the vaccine. To date, little is known about the factors that contribute to vaccine uptake and vaccine avoidance in this population. Conversely, field studies conducted elsewhere in North America suggest that vaccine acceptance is, in part, determined by factors like parental health beliefs (e.g., perceived susceptibility to infection), history of sexually transmitted infections, and moral and religious viewpoints.

Research on the sources of confounding bias in observational studies of vaccine effects has demonstrated that a number of social and medical characteristics associated with vaccine avoidance are also associated with an increased risk of adverse events. For example, low parental education is a predictor of both failure to receive vaccines and sudden infant death syndrome (SIDS). Consequently, parental education may act as a confounder in studies of adverse reactions following immunization. Unfortunately, the determinants of vaccine uptake are generally difficult to identify and measure. Even
when they are known, this information is often unavailable in administrative health databases. Since failing to control for these factors may create spurious negative associations or may mask true associations between vaccination and adverse outcomes, it is important to account for them at either the design or analysis stage of a study. With respect to HPV vaccine use in Ontario, the determinants of uptake among Grade 8 girls have yet to be determined and must therefore be taken into account at the design stage.

2.6 Conclusion

Every year, approximately 84,000 girls are eligible for Ontario’s publicly funded HPV vaccination program. The evidence contributing to the vaccine’s safety profile, however, has a number of important limitations, particularly with respect to power and representativeness. Moreover, there is sufficient evidence to suggest that safety concerns raised to date are biologically plausible. Therefore, it is not surprising that safety continues to be an important concern among the parents and guardians of Grade 8 girls and thus a barrier to HPV vaccine use. As a result, population-based observational studies are needed to investigate reported and hypothesized associations between HPV vaccination and adverse health outcomes within Ontario’s Grade 8 vaccination program.
2.5 References


73. Health Canada. Summary basis of decision: GARSASIL Quadrivalent human papillomavirus (Types 6, 11, 16, 18) recombinant vaccine. 2007


CHAPTER 3: METHODOLOGICAL CONSIDERATIONS
3.1 Empirical Objectives

The objectives of this thesis were to:

- Describe the patterns of use of the HPV vaccine in terms of uptake and adherence, and evaluate uptake and adherence according to year of vaccination campaign, socio-demographics, vaccination history, health services utilization, and medical history.
- Estimate the risk of autoimmune diseases (Guillain-Barré syndrome, multiple sclerosis, juvenile arthritis, systemic lupus erythematosus, type 1 diabetes, and Bell’s palsy) following immunization with the HPV vaccine.

3.2 Overview of Study Design

To study the use and safety of the HPV vaccine, a population-based cohort was formed of all girls eligible for Ontario’s Grade 8 HPV vaccination program in Kingston, Frontenac, Lennox, and Addington (KFL&A) during the 2007/08 and 2008/09 campaign years. Information on the vaccination status of individual cohort members was obtained from the Immunization Records Information System (IRIS) database. Information on socio-demographics, physician services, emergency room visits, and hospitalizations was obtained through record linkage with Ontario’s administrative health databases. Using these data, the patterns of use of the HPV vaccine in KFL&A were determined, and the socio-demographic and clinical profiles of the vaccination groups were compared. In addition, the relative incidence of each autoimmune disease following HPV vaccination was estimated. This safety analysis was executed using the self-controlled case series method, a self-matched approach developed specifically to address the challenges of
evaluating associations between vaccination and potential adverse events using observational methodology.\textsuperscript{1-3}

3.3 \textbf{Data Sources and Quality}

Vaccination data for this study were obtained from the KFL&A IRIS database. The IRIS databases, maintained by each of Ontario’s 36 local public health agencies (LPHAs), were developed by the Ministry of Health and Long-Term Care (MOHLTC) to track and record all immunizations of school-aged children across the province.\textsuperscript{4} Specifically, when an immunization is administered though a school-based program, public health employees record the immunization information into IRIS. Similarly, when a child begins school or transfers from a school in a different area, parents/guardians are required to provide the child’s immunization records to the LPHA so the information can be recorded into the database.\textsuperscript{5} We have completed a re-abstraction study of the HPV data of the KFL&A IRIS database and found the sensitivity and specificity of individuals’ HPV vaccination status to be 99.8\% and 95.4\%, respectively.\textsuperscript{6} The results for dates of HPV vaccination were equally valid. The IRIS database also captures self-reported information on the HPV immunization of eligible girls who obtained vaccinations outside of the publicly funded program (e.g., in Grade 7). Although the validity of these reports has not been evaluated, they are expected to represent a very small proportion of all vaccinations given the high cost of the vaccine (approximately $400.00) and the availability of a publicly funded program.

Ontario’s computerized health insurance databases, access to which is available through the Institute of Clinical Evaluative Sciences (ICES), comprised the remaining
sources of data for this study. These administrative health databases are generated by the universal health care programs offered to residents of the province and are currently used extensively for health research.\(^7\)\(^9\) Four of these databases were used for this thesis: (1) the Registered Persons Database (RPDB) for information on demographics and health insurance coverage, (2) the Canadian Institute for Health Information’s (CIHI) Discharge Abstract Database (DAD) for information on hospitalizations, (3) the National Ambulatory Care Reporting System (NACRS) for information on emergency room visits, and (4) the Ontario Health Insurance Plan (OHIP) database for information on physician services claims.

The RPDB was used to identify the study cohort. This database contains information on demographics (e.g., date of birth, age, sex, postal code) and dates of insurance coverage for all residents who have ever been covered by OHIP. While most of the information held within the RPDB is considered accurate, some geographic information provided by the MOHLTC is sometimes out-of-date or incorrect.\(^10\) To address this concern, ICES now updates information in the RPDB using data from its other holdings (e.g. DAD, NACRS). This update was essential in obtaining more accurate postal codes, which were merged with census tract data to provide ecologic-level information on individuals’ neighbourhood income quintiles and places of residence.\(^11\)

The DAD, NACRS, and OHIP databases were used to ascertain study outcomes for the safety analysis (e.g., dates and diagnoses), medical histories (e.g., presence of pre-existing medical conditions), and information on health services utilization. A re-abstraction study of the DAD database found that demographic data and most procedures were coded with high sensitivity (>80%) and near-perfect specificity (>95%), but co-
morbidities were generally poorly documented. Similarly, a study of the NACRS database found high rates of agreement for demographic data and visit assessment dates. Although there was also high agreement (85.5%) in the selection of patients’ main problem, there was lower agreement for the diagnostic code used to describe the main problem (68.8%). There was also under-reporting of concomitant problems. In particular, when patients presented with multiple conditions or problems, often only one was reported to NACRS.

The OHIP database contains information on physician services claims for different types of consultations, including those given in private practices, emergency departments, and during hospitalizations. Unfortunately, physicians do not always remember to bill for their services, meaning records may not be 100% complete. In addition, there is some indication that a small percent of OHIP service dates are not always correct, though they tend to fall within a week of CIHI record dates. Another limitation of the OHIP database is that most of the diagnostic codes have not yet been validated, including those used in this thesis. In addition, it is important to recognize that individual diagnostic codes normally refer to major disease categories rather than specific diseases.

Despite some limitations, Ontario’s administrative health databases provide a wealth of otherwise unavailable health information. As such, these databases have been used extensively to carry out important health research. A detailed description of the data contained within these databases and how they were used is provided in Table 3.1.
3.4 Data Access, Linkages, and Management

Access to the administrative health databases housed at ICES was secured through Dr. Lévesque’s appointment as an ICES Research Scientist. Moreover, the proposed thesis underwent internal review at ICES and was approved by the institute’s President and CEO. Access to the KFL&A IRIS database was obtained through a Data Sharing Agreement between the KFL&A Medical Officer of Health (Dr. Ian Gemmill) and ICES. A copy of this database was electronically transferred from KFL&A Public Health to ICES in Toronto (ICES-Toronto) by means of a high-encryption, secured portal.

At ICES, each Ontario resident is represented by an ICES key number (IKN), a unique encrypted identifier that permits complete record linkage at the level of the individual across databases and across time. Because the IRIS database was not originally an ICES data holding, upon its transfer to ICES, an ICES data custodian used the data in IRIS to identify the IKN corresponding to each IRIS record. The majority of IKNs (>95%) was identified using deterministic linkage based on individuals’ Ontario health card number (HCN). In instances where the HCN was not available or not valid in the IRIS record, the IKN was identified using probabilistic matching based on first and last names, date of birth, and sex (Table 3.2).
### Table 3.2  Records linkage of all KFL&A IRIS records*

<table>
<thead>
<tr>
<th>Type of Linkage</th>
<th>Number of IKNs identified</th>
<th>Proportion of total number of records (N=127,004)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful</td>
<td>121,438</td>
<td>95.62%</td>
</tr>
<tr>
<td>Deterministic</td>
<td>103,407</td>
<td>81.42%</td>
</tr>
<tr>
<td>Probabilistic</td>
<td>18,031</td>
<td>14.20%</td>
</tr>
<tr>
<td>Unsuccessful</td>
<td>5,566</td>
<td>4.38%</td>
</tr>
</tbody>
</table>

* Results obtained from data custodian, Nick Gnidziejko, who performed the record linkage at ICES.

All data used for this thesis were stored on the ICES-Toronto server and accessed from ICES’s satellite unit located at Queen’s University (ICES-Queen’s). Both ICES sites have a number of security and privacy safeguards in place to ensure data protection and confidentiality.

### 3.5 Cohort Formation

A population-based cohort was formed of all girls eligible for Ontario’s Grade 8 HPV vaccination program in KFL&A during the 2007/08 and 2008/09 school years using the RPDB and the KFL&A IRIS database. The RPDB was used to identify all girls born in 1994 and 1995 residing in Ontario in September 2007 and 2008, respectively. Through record linkage with the KFL&A IRIS database, this cohort was restricted to girls who were also in the KFL&A school system at that time. Cohort members were followed from September 1 of their Grade 8 school year (cohort entry) until the first of date of death or December 31 of the following year (end of follow-up). Since school grade was not available in the databases, the cohort of girls eligible for the province’s HPV
immunization program was based on birth year and it was assumed that all girls entered Grade 8 in their thirteenth year. The implications of these assumptions are discussed elsewhere (4.2).

3.6 Ascertainment and Classification of Exposure

The HPV vaccination status of individual cohort members was determined using the IRIS database. This database contains information on the date of administration of HPV vaccines provided through Ontario’s Grade 8 HPV vaccination program as well as parental reports about eligible girls who obtained the vaccine outside of the publicly funded program (e.g., in Grade 7). Consequently, the IRIS database was used to ascertain individual-level information about the number of HPV vaccine doses administered to each cohort member, as well as the dates of each administration.

In order to determine vaccine uptake, vaccine exposure was dichotomized into vaccinated (at least one dose) and unvaccinated (no doses). To determine vaccine adherence, only vaccinated members were considered. Since the quadrivalent HPV vaccine is indicated as a three-dose regimen, adherence was dichotomized into adherers (all three doses received) and non-adherers (only one or two doses).

3.7 Ascertainment and Classification of Outcomes

The outcomes studied were ascertained using the DAD, NACRS, and OHIP databases previously described (Table 3.1). These databases contain information on health services (dates and diagnoses), and were used to determine whether or not a cohort member had been diagnosed with a study outcome during follow-up.
Autoimmune diseases were chosen as study outcomes because they have been reported with other vaccines, have been identified in the US passive surveillance reporting system (i.e., VAERS), are biologically plausible, and have potentially devastating consequences. The specific autoimmune diseases of interest were Guillain-Barré syndrome (GBS), multiple sclerosis (MS), juvenile arthritis (JA), systemic lupus erythematosus (SLE), type 1 diabetes, and Bell’s palsy. Corresponding diagnoses were identified in the NACRS and DAD databases using International Classification of Diseases, version 10 (ICD-10-CA) codes, and in the OHIP claims database using OHIP diagnostic codes (Table 3.3). Other than for GBS and Bell’s palsy, which are potentially recurrent, only new diagnoses were considered. As such, cohort members who had experienced the outcome of interest prior to cohort entry were excluded from the analysis of that outcome. Each study outcome was analyzed separately and the date of diagnosis was taken as the event date.

### Table 3.3 Outcomes and corresponding ICD-10-CA and OHIP diagnostic codes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ICD-10-CA code</th>
<th>OHIP code</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autoimmune Diseases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bell’s palsy, facial paralysis, and facial nerve disorders</td>
<td>G51</td>
<td>351</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>G610</td>
<td>N/A</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>E10</td>
<td>250</td>
</tr>
<tr>
<td>Juvenile arthritis</td>
<td>MO8</td>
<td>711, 714, 715</td>
</tr>
<tr>
<td>Multiple sclerosis (and other demyelinating diseases)</td>
<td>G35</td>
<td>340</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>M32</td>
<td>N/A</td>
</tr>
</tbody>
</table>
3.8 Ascertainment and Classification of Baseline Characteristics

A goal of this thesis was to determine the baseline characteristics of uptake and adherence groups. The characteristics of interest included socio-demographics, vaccination history, frequency of health services utilization, and medical history.

Age, neighbourhood income quintile, and place of residence (urban vs. rural) comprised the socio-demographic profile, and were ascertained using the RPDB. The neighbourhood income quintile of each girl was estimated by linking her postal code at cohort entry with data from the 2006 Canadian Census. A girl’s postal code was also used to determine whether she resided in an urban or rural area. Urban areas were defined based on a community size of greater than 10,000 persons; rural areas were those that remained after delineation of urban areas.\footnote{11}

Information on vaccination history was obtained from the IRIS database. Specifically, this database was used to determine if cohort members had been immunized (yes/no) against measles, mumps, and rubella (MMR vaccine; at least two doses); hepatitis B (at least two doses); and meningococcal C (at least one dose). A category was also formed to indicate whether or not an individual had received all three of these vaccines. The MMR vaccine represents a vaccine that, unlike the HPV vaccine, is mandatory and administered in early childhood while, like the HPV vaccine, has had its safety called into question. Hepatitis B and meningococcal C vaccines, on the other hand, are like the HPV vaccine in that they are optional and administered to a similar age-group (i.e., children in Grade 7) through school-clinics. Since refusal of a mandatory vaccine is relatively unusual, we hypothesized that, compared to hepatitis B and meningococcal C vaccination, absence of MMR vaccination would be a stronger predictor of anti-vaccine
sentiments. Overall, vaccination history was used to assess a tendency to avail of publicly funded immunization programs (i.e., a proxy for vaccine acceptance).

History of health services utilization was determined using the DAD, NACRS, and OHIP databases, and was based on the number of hospital admissions, emergency department visits, or outpatient physician visits occurring any time prior to cohort. Each type of health service was considered separately and was used as an indicator of both the health status of individual girls and a propensity to avail of health services.

The medical histories of each girl was established by identifying illnesses leading to a hospital admission (DAD), an emergency department visit (NACRS), or a physician visit (OHIP) any time prior to cohort entry. However, because individual OHIP diagnostic codes normally refer to major disease categories rather than specific illnesses, medical histories were based primarily on the DAD and NACRS databases. Medical conditions of interest included a history of autoimmune disease, the presence of a risk factor for autoimmune diseases, a history of an immune-mediated disease, and specific illnesses leading to an emergency department visit or hospital admission. In addition, a composite variable consisting of other serious diagnoses was identified (Appendix II). Medical conditions of interest were identified *a priori* in consultation with a clinician-scientist in allergy and clinical immunology as well as two community medicine physicians. The chosen diagnoses represent conditions that could be associated with both the decision to vaccinate and the risk of an adverse event following immunization.
3.9  **Statistical Analyses**

3.9.1  *Patterns of Use Analysis*

To determine the patterns of use, the cohort was described in terms of HPV vaccine uptake and adherence. Specifically, to describe vaccine uptake, the percentage of *vaccinated* and *unvaccinated* cohort members was calculated. In addition, to describe vaccine adherence, the percentage of *adherers* (all three doses) and *non-adherers* (1-2 doses) was calculated. Using cross-tabulations, the distribution of uptake and adherence groups was determined according to year of vaccination campaign (2007/08 and 2008/09), socio-demographics, vaccination history, frequency of health services utilization, and medical history. The strength of the relationship between each of these characteristics and the probability of being vaccinated was estimated using logistic regression. First, univariate logistic regression was used to estimate the strength of association between the groups (vaccinated *vs.* unvaccinated) and each of the characteristics. Second, multivariable logistic regression was used to estimate the strength of association between groups and each of the characteristics, adjusted for all other characteristics. A similar approach was used for the analysis of adherence. The strengths of association between these characteristics and vaccine adherence were estimated in a similar manner.

3.9.2  *Safety Analysis*

Cohort data are most often analyzed using time-to-event Cox Proportional Hazards regression. However, since little is known about factors that predict vaccine-induced adverse events and factors that influence HPV vaccine uptake or avoidance in the
Ontario Grade 8 population, the traditional time-to-event analysis may be susceptible to confounding bias. Consequently, the self-controlled case series (SCCS) method, also known as the case series method, was employed for the safety analyses.\textsuperscript{1, 2}

3.9.2.1 The Self-Controlled Case-Series

The self-controlled case series, or case series for short, was developed specifically for post-marketing evaluations of adverse reactions following immunization and is typically applied to study the association between a transient exposure and an acute event.\textsuperscript{1, 2, 3} A main feature of this method is that it uses only data on cases (i.e., those who have experienced the outcome of interest). Therefore, it is valuable for situations in which no precise denominator or underlying cohort is identifiable.

The case series is derived from an underlying Poisson cohort model by conditioning the event on an individual’s vaccination history. Accordingly, the method assumes that events occur randomly, the probability of an event is small and constant over the observation period, and events are independent. The method distinguishes from traditional cohort analyses, however, in that it is a self-matched approach and therefore compares an individual to himself/herself over different periods of time. The major advantage of this method is that, since estimation is within individuals, it controls completely for individual-level, time-independent confounders, including genetic susceptibility, health beliefs, and values. Consequently, the case series is particularly useful when confounders are either unknown or unmeasured, as is likely the case for database studies of HPV vaccination. Of course, this method also has a number of important limitations. Specifically, the occurrence of an event cannot alter the probability of subsequent exposure, the occurrence of an event must not censor or affect the
observation period, and it does not produce an estimate of absolute incidence, only of relative incidence. The method is typically applied to recurrent events (e.g., Bell’s palsy), but can also be used for non-recurrent events (e.g. type 1 diabetes), provided the risk is small over the observation period. Importantly, studies show that the case series is a powerful and practical alternative to the cohort and case-control analyses, particularly when confounding bias is of concern.\textsuperscript{16-18}

3.9.2.2 Statistical Analysis

For the safety analysis, each case’s observation time was divided into risk and control periods, defined \textit{a priori} (Figure 3.1).\textsuperscript{1, 2}

![Diagram](https://via.placeholder.com/150)

\textbf{Figure 3.1 Depiction of Self-controlled Case Series Method}\textsuperscript{16}

In the case series, an exposure risk period (i.e., “exposed” person-time) is the time following immunization during which an individual is considered etiologically or biologically exposed to the vaccine. In other words, an exposure risk period refers to the time period during which one is conceivably at an increased risk of the event of interest. Accordingly, \textit{unvaccinated} girls in this study had no risk windows, while \textit{adherers} had
three. Events occurring during risk windows are attributed to the vaccine (i.e., are exposed events) and events occurring outside the risk windows are not attributed to the event (i.e., are unexposed events). Since the aetiology of many AEFIs remains to some degree uncertain, the duration of the exposure risk periods was established based on evidence of the timing of individual events reported to VAERS, as well as previously published studies of AEFIs associated with vaccine use. In the primary safety analysis, the duration of the risk window was 1-60 days following vaccination. The day following vaccination (day 1) was chosen as the start of the exposure period instead of the day of vaccination (day 0) to ensure that all events classified as exposed truly followed an injection of the HPV vaccine. Secondarily, in order to assess the potential for time-varying risk, the exposure risk window was divided into 1-7, 8-21, and 22-60 days (Table 3.4). The control periods (i.e., “unexposed” person-time) were defined as all follow-up time that did not fall within an exposure risk period. For each outcome, the incidence rate during the exposure risk periods was compared with the incidence rate during control periods. Using conditional Poisson regression and treating each case as unique stratum, the relative incidence (RI) and 95% confidence interval of each outcome was estimated.

### Table 3.4 Exposure risk periods (days)

<table>
<thead>
<tr>
<th>Primary analysis</th>
<th>Secondary analyses</th>
<th>Sensitivity analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*-60</td>
<td>1-7, 8-21, 22-60</td>
<td>0-59, 1-100, 8-60, 61-100</td>
</tr>
</tbody>
</table>

* Refers to the day following vaccination

### 3.9.2.3 Sensitivity Analysis

A number of assumptions had to be made for the safety analysis. The robustness of the results under these assumptions was tested in sensitivity analyses. First, to verify if
the duration of the exposure risk period chosen was a source of exposure misclassification, the primary analysis was repeated by altering the periods (Table 3.4). In particular, to address concerns about the potential for delayed diagnosis of autoimmune diseases, the duration of the exposure risk window was lengthened. Second, since the age cut-point chosen was relatively arbitrary, the primary analysis was replicated with no age stratification. Third, an assumption of the case series is that the occurrence of an event does not censor or affect the observation period. To test the robustness of this assumption, the primary analysis was also executed where cases were censored on the day following their event.
3.10 References


<table>
<thead>
<tr>
<th>Database</th>
<th>Description</th>
<th>Original Data Source</th>
<th>Main data elements</th>
<th>Information Obtained</th>
<th>Use of data/time-windows</th>
<th>Diagnostic record</th>
</tr>
</thead>
</table>
| RPDB Registered Persons’ Database| Information about anyone who has ever received an Ontario health card number (OHCN) | MOHLTC (enriched by ICES in-house datasets) | • Demographics (e.g., date of birth, sex)  
• Geographic information (e.g., postal code)  
• Date of last contact with health care system (DOLC) | • ICES Key Number (IKN; unique identifier anonymously linkable to other individual-level data holdings)  
• Birth month and year, sex, income quintile, place of residence | • Sex, and date of birth for the identification of cohort members through linkage with IRIS  
• Other demographic and geographic information  
• January 1994-December 2009 | N/A |
| DAD (CIHI) Discharge Abstract Database | Record on inpatient hospital activity | CIHI | • Patient demographics (e.g., sex, age)  
• Clinical data (e.g. diagnoses, procedures)  
• Administrative data (e.g. hospital, length of stay) | • IKN  
• Admission date  
• Length of stay  
• Diagnosis code, diagnosis type | • Dates and diagnoses related to hospitalizations for identification of study outcomes  
• January 1994-March 2009 | 1-25 diagnoses per admission  
3-4 character ICD-9 codes  
3-4 character ICD-10 codes  
1-character ‘type of diagnosis’ codes |
| NACRS National Ambulatory Care Reporting System | Record on patient visits to hospital emergency departments, same day surgery, and selected outpatient services | CIHI | • Patient demographics  
• Clinical data  
• Administrative data  
• Financial data  
• Service-specific data elements for day surgery and emergency | • IKN  
• Arrival date  
• Diagnosis code, diagnosis type | • Identification of date and diagnoses related to emergency consultations for identification of study outcomes  
• July 2000-March 2009 | 1-10 diagnoses per consultation  
3-4 character ICD-9 codes  
3-4 character ICD-10 codes  
1-character ‘type of diagnosis’ codes |
| **OHIP**  
Ontario Health Insurance Plan | Record of services from health care providers that claim under OHIP | **MOHLTC** | • patient and physician identifiers (encrypted)  
• code for service provided, date of service, and associated diagnosis  
• fee paid  
• IKN  
• Date of admission  
• OHIP fee code and suffix  
OR diagnosis code and explanatory code  
• Identification of dates and diagnoses related to physician consultations for identification of study outcomes, and individual’s medical histories  
• January 1994-December 2009  
• 1 diagnosis per visit  
• 3-digit diagnosis code (variant of ICD-9)  
• 1-character ‘type of diagnosis’ code  
• 1-digit diagnosis code suffix |
| **IRIS**  
Immunization Record Information System | Record of the immunization status of school-aged children and children in licensed child care facilities | **Local Public Health Units (LPHAs)** | • student demographics (e.g. date of birth, sex, school)  
• vaccine type and immunization dates  
• list of girls born in 1994 and 1995 for cohort  
• dates of HPV immunizations  
• Identification of cohort through linkage to RPDB  
• Dates of HPV immunization for exposure status  
• January 1994-April 2010 |
CHAPTER 4: PATTERNS OF USE OF THE HPV VACCINE
4.1 Preface to the manuscript

This chapter contains the first of two manuscripts of this thesis addressing the use and safety of the HPV vaccine for a cohort of Grade 8 girls residing in KFL&A. Specifically, the following manuscript describes the patterns of use of the KFL&A cohort and evaluates this use according to socio-demographic and clinical factors.

Only about 50% of girls eligible for Ontario’s publicly funded HPV vaccination program are availing of the service and even less are receiving all three indicated doses. While low rates of uptake and adherence undermine public health efforts aimed at reducing the burden of HPV-related illnesses and making the program cost effective, little is known about the factors that influence HPV vaccine use in this population. In the current study, we address this knowledge gap by exploring differences between girls who receive the vaccine and those who do not, as well as between those who complete the three-dose schedule and those who do not. This study is based on the first two years of the HPV vaccination program in KFL&A and relies entirely on data from administrative health and vaccination databases.
4.2 Factors associated with HPV vaccine uptake and adherence in an Ontario cohort of Grade 8 girls

ABSTRACT

Background: Publicly funded, school-based HPV immunization programs overcome financial and accessibility barriers to healthcare, thereby creating an ideal setting in which vaccine uptake and adherence can be optimized. Nevertheless, usage of the quadrivalent HPV vaccine through Ontario’s $117 million program has been low, reaching only half of the eligible population. In order to improve the success of this program, it is important to identify the factors associated with vaccine use in this population.

Methods: We conducted a population-based, retrospective cohort study of girls eligible for Ontario’s Grade 8 HPV vaccination program in 2007 and 2008 to describe the patterns of use of this vaccine in terms of uptake and adherence and identify factors associated with this use. Using data from the province’s administrative health databases and the Immunization Recording Information System (IRIS) database of Kingston, Frontenac, Lennox and Addington (KFL&A) Public Health, we identified 2,519 girls eligible for this program. Cross-tabulations were used to determine the vaccination and adherence status of these girls according to socio-demographics, vaccination history, health services utilization, and medical history, as well as over time. We used multivariable logistic regression to estimate the association between individual factors and uptake and adherence while adjusting for the influence of all other factors.

Results: 56.6% of eligible girls received at least one dose of the HPV vaccine, 85.3% of whom adhered to the three-dose regimen. Although vaccine uptake was significantly higher in the second year of the program (OR 1.29, 95% CI 1.08-1.53), the absolute
increase was negligible (4%, 95% CI 1.30-7.86). Vaccinated and unvaccinated girls differed only on the basis of vaccination history, whereby those previously immunized against measles-mumps-rubella, meningococcal C, or hepatitis B were two to three times more likely to obtain the HPV vaccine (OR 3.21, 95% CI 2.25-4.57; OR 2.16, 1.64-2.84; OR 2.86, 2.14-3.83, respectively). On the other hand, adherers and non-adherers differed on the basis of socio-demographics in that adherers were more likely to live in a rural setting (OR 1.76, 95% CI 1.14-2.74) and less likely to be in the lowest income quintile (OR 0.45, 95% CI 0.28-0.72).

**Interpretation:** The level of uptake of the HPV vaccine in Ontario is still well below that of other optional vaccines. Our results suggest that previous vaccination history is strongly associated with uptake of the HPV vaccine, while socio-demographic factors appear to be important determinants of adherence. Additional studies are needed to assess other factors that may be associated with the uptake and adherence of the HPV vaccine and to assess the generalizability of our findings.
INTRODUCTION

The quadrivalent human papillomavirus (HPV) vaccine is designed to prevent infections with strains of HPV that cause 70% of cervical cancers\(^1\) and 90% of genital warts.\(^2\) In March 2007, the Canadian government allocated $300 million to the provinces and territories on a per-capita basis to launch a national HPV immunization program for young girls. By September 2007, the Ontario government had implemented a three-year, $117 million program aimed at offering the vaccine to all Grade 8 girls in the province through school clinics.\(^3\)

Ontario’s Grade 8 HPV vaccination program is administered by each of the province’s 36 local public health agencies (LPHAs) and covers all three indicated doses of the vaccine. Although the initiative is primarily school-based, eligible girls also have the option of obtaining the vaccine for free at their LPHA or from their family physician. Since the HPV vaccine is not mandatory, the decision of whether or not to receive the vaccine is left to parents and guardians of eligible girls.\(^4\)

While it was expected that vaccine uptake through Ontario’s program would exceed 80\%, only about 50\% of eligible girls received the first dose of the vaccine.\(^3\) In addition, not all girls who received the first injection proceeded to obtain all three required doses. This rate of uptake is not only considerably lower than rates of similar school-based vaccination programs in Ontario,\(^5\) but it also represents the lowest rate of HPV vaccine uptake in Canada’s publicly funded program.\(^6\) Given that low levels of vaccine uptake undermine public health efforts aimed at reducing the burden of HPV-related illnesses and making the program cost-effective, it is important to identify the factors that influence use of the HPV vaccine in this population.
We conducted a retrospective, population-based cohort study of girls eligible for Ontario’s Grade 8 HPV vaccination program in order to describe the patterns of use of this vaccine in terms of vaccine uptake and adherence, as well as to identify factors associated with these patterns of use.

METHODS

Study population and data sources

Using the province’s administrative databases, we identified a cohort of girls eligible for Ontario’s Grade 8 HPV vaccination program residing in the Kingston, Frontenac, Lennox, and Addington (KFL&A) public health region. Four administrative health databases were used for this study: (1) the Registered Persons Database (RPDB) for information on dates of health insurance coverage and socio-demographics, (2) the Canadian Institute for Health Information’s (CIHI) Discharge Abstract Database (DAD) for information on dates of hospital admissions and discharge diagnoses (coded using the International Classification of Diseases, Ninth and Tenth Revision [ICD-9 and ICD-10]), (3) the National Ambulatory Care Reporting System (NACRS) database for information on emergency department visits, including visit dates and diagnoses (coded using ICD-9 and ICD-10), and (4) the Ontario Health Insurance Plan (OHIP) database for information on all fee-for-service claims by physicians, including service dates and diagnoses (coded using OHIP diagnostic codes, three-digit variants of the ICD-9 codes). These databases are generated by the province’s universal health insurance programs and are accessible through the Institute for Clinical Evaluative Sciences (ICES). Described elsewhere in detail, our theses databases have been used extensively in health research, including in the
post-marketing evaluation of drug and vaccine safety. In these databases, each resident of Ontario is represented by a unique encrypted identifier that enables complete record linkage at the level of the individual across databases and calendar time.

Also, we used the Immunization Recording Information System (IRIS) database for information on vaccinations. The IRIS databases, maintained by each of Ontario’s 36 LPHAs, were developed by the Ministry of Health and Long-Term Care (MOHLTC) to track and record immunizations of school-aged children across the province. In particular, they are used to monitor coverage of mandatory vaccines and vaccines administered in school clinics. As such, individual-level information on all HPV vaccines administered through the publicly funded program is recorded into IRIS by the LPHA. A recent re-abstraction study demonstrated that the KFL&A IRIS database captured individual girls’ vaccination status with high sensitivity (99.8%; 95% CI 99.3-99.9) and specificity (97.7%; 95% CI 96.3-98.7). The KFL&A IRIS database was electronically transferred to ICES for this study by means of a high encryption portal that is both monitored and secured. The data transfer required that a data sharing agreement be signed between the local Medical Officer of Health and ICES. Since the IRIS database contains first and last names, sex, date of birth, and health card number, complete record linkage with Ontario’s administrative health databases was possible for 95.62% of records in the KFL&A IRIS database used for the current study (Table 3.2). This is the first study to use the IRIS database for analytical purposes.
Study design

We conducted a population-based, retrospective cohort study of girls eligible for Ontario’s Grade 8 HPV vaccination program in KFL&A. The RPDB and IRIS databases were used to identify girls eligible for the 2007/08 and 2008/09 campaign years. Since school grade is not recorded in these databases, we defined the cohorts based on birth year and assumed all girls entered Grade 8 in their thirteenth year of life. Accordingly, we identified a cohort of girls born in 1994 and 1995 who were residing in KFL&A on September 1 of 2007 and 2008, respectively. Girls were followed from September 1 of their Grade 8 school year (cohort entry) until their date of death or April 13, 2010 (end of study).

HPV vaccination history

We ascertained data on HPV vaccination any time up to and including April 13, 2010, the date on which a copy of the KFL&A IRIS database was transferred to ICES for record linkage. These data were used to determine the number of doses administered to each girl and the date each dose was received.

We described the patterns of use for each girl in terms of her vaccine uptake as well as her adherence to the three-dose schedule. In order to determine uptake, vaccine exposure was classified as either vaccinated (at least one dose) or unvaccinated (no doses). To determine adherence, only vaccinated girls were considered. Adherence was dichotomized into adherers (having received all three doses) and non-adherers (having received only one or two doses).
Baseline characteristics

We determined the socio-demographic and clinical profile of each girl using the administrative health databases previously described. The socio-demographic factors considered consisted of age, neighbourhood income quintile, and place of residence (urban vs. rural) and were ascertained using the RPDB. Income and place of residence were based on data from the 2006 Canadian Census. The neighbourhood income quintile of each girl was ascertained by linking her postal code at cohort entry with an ecologic-level (i.e., neighbourhood) measure of adjusted household income that had been categorized into provincial quintiles. A girl’s postal code was also used to determine whether she resided in an urban or rural area. Urban areas were defined based on a community size of greater than 10,000 persons; rural areas were those that remained after delineation of urban areas.17

The clinical profile of each girl consisted of her vaccination history, health services utilization, and medical history.

We ascertained the vaccination history of each girl using information obtained from the KFL&A IRIS database. Specifically, data from IRIS were used to determine if cohort members had been immunized against measles, mumps, and rubella (MMR; at least two doses); hepatitis B (at least two doses); and meningococcal C (at least one dose). We used vaccination history to assess a tendency to make use of publicly funded immunization programs (i.e., a proxy for vaccine acceptance). The MMR vaccine represents a vaccine that, unlike the HPV vaccine, is mandatory and administered in early childhood while, like the HPV vaccine, has had its safety called into question. Hepatitis B and meningococcal C vaccines, on the other hand, are similar to the HPV vaccine in that
they are optional and administered in school clinics to a similar age-group (i.e., children in Grade 7). Post priori, we also considered uptake of all three vaccines (yes/no) as a proxy for strong pro-vaccine sentiments.

We classified health services utilization in terms of the number of hospital admissions, emergency department visits, or outpatient physician visits occurring any time prior to cohort entry using the DAD, NACRS, and OHIP databases, respectively. Each type of service was considered separately and used as an indicator of both health status and a propensity to avail of health services.

We established medical histories by identifying illnesses leading to a hospital admission (DAD), an emergency department visit (NACRS), or a physician visit (OHIP) any time prior to cohort entry. However, because individual OHIP diagnostic codes often represent a number of different diagnoses, medical histories were based primarily on the DAD and NACRS databases. Medical conditions of interest included a history of autoimmune disease, the presence of a risk factor for autoimmune diseases, a history of an immune-mediated disease, and specific illnesses leading to an emergency department visit or hospital admission. In addition, a composite variable consisting of other serious diagnoses was identified (Appendix II). Medical conditions of interest were identified a priori in consultation with a clinician-scientist in allergy and clinical immunology and two community medicine physicians and epidemiologists. The chosen diagnoses represent conditions that could be associated with the decision to vaccinate and the risk of an adverse event following immunization.
**Statistical analysis**

To describe the patterns of use of the HPV vaccine, we calculated the percentage of vaccinated and unvaccinated girls (vaccine uptake) and the percentage of adherers and non-adherers (vaccine adherence) in the KFL&A cohort. Subsequently, these analyses were stratified by campaign year.

We used cross-tabulations to determine the distributions of the various socio-demographic and clinical characteristics across vaccination groups. The associations between vaccine uptake and individual baseline characteristics were estimated using logistic regression. First, univariate logistic regression was used to estimate the strength of association between the groups (vaccinated vs. unvaccinated) and each of the characteristics. Second, multivariable logistic regression was used to estimate the strength of association between groups and each of the characteristics, adjusted for all other characteristics. A similar approach was used for the analysis of adherence.

Neighbourhood income quintile was analyzed using dummy variables for categories 1 through 5, with the third quintile serving as the reference category in the multivariable model. Similarly, each type of health services utilization was analyzed using dummy variables for low (reference), medium-low, medium-high, and high utilization. The cut-offs for these categories were based on the frequency distributions of the data.

All statistical analyses were conducted using SAS 9.2 on the SunOS 5.9 (SUN 64) platform.
RESULTS

Based on birth year, we determined that 185,398 girls were eligible for Ontario’s Grade 8 HPV Vaccination program in 2007-08 and 2008-09. Of these, 2519 were residing in KFL&A and comprised our study cohort (Figure 4.1). These girls were between 12.7 and 13.6 years of age (mean=13.2 years) at cohort entry.

Overall, 56.6% (n=1425) of eligible girls received at least one dose of the HPV vaccine and, among those who had been vaccinated, 85.3% (n=1215) adhered to the three-dose regimen (Figure 4.2). Among non-adherers, 76.2% (n=160) received two of the three recommended doses of the vaccine.

Figure 4.1 Cohort Flow Diagram

Overall, 56.6% (n=1425) of eligible girls received at least one dose of the HPV vaccine and, among those who had been vaccinated, 85.3% (n=1215) adhered to the three-dose regimen (Figure 4.2). Among non-adherers, 76.2% (n=160) received two of the three recommended doses of the vaccine.
Between campaign years, uptake increased significantly by 4.0% (OR=1.28, 95% C.I. 1.07-1.53). While there was no significant change in adherence (OR =0.89, 95% C.I. 0.65-1.20) (Table 4.1), the proportion of non-adherers receiving two doses was significantly higher in the second year than in the first (13.1% vs. 9.4%; P=0.03).
After adjusting for a number of potential confounders, there were no significant differences between vaccinated and unvaccinated girls with respect to socio-demographics, health services utilization, or medical history, although girls in the fourth income quintile appeared less likely to receive the HPV vaccine than those in the third quintile (Table 4.2). Conversely, compared to their unvaccinated counterparts, HPV vaccinated girls were significantly more likely to have also been vaccinated against MMR (OR=3.21; 95% CI 2.25-4.57), meningococcal C (OR=2.16; 95% CI 1.64-2.84), and hepatitis B (OR=2.86, 95% CI 2.14-3.83), and were even more likely to have received all three vaccines (OR=4.89; 95% CI 4.04-5.92).

Similar to that observed with vaccination status, vaccine adherence was also not associated with age, health services utilization, or medical history (Table 4.3). On the other hand, girls from families in the lowest income quintile appeared significantly less likely to adhere to the three dose regimen than those from middle income families.
(OR=0.45; 95% CI 0.28-0.72), while girls residing in rural areas were significantly more likely to complete their HPV immunization schedule than those residing in urban areas (OR=1.76; 95% CI 1.14-2.74). Previous immunization from other individual vaccines was not significantly associated with HPV vaccine adherence, but receipt of all three vaccines was (OR=1.85; 95% CI 1.29-2.65).

Table 4.2 Baseline characteristics of girls vaccinated and unvaccinated with the quadrivalent HPV vaccine

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Vaccinated (N=1425)</th>
<th>Unvaccinated (N=1094)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Socio-demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (average ± SD)</td>
<td>13.2±0.3</td>
<td>13.2±0.3</td>
<td>1.16 (0.88-1.52)</td>
<td>1.10 (0.81-1.50)</td>
</tr>
<tr>
<td>Neighbourhood income quintile (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st</td>
<td>18.9</td>
<td>20.8</td>
<td>0.79 (0.61-1.02)</td>
<td>0.87 (0.65-1.15)</td>
</tr>
<tr>
<td>2nd</td>
<td>17.5</td>
<td>19.9</td>
<td>0.81 (0.62-1.04)</td>
<td>0.80 (0.60-1.06)</td>
</tr>
<tr>
<td>3rd (reference)</td>
<td>20.8</td>
<td>18.1</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>4th</td>
<td>20.4</td>
<td>21.3</td>
<td>0.83 (0.65-1.07)</td>
<td>0.75 (0.57-0.99)</td>
</tr>
<tr>
<td>5th</td>
<td>21.8</td>
<td>19.4</td>
<td>0.98 (0.76-1.25)</td>
<td>0.91 (0.69-1.19)</td>
</tr>
<tr>
<td>Missing‡</td>
<td>0.6</td>
<td>1.5</td>
<td>0.33 (0.14-0.79)</td>
<td>1.34 (0.50-3.61)</td>
</tr>
<tr>
<td><strong>Place of residence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban (reference)</td>
<td>78.3</td>
<td>77.5</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Rural</td>
<td>21.1</td>
<td>21.0</td>
<td>0.99 (0.82-1.20)</td>
<td>1.14 (0.90-1.43)</td>
</tr>
<tr>
<td>Missing†</td>
<td>0.6</td>
<td>1.5</td>
<td>0.38 (0.16-0.89)</td>
<td>1.34 (0.50-3.61)</td>
</tr>
<tr>
<td><strong>Vaccination History (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMR</td>
<td>96.1</td>
<td>78.9</td>
<td>6.67 (4.91-9.06)</td>
<td>3.21 (2.25-4.57)</td>
</tr>
<tr>
<td>Meningococcal C</td>
<td>88.5</td>
<td>60.2</td>
<td>5.10 (4.16-6.24)</td>
<td>2.16 (1.64-2.84)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>90.7</td>
<td>62.2</td>
<td>5.96 (4.80-7.41)</td>
<td>2.86 (2.14-3.83)</td>
</tr>
<tr>
<td>All three vaccines††</td>
<td>83.2</td>
<td>51.1</td>
<td>4.75 (3.96-5.70)</td>
<td>4.89 (4.04-5.92)</td>
</tr>
<tr>
<td><strong>Health Services Utilisation (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (0; reference)</td>
<td>19.5</td>
<td>20.4</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Med-low (1)</td>
<td>61.9</td>
<td>59.7</td>
<td>1.08 (0.88-1.33)</td>
<td>0.82 (0.63-1.07)</td>
</tr>
<tr>
<td>Med-high (2)</td>
<td>13.1</td>
<td>13.6</td>
<td>1.00 (0.76-1.32)</td>
<td>0.71 (0.50-1.01)</td>
</tr>
<tr>
<td>High (≥3)</td>
<td>5.5</td>
<td>6.3</td>
<td>0.92 (0.64-1.33)</td>
<td>0.64 (0.38-1.06)</td>
</tr>
<tr>
<td>Emergency visits</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (0; reference)</td>
<td>25.9</td>
<td>30.2</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Med-low (1)</td>
<td>21.5</td>
<td>22.2</td>
<td>1.13 (0.90-1.41)</td>
<td>1.00 (0.78-1.28)</td>
</tr>
<tr>
<td>Med-high (2-7)</td>
<td>43.4</td>
<td>38.9</td>
<td>1.30 (1.07-1.57)</td>
<td>1.16 (0.92-1.46)</td>
</tr>
<tr>
<td>High (≥8)</td>
<td>9.2</td>
<td>8.7</td>
<td>1.23 (0.91-1.67)</td>
<td>1.13 (0.77-1.66)</td>
</tr>
<tr>
<td>-----------</td>
<td>-----</td>
<td>-----</td>
<td>-----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Outpatient visits</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (0-13; reference)</td>
<td>8.5</td>
<td>12.0</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Med-low (14-45)</td>
<td>40.8</td>
<td>42.3</td>
<td>1.36 (1.03-1.79)</td>
<td>0.91 (0.64-1.31)</td>
</tr>
<tr>
<td>Med-high (46-92)</td>
<td>39.9</td>
<td>37.5</td>
<td>1.50 (0.14-1.98)</td>
<td>1.07 (0.73-1.57)</td>
</tr>
<tr>
<td>High (≥93)</td>
<td>10.8</td>
<td>8.2</td>
<td>1.85 (1.29-2.65)</td>
<td>1.31 (0.82-2.11)</td>
</tr>
</tbody>
</table>

**Medical History (%)**

### Previous diagnosis

- **Infectious and parasitic diseases**
  - Intestinal infections: 15.2 (13.9) 1.11 (0.89-1.39) 0.96 (0.70-1.32)
  - Chickenpox: 3.7 3.3 1.14 (0.74-1.75) 1.25 (0.71-2.20)
  - Cancer: 0.9 0.6 1.67 (0.63-4.41) 1.55 (0.52-4.60)
  - Metabolic disorders: 3.0 3.0 1.00 (0.63-1.59) 0.90 (0.50-1.61)
  - Disorders of the immune system: 0.1 0.1 0.77 (0.05-12.25) 2.18 (0.07-73.24)

- **Diseases of the blood**
  - Gastroenteritis: 5.5 4.3 1.31 (0.90-1.89) 1.10 (0.71-1.72)
  - Nephritis: 3.9 3.4 1.15 (0.75-1.75) 1.24 (0.75-2.04)
  - Congenital anomalies: 7.0 8.9 0.78 (0.58-1.04) 0.78 (0.56-1.09)
  - Syncope: 1.2 1.3 0.93 (0.46-1.90) 1.05 (0.47-2.35)
  - Other serious illness: 2.0 1.8 1.12 (0.63-1.98) 1.05 (0.55-2.00)

### Immune-mediated events

- Allergic rhinitis: 0.2 0.4 0.58 (0.13-2.58) 0.53 (0.10-2.87)
- Asthma: 5.6 6.0 0.93 (0.66-1.30) 0.96 (0.64-1.44)
- Dermatitis: 4.3 3.0 1.44 (0.93-2.21) 1.46 (0.89-2.40)

### Autoimmune diseases

- Diabetes mellitus: 1.3 1.7 0.81 (0.42-1.55) 0.57 (0.28-1.15)
- Multiple sclerosis: 0.0 0.1 - -
- Bell’s palsy: 0.2 0.5 0.46 (0.11-1.93) 0.38 (0.08-1.69)
- Guillain-Barré Syndrome: 0.0 0.0 - -
- Juvenile Arthritis: 2.2 1.7 1.26 (0.71-2.24) 1.28 (0.66-2.44)
- Systemic Lupus: 0.0 0.0 - -
- Erythematous: - - - -

### Risk factors for autoimmune diseases

- Cytomegalovirus: 0.0 0.1 - -
- Epstein-Barr virus: 0.2 0.1 2.30 (0.24-22.14) 4.29 (0.26-71.21)
- Campylobacter: 0.0 0.0 - -
- Influenza: 15.5 13.2 1.21 (0.97-1.52) 1.13 (0.88-1.46)
- Mycoplasma: 0.1 0.1 0.77 (0.05-12.25) 2.81 (0.09-87.47)

* OR = Odds Ratio; CI = Confidence Interval; SD = Standard deviation; MMR = Measles, mumps and rubella
* Expressed as percentages (%) unless otherwise indicated
† Adjusted for all characteristics listed in table as well as campaign year
‡ Missing because postal code in RPDB was either incorrect or unavailable
§ The adjusted odds ratio for this variable was determined post-hoc using a regression analysis that included all listed characteristics except previous, meningococcal C, and hepatitis B.
Table 4.3  Baseline characteristics of girls immunized with the HPV vaccine according to their adherence with the three-dose regimen

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adherers (N=1215)</th>
<th>Non-adherers (N=210)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Socio-demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (average ± SD)</td>
<td>13.2±0.3</td>
<td>13.2±0.3</td>
<td>0.99 (0.59-1.66)</td>
<td>1.02 (0.60-1.75)</td>
</tr>
<tr>
<td>Neighbourhood income quintile (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st</td>
<td>16.9</td>
<td>31.0</td>
<td>0.44 (0.28-0.68)</td>
<td>0.45 (0.28-0.72)</td>
</tr>
<tr>
<td>2nd</td>
<td>17.5</td>
<td>17.6</td>
<td>0.79 (0.49-1.30)</td>
<td>0.80 (0.48-1.33)</td>
</tr>
<tr>
<td>3rd</td>
<td>21.5</td>
<td>17.1</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>4th</td>
<td>21.0</td>
<td>16.7</td>
<td>1.01 (0.61-1.65)</td>
<td>0.98 (0.59-1.62)</td>
</tr>
<tr>
<td>5th</td>
<td>22.7</td>
<td>16.2</td>
<td>1.12 (0.68-1.84)</td>
<td>1.15 (0.68-1.92)</td>
</tr>
<tr>
<td>Missing†</td>
<td>0.4</td>
<td>1.4</td>
<td>0.23 (0.53-1.00)</td>
<td>0.56 (0.12-2.66)</td>
</tr>
<tr>
<td>Place of residence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>77.7</td>
<td>82.4</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Rural</td>
<td>22.0</td>
<td>16.4</td>
<td>1.43 (0.97-2.12)</td>
<td>1.76 (1.14-2.74)</td>
</tr>
<tr>
<td>Missing†</td>
<td>0.4</td>
<td>1.4</td>
<td>0.31 (0.07-1.29)</td>
<td>0.56 (0.12-2.66)</td>
</tr>
<tr>
<td><strong>Vaccination History (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMR</td>
<td>96.8</td>
<td>92.4</td>
<td>2.49 (1.36-4.54)</td>
<td>1.61 (0.81-3.19)</td>
</tr>
<tr>
<td>Meningococcal C</td>
<td>90.0</td>
<td>79.5</td>
<td>2.33 (1.59-3.42)</td>
<td>1.39 (0.83-2.35)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>92.3</td>
<td>81.9</td>
<td>2.64 (1.75-3.97)</td>
<td>1.67 (0.95-2.92)</td>
</tr>
<tr>
<td>All three vaccines††</td>
<td>85.1</td>
<td>72.4</td>
<td>2.18 (1.55-3.07)</td>
<td>1.85 (1.29-2.65)</td>
</tr>
<tr>
<td><strong>Health Services Utilisation (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (0)</td>
<td>18.8</td>
<td>23.8</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Med-low (1)</td>
<td>63.1</td>
<td>54.8</td>
<td>1.46 (1.02-2.10)</td>
<td>1.23 (0.80-1.91)</td>
</tr>
<tr>
<td>Med-high (2)</td>
<td>12.9</td>
<td>13.8</td>
<td>1.19 (0.72-2.00)</td>
<td>1.08 (0.59-1.98)</td>
</tr>
<tr>
<td>High (≥3)</td>
<td>5.2</td>
<td>7.6</td>
<td>0.86 (0.46-1.62)</td>
<td>1.04 (0.45-2.37)</td>
</tr>
<tr>
<td>Emergency visits</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (0)</td>
<td>26.3</td>
<td>23.3</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Med-low (1)</td>
<td>21.5</td>
<td>21.9</td>
<td>0.78 (0.56-1.34)</td>
<td>0.85 (0.53-1.35)</td>
</tr>
<tr>
<td>Med-high (2-7)</td>
<td>43.3</td>
<td>43.8</td>
<td>0.88 (0.60-1.27)</td>
<td>0.88 (0.58-1.35)</td>
</tr>
<tr>
<td>High (≥8)</td>
<td>8.9</td>
<td>11.0</td>
<td>0.72 (0.42-1.24)</td>
<td>0.73 (0.38-1.40)</td>
</tr>
<tr>
<td>Outpatient visits</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (0-13)</td>
<td>7.6</td>
<td>13.8</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Med-low (14-45)</td>
<td>41.2</td>
<td>38.1</td>
<td>1.97 (1.22-3.19)</td>
<td>1.42 (0.79-2.54)</td>
</tr>
<tr>
<td>Med-high (46-92)</td>
<td>40.7</td>
<td>35.7</td>
<td>2.08 (1.28-3.37)</td>
<td>1.55 (0.83-2.89)</td>
</tr>
<tr>
<td>High (≥93)</td>
<td>10.5</td>
<td>12.4</td>
<td>1.55 (0.86-2.81)</td>
<td>1.43 (0.67-3.05)</td>
</tr>
<tr>
<td><strong>Medical History (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infectious and parasitic diseases</td>
<td>14.5</td>
<td>19.1</td>
<td>0.72 (0.49-1.05)</td>
<td>0.83 (0.48-1.42)</td>
</tr>
<tr>
<td>Intestinal infections</td>
<td>3.2</td>
<td>6.7</td>
<td>0.46 (0.25-0.87)</td>
<td>0.64 (0.28-1.45)</td>
</tr>
<tr>
<td>Chickenpox</td>
<td>1.5</td>
<td>2.4</td>
<td>0.62 (0.23-1.68)</td>
<td>0.80 (0.25-2.59)</td>
</tr>
<tr>
<td>Category</td>
<td>OR</td>
<td>95% CI</td>
<td>Adjusted OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-----</td>
<td>--------</td>
<td>--------------</td>
<td>--------</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.9</td>
<td>0.95 (0.21-4.31)</td>
<td>0.80 (0.16-3.98)</td>
<td></td>
</tr>
<tr>
<td>Metabolic disorders</td>
<td>3.0</td>
<td>3.3 (0.39-2.02)</td>
<td>1.33 (0.50-3.56)</td>
<td></td>
</tr>
<tr>
<td>Disorders of the immune system</td>
<td>0.1</td>
<td>0.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diseases of the blood</td>
<td>1.6</td>
<td>0.5 (0.44-24.84)</td>
<td>4.60 (0.56-37.84)</td>
<td></td>
</tr>
<tr>
<td>Mental disorders</td>
<td>0.5</td>
<td>0.5 (0.12-8.65)</td>
<td>0.84 (0.09-8.36)</td>
<td></td>
</tr>
<tr>
<td>Epilepsy, seizures, and convulsions</td>
<td>3.1</td>
<td>3.8 (0.38-1.77)</td>
<td>0.89 (0.38-2.07)</td>
<td></td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>5.3</td>
<td>7.1 (0.40-1.29)</td>
<td>0.70 (0.36-1.37)</td>
<td></td>
</tr>
<tr>
<td>Nephritis</td>
<td>3.5</td>
<td>5.7 (0.31-1.17)</td>
<td>0.62 (0.29-1.30)</td>
<td></td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>7.0</td>
<td>7.1 (0.55-1.73)</td>
<td>0.96 (0.52-1.78)</td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td>1.2</td>
<td>1.0 (0.30-5.73)</td>
<td>1.62 (0.34-7.77)</td>
<td></td>
</tr>
<tr>
<td>Other serious illness</td>
<td>2.1</td>
<td>1.4 (0.45-5.02)</td>
<td>1.66 (0.45-6.14)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category</th>
<th>OR</th>
<th>95% CI</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic rhinitis‡‡</td>
<td>0.3</td>
<td>0.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Asthma</td>
<td>5.4</td>
<td>6.7 (0.44-1.46)</td>
<td>0.89 (0.46-1.75)</td>
<td></td>
</tr>
<tr>
<td>Dermatitis</td>
<td>4.4</td>
<td>3.3 (0.61-3.01)</td>
<td>1.72 (0.72-4.14)</td>
<td></td>
</tr>
</tbody>
</table>

Autoimmune diseases

<table>
<thead>
<tr>
<th>Category</th>
<th>OR</th>
<th>95% CI</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>1.3</td>
<td>1.43 (0.27-3.19)</td>
<td>0.77 (0.21-2.83)</td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>0.0</td>
<td>0.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bell’s palsy</td>
<td>0.3</td>
<td>0.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Guillain-Barré Syndrome</td>
<td>0.0</td>
<td>0.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Juvenile Arthritis</td>
<td>1.9</td>
<td>3.8 (0.22-1.10)</td>
<td>0.58 (0.24-1.41)</td>
<td></td>
</tr>
<tr>
<td>Systemic Lupus</td>
<td>0.0</td>
<td>0.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Systemic Lupus</td>
<td>0.0</td>
<td>0.0</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Risk factors for autoimmune diseases

<table>
<thead>
<tr>
<th>Category</th>
<th>OR</th>
<th>95% CI</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytomegalovirus</td>
<td>0.0</td>
<td>0.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Epstein-Barr virus‡‡</td>
<td>0.3</td>
<td>0.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>0.0</td>
<td>0.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Influenza</td>
<td>15.9</td>
<td>13.3 (0.80-1.88)</td>
<td>1.26 (0.80-1.97)</td>
<td></td>
</tr>
<tr>
<td>Mycoplasma pneumonia‡‡</td>
<td>0.1</td>
<td>0.0</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

OR = Odds Ratio; CI = Confidence Interval; SD = Standard deviation; MMR = Measles, mumps and rubella
* Expressed as percentages (%) unless otherwise indicated
† Adjusted for all characteristics listed in table as well as campaign year
‡ Missing because postal code in RPDB was either incorrect or unavailable
‡‡ The adjusted odds ratio for this variable was determined post-hoc using a regression analysis that included all listed characteristics except previous immunization against MMR, meningococcal C, and hepatitis B.

**DISCUSSION**

Only 57% of eligible girls in KFL&A received the first dose of the HPV vaccine and less than half (48%) received all three recommended doses. Although vaccine uptake increased significantly between the first two years of Ontario’s HPV immunization program, the absolute increase was small and uptake remains far below that needed to
make this program cost-effective. The factor most strongly associated with HPV vaccine use was a prior history of vaccine acceptance, particularly a history of having received all three vaccines. A low family income was associated with non-adherence, but not uptake.

This is the first study to report on the patterns of use of the HPV vaccine and generate hypotheses about the determinants of vaccine uptake and adherence using a population-based approach. In particular, record linkage of the province’s administrative health and immunization databases permitted the ascertainment of objective information on medical, vaccination, and demographic status girls eligible for the publicly funded HPV vaccination program. Importantly, these data allowed us to explore the potential influence of clinical characteristics, such as medical history and health services utilization, which have never before been considered in this context.

Perhaps the most important finding of this study is that vaccinated and unvaccinated girls differed dramatically on vaccination history, whereby those who received the HPV vaccine were two to three times more likely to have also received the MMR, meningococcal C, or hepatitis B vaccines. In other words, it appears prior vaccine use is an important determinant HPV vaccine uptake. These findings are consistent with survey data that indicate that parental attitudes and beliefs about vaccines in general predict their attitudes toward the HPV vaccine. Nevertheless, the level of uptake of the HPV vaccine in our study is still well below that of other optional vaccines given at a similar age (i.e., meningococcal C and hepatitis B). This suggests that attitudes toward vaccination in general are not sufficient to explain the low uptake of the HPV vaccine in Ontario. Indeed, previous surveys on parental acceptance of the HPV vaccine have shown that concerns about its safety, long-term effects, and a negative influence on sexual
behaviour are also significant predictors of the HPV vaccine avoidance. Future studies will need to consider all of these factors simultaneously.

The propensity to avail of publicly funded vaccination programs is a health behaviour that likely reflects certain health beliefs and attitudes. Although our use of administrative databases limited our ability to evaluate health beliefs and attitudes directly, we were able to explore the influence of these factors on uptake and adherence by using individuals’ history of health services utilization. This relationship was not statistically significant for uptake or adherence; however, there was a trend toward decreased uptake with an increasing number of hospitalizations. Since admission to a hospital is a medical decision, high service utilization is likely an indicator of the presence of serious health conditions. In that sense, these results indicate that parents with sicker children may be less likely to consent to vaccination for their daughters. Consequently, it will also be important to assess the safety of the HPV vaccine in such populations. We also assessed the influence of individual previous diagnoses and pre-existing health conditions on the decision to immunize against HPV and, again, found no statistically significant relationships. Notably, however, we had limited power to assess the influence of health services utilization and medical history given the general good health of this age group.

We also examined factors that influence adherence to the three-dose schedule of the quadrivalent HPV vaccine. In general, non-adherers represent individuals who agree to receive the vaccine but subsequently decide against further immunization or are absent during a school clinic and neglect to go to their LPHA to obtain their missed dose. Since non-adherers may not acquire the full benefits of HPV immunization, it is important for
public health decision makers to consider vaccine adherence in the planning and delivery of HPV immunization programs.

Adherence was high in our study population. This likely reflects the convenience of a school-based program, where a student need only be present at school to receive a dose of the vaccine. In fact, among non-adherers, girls were over three times more likely to receive two doses of the HPV vaccine than only one. This patterns suggests that lack of adherence may be attributable to circumstance rather than a change in opinion about vaccination. It also draws attention to the fact that school absenteeism may be an important predictor of adherence.

The results of our study also suggest that both income and place of residence are associated with adherence. In particular, those in the lowest income quintile were the least likely to receive all three doses of the vaccine. These results are not surprising given that low income has been consistently associated with poor school attendance.\textsuperscript{25-27} Nevertheless, these results are important given that rates of cervical cancer screening tend to lower among low-income individuals\textsuperscript{28,29} and cervical cancer incidence and mortality tend to be higher.\textsuperscript{30,31} Since individuals of low income have increased need for protection against HPV infections, low adherence among these individuals could have important public health ramifications.

As with most studies utilizing administrative databases, an important limitation of our study relates to the quality of the data available from Ontario’s administrative databases. While this study benefits from the use of validated exposure data, the accuracy of the covariates data has not yet been assessed. In addition, data on clinical history is based on health services provided in Ontario only. As such, the clinical history of girls
who were not born in Ontario may be incomplete. Since such errors are likely to be independent of vaccination history, they should result in non-differential misclassification, thus biasing the results toward the null. Consequently, it is necessary to interpret our null findings with due caution.

Another limitation is that, since the IRIS database does not include information on school grade, the cohort was based on birth year. Consequently, some girls who were eligible were not included in the cohort (e.g., a girl born in 1996 who advanced one school grade). Of concern, however, are instances in which a girl was included in the cohort but was not eligible for publicly funded HPV vaccination, such is the case with girls born in 1995 who had been held back a year (i.e., were in Grade 7 in 2008/09) and girls born in 1994 who had been advanced a year (i.e., were in Grade 9 in 2007/08). With respect to the latter, since the girls would have had the opportunity to avail of the publicly funded program in the following year (2009/10), it is unlikely they would have invested $400 in order to receive the vaccine one year early. Consequently, the resulting level of misclassification from this source of error is expected to be low. With respect to the former, however, since these girls would never be eligible for the publicly funded program, it is possible they would have chosen to receive the vaccine at their own expense. Such girls would be incorrectly classified as unvaccinated in our study thereby diluting differences between the groups being compared. Given the small proportion of students who advance a school grade, this source of exposure misclassification is expected to be negligible.

Given the limitations of administrative data, we were not able to include factors that have previously been identified as predictors of HPV vaccine avoidance, such as such
as concerns about the safety and long-term effects, moral concerns about the impact on sexual behaviour, low perceived risk, and lack of knowledge about HPV.\textsuperscript{20,23}

In addition, there may be other factors, not yet studied, that are determinants of HPV vaccine uptake and/or adherence. Since the adjusted analysis only included socio-demographic and clinical characteristics, it is possible that the results were influenced by residual confounding.

KFL&A represents a medium sized health region. In addition, the vast majority of information about the HPV vaccine is disseminated from the Ontario government or from the media, rather than from individual LPHAs. Therefore, it is likely that the results of this study can be applied to other regions of the province. Nevertheless, the generalizability of our findings needs to be assessed.

CONCLUSION

The current low rate of HPV vaccine uptake in Ontario will likely have important implications in terms of the cost-effectiveness and health benefits of the publicly funded program. Our findings suggest that previous vaccination is the greatest predictor of subsequent HPV vaccine uptake, indicating that health beliefs play a central role HPV vaccine uptake. Conversely, socio-demographics appear to be to be important to consider in efforts to maximize vaccine adherence. These relationships need to be verified in larger cohorts using techniques that identify significant determinants of HPV vaccine uptake and adherence.
4.3 References


CHAPTER 5: THE RISK OF AUTOIMMUNE DISEASES FOLLOWING HPV VACCINATION
5.1 Preface to the manuscript

This chapter contains the second of two manuscripts of this thesis addressing the use and safety of the HPV vaccine in KFL&A. The focus of this manuscript is on the potential adverse effects of the HPV vaccine.

As previously discussed, low uptake of the HPV vaccine in Ontario has been partly attributed to safety concerns among parents who feel they have insufficient information to consent to vaccination for their daughters.

Manuscript 1 confirmed that there are important differences between vaccinated and unvaccinated girls with regards to previous vaccination history, a proxy for vaccination avoidance or acceptance. If the factors that explain vaccination avoidance are also risk factors for the adverse outcomes being studied then the results of a traditional cohort analysis comparing vaccinated and unvaccinated girls would be confounded. For this reason, the safety analysis of the following manuscript was executed using a self-matched approach that intrinsically controls for all individual-level, time-fixed confounders.

As discussed in Chapter 2, autoimmune diseases were selected as the study endpoints due to their potentially devastating effects and because they have been associated with other vaccines. In this thesis cohort, juvenile arthritis was the only autoimmune disease for which there were sufficient cases to permit further analyses. As such, the following manuscript is based solely on this condition.
5.2 The risk of juvenile arthritis following quadrivalent HPV vaccination in Grade 8 girls: a population-based cohort study

ABSTRACT

Background: The incidence of juvenile arthritis is high in age groups targeted by the HPV immunization recommendations of national advisory committees and public health vaccination programs. While this condition has been associated with other vaccines, it has yet to be studied in relation to the HPV vaccine. Given the escalating controversy about the safety of the HPV vaccine in young girls, we evaluated the risk of juvenile arthritis following quadrivalent HPV vaccination in Grade 8 girls.

Methods: We identified a cohort of all girls eligible for Ontario’s Grade 8 HPV vaccination program between 2007 and 2009 residing in Kingston, Frontenac, Lennox, and Addington (KFL&A). Using Ontario immunization and health databases, we identified dates of HPV vaccination and diagnoses of juvenile arthritis. Using a self-matched, case only approach, we estimated the rate ratio of juvenile arthritis 60 days following a dose of the HPV vaccine, adjusted for age. Secondarily, to assess the potential of time-varying risk, the primary risk period was divided into smaller, contiguous periods.

Results: HPV vaccination was associated with a greater than four-fold increase in the risk of juvenile arthritis 60 days following administration of a dose (RR 4.33; 95% CI 1.36-13.73). The risk was inestimable between days 1 and 7 (no cases), increased two-fold between days 8 and 21 (RR 2.03, 95% CI 0.44-9.27), increased four-fold between days 22
and 60 (RR 4.06, 95% CI 1.36-12.1), and returned to baseline between days 61 and 100 (RR 1.00, 95% CI 0.27-3.68).

Conclusions: These results provide new evidence of an increased risk of juvenile arthritis following quadrivalent HPV vaccination in girls aged approximately 13-15 years. These findings require confirmation in a larger cohort.
INTRODUCTION

The quadrivalent human papillomavirus (HPV) vaccine is designed to prevent infections with strains of HPV that cause 70% of cervical cancers\(^1\) and 90% of genital warts.\(^2\) In 2006, this vaccine was approved for use in females aged 9-26 years in Canada and the United States (US).\(^3,4\) Currently, national advisory committees recommend that girls be immunized between the ages of 9-13 in Canada and 11-12 in the US; that is, before the onset of sexual activity.\(^5,6\)

Although reports from randomized control trials of the HPV vaccine suggest the vaccine is safe and effective,\(^7\) the vaccine’s licensure was met with heated debate about the adequacy of this evidence, particularly with respect to safety.\(^8\) The controversy escalated with case reports of adverse events experienced following HPV vaccination and, not surprisingly, some parents were reluctant to consent to immunization for their daughters.\(^8,9\) Indeed, even individuals who support HPV vaccination have identified safety as an important concern.\(^10-12\)

In the face of public reservation, regulatory bodies and pharmaceutical companies maintain that the quadrivalent HPV vaccine is safe and effective and that its benefits outweigh any harms. Nevertheless, concerns about safety are supported by evidence that published trials have been limited in their ability (i.e., \(<80\%\) power) to detect serious adverse events putatively associated with the vaccine.\(^13\) In addition, the average age of girls in these trials was 20 years and less than 5% were under the age of 16. This is particularly important given the qualitative and quantitative differences in immune function and response that exist between children and adults and the state of heightened immunity among adolescent girls.\(^14-16\) In fact, a study comparing the immunogenicity of
the HPV vaccine in children aged 10-15 years to that of women aged 16-23 years found the immune response to be 1.7-2.7 times higher among the younger participants.\textsuperscript{17} Since the vaccine appears to be more immunogenic in children, it may also be more likely to cause immune-mediated adverse effects in this age group.

Juvenile arthritis (JA) is the most common rheumatic condition in children, with a reported prevalence of 7 to 401 per 100,000 children and annual incidence of 0.8 to 22.6 per 100,000 person-years.\textsuperscript{18,19} The risk is particularly high among females aged 9-16 years.\textsuperscript{20} The major symptom of JA is immune-mediated joint inflammation that, if not treated early and aggressively enough, can have devastating effects that last a lifetime. Potential consequences of this condition include growth disturbances, joint deformities, and significant delays in gross and fine motor skills.\textsuperscript{21} While arthritis has been associated with a number of vaccines,\textsuperscript{22} it has never been studied in relation to the newly licensed HPV vaccine. Given the increased risk of JA in the younger age groups targeted by the HPV immunization recommendations of national advisory committees and public health vaccination programs, as well as the potentially heightened immunogenicity of the vaccine in this age group, it is a relationship that merits consideration.

We undertook a population-based, retrospective cohort study to evaluate the risk of JA associated with the use of the quadrivalent HPV vaccine.

**METHODS**

**Ontario’s Grade 8 HPV vaccination program**

In March 2007, the Canadian government allocated $300 million to provinces and territories on a per-capita basis to provide free HPV immunization to young girls.\textsuperscript{23} By
September of that year, Canada’s most populous province, Ontario, had implemented a three-year, $117 million program aimed at offering the quadrivalent HPV vaccine free of charge to all Grade 8 girls in the province. Ontario’s HPV vaccination program is delivered by each of the 36 local public health agencies (LPHAs) as a school-based initiative and funds all three recommended doses of the vaccine. These doses are typically administered by public health nurses in September/October, November/December, and March/April of each school year. Eligible girls are also able to obtain the vaccine at their LPHA or through their family physician. Girls have until the end of August of their Grade 8 year to start their dosing regimen under the publicly funded program.

**Study Population and Data Sources**

We identified a population-based cohort of girls eligible for Ontario’s publicly funded HPV vaccination program in the Kingston, Frontenac, Lennox, and Addington (KFL&A) health region using the computerized administrative health and immunization databases of Ontario, Canada. The administrative health databases were developed to maintain records on the universal health care programs offered to residents of the province. In this study, we used the: (1) Registered Persons Database (RPDB) for information on socio-demographics and health insurance coverage, (2) Canadian Institute for Health Information’s (CIHI) Discharge Abstract Database (DAD) for information on hospitalizations, (3) National Ambulatory Care Reporting System (NACRS) database for information on emergency department visits, and (4) Ontario Health Insurance Plan (OHIP) database for information on physician services. These databases, described elsewhere in detail, have been used extensively in health research, including in post-
marketing evaluations of drug and vaccine safety.\textsuperscript{30,31,32} In addition, we used the Immunization Recording Information System (IRIS) database for information on immunization. The IRIS databases, maintained by individual LPHAs, were developed by the Ontario Ministry of Health and Long-Term Care (MOHLTC) to track and record immunizations of school-aged children.\textsuperscript{33} As a result, they contain individual-level information on all HPV vaccine doses administered through the publicly funded program. A recent re-abstraction study demonstrated that the KFL&A IRIS database captured individual girls’ HPV vaccination status with high sensitivity (99.8%; 95% CI 99.3-99.9) and specificity (97.7%; 95% CI 96.3-98.7).\textsuperscript{34} The results for dates of vaccination were equally good. Residents of Ontario are represented in each of these databases by a unique encrypted identifier, thus permitting complete record linkage at the level of the individual across databases and across time.

This study was approved by Queen’s University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board.

**Study Design**

We conducted a population-based, retrospective cohort study that was analyzed using a self-matched, case-only approach. The cohort consisted of girls eligible for Ontario’s Grade 8 HPV vaccination program in the 2007-08 and 2008-09 school years. Because school grade is not available in the administrative databases, we identified the cohort based on birth year, selecting all girls born in 1994 and 1995 residing in KFL&A on September 1\textsuperscript{st} of 2007 and 2008, respectively. The study cohort was restricted to the KFL&A health unit because their immunization database was readily available to study
investigators. We followed cohort members from September 1st of their Grade 8 school year (cohort entry) until the first of: date of death or December 31st of the following year (end of follow-up).

**HPV Vaccine Exposure**

All doses of the quadrivalent HPV vaccine administered during follow-up were identified using the KFL&A IRIS database. The dates of administration of individual doses were used to identify the start of pre-specified periods of follow-up time during which an individual was considered at increased risk of juvenile arthritis (i.e., etiologically exposed person-time). These time periods are herein referred to as **exposure risk periods**. The duration of these periods was based on the purported mechanism of adverse effect (i.e., hyperactivation of the immune system), the timing of post-vaccination autoimmune disease reactions reported to the Vaccine Adverse Events Reporting System (VAERS), and previous studies of autoimmune diseases following vaccination. Unexposed person-time was all follow-up that did not fall within an exposure risk period (Figure 3.1).

**Study End Point**

The case-defining event was a first-ever diagnosis of arthritis [International Classification of Diseases, tenth revision (ICD-10), code M08; OHIP fee-for-service medical claims codes 711, 714, 715] occurring during study follow-up. As such, girls with a diagnosis of juvenile arthritis any time prior to cohort entry were excluded from
the analysis. The DAD, NACRS, and OHIP databases were used to identify the study end point.

**Statistical Analysis**

Cohort data are typically analyzed using time-to-event Cox Proportional Hazards regression. However, since little is known about the factors that influence HPV vaccine uptake or avoidance in the Ontario Grade 8 population, the traditional time-to-event analysis may be susceptible to confounding bias. Consequently, we used a self-matched analysis known as the self-controlled case series method, or case series for short, to assess the risk of juvenile arthritis associated with the use of the quadrivalent HPV vaccine. This method, described by Farrington, Whitaker, and colleagues,\(^\text{36-39}\) was developed specifically for the post-marketing evaluation of adverse effects following immunization. Some of the defining features of the case series are that it uses only data on cases (i.e., patients who experience the study end point) and it does not censor follow-up after an event. Rate ratios are estimated by comparing the event rate during exposed person-time (exposure risk periods) with that during unexposed time for the same individual. A major advantage of this method is that, since estimation is within an individual, it inherently controls for all individual-level, time-independent confounders (e.g., health beliefs, health behaviours, genetic predisposition). As a result, the case series is particularly useful when confounders are either unknown or unmeasured, as was likely the case in our study. In addition, since the case series is derived from the cohort model, it is possible to control for time effects such as age and seasonality by dividing the follow up time into appropriate person-time strata.
The primary analysis was based on an exposure risk period of 60 days following vaccination, beginning on the day after each dose of the vaccine was received (day 1), to ensure that the exposure preceded the event and ending 60 days later (day 60). To account for the possibility of residual confounding by age, we further divided person-time of follow up into two age groups, <14 years and ≥14 years, approximately the mid-point age during study follow-up. We also assessed the potential for time-varying risk by dividing each exposure risk period into smaller, consecutive time slices (Table 5.2). Incidence rate ratios (RRs) and 95% confidence intervals (CIs) were estimated using conditional Poisson regression to account for the individual level matching.

A number of assumptions had to be made for the primary analysis. To test the robustness of our findings under these assumptions, we repeated the primary analysis by first extending the exposure risk period to 100 days to account for the possibility of delayed diagnoses, second by including the day of vaccination (day 0) in the exposure risk period (days 0-59), third by removing the control for age effects, and finally by censoring follow up after the event date.

Role of the Funding Source

KFL&A Public Health funded this study and had no role in its design, conduct, or reporting.

RESULTS

The cohort consisted of 2519 girls (Figure 4.1) with a mean age of 13.2 years (range =12.7-13.6) at cohort entry. All girls were followed for a total of 16 months (the
duration of the study) since no deaths occurred during follow up. During this time, 56.6% (n=1425) received at least one dose of the quadrivalent HPV vaccine and were classified as vaccinated, while 43.3% (n=1094) were unvaccinated.

Vaccinated and unvaccinated girls were similar with respect to socio-demographic characteristics, history of health services utilization, and medical history (Table 4.2). Conversely, there was a significant difference in vaccination history between groups, whereby vaccinated girls were more likely to have previously received the MMR (OR 3.21, 95% CI 2.25-4.57), meningococcal C (OR 2.16, 1.64-2.84), and hepatitis B vaccines (OR 2.86, 2.14-3.83).

Table 5.1  Rate ratio for Juvenile Arthritis following HPV vaccination

<table>
<thead>
<tr>
<th>Risk Window</th>
<th>Unadjusted RR (95% CI)</th>
<th>Adjusted* RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-60</td>
<td>3.89 (1.26-12.00)</td>
<td>4.33 (1.36-13.73)</td>
</tr>
<tr>
<td>1-7</td>
<td>-- †</td>
<td>-- †</td>
</tr>
<tr>
<td>8-21</td>
<td>1.98 (0.44-8.89)</td>
<td>2.03 (0.44-9.27)</td>
</tr>
<tr>
<td>22-60</td>
<td>3.81 (1.30-11.15)</td>
<td>4.06 (1.36-12.1)</td>
</tr>
<tr>
<td>1-100</td>
<td>4.35 (1.11-16.92)</td>
<td>4.92 (1.25-19.37)</td>
</tr>
<tr>
<td>1-7</td>
<td>-- †</td>
<td>-- †</td>
</tr>
<tr>
<td>8-60</td>
<td>4.65 (1.50-14.29)</td>
<td>5.11 (1.62-16.11)</td>
</tr>
<tr>
<td>61-100</td>
<td>0.98 (0.27-3.59)</td>
<td>1.00 (0.27-3.68)</td>
</tr>
</tbody>
</table>

RR = Rate Ratio; CI = Confidence Interval
* Adjusted for age (<14 years and ≥14)
† RR inestimable because no cases were observed during that time period

During study follow-up, we identified 17 new cases of arthritis, all of which were identified from the physicians’ claims database (OHIP). Of the 17 cases, 12 received three doses of the HPV vaccine, two received two doses, and three did not receive any. The timing of events relative to study follow-up is depicted in Figure 5.1.
Immunization with the quadrivalent HPV vaccine was associated with a greater than four-fold increase in the risk of arthritis in the 60 days following a dose (RR 4.33, 95% CI 1.36-13.73). The risk appeared to vary over time, being inestimable between days 1 and 7 because of an absence of cases, and indicating a two-fold increase between days 8 and 21 (2 cases; RR 2.03, 95% CI 0.44-9.27) and a four-fold increase between days 22 and 60 (4 cases; RR 4.06, 95% CI 1.36-12.1) (Table 5.1).

The results of the primary analyses were essentially unchanged by the various sensitivity analyses. For example, extending the exposure risk window to 100 days yielded an overall rate ratio of 4.92 (95% CI 1.25-19.37) compared with 4.33 (95% CI 1.36-13.73) in the primary analysis. This was due to the fact that the risk was not increased between days 61-100 (RR=1.00, 95% CI 0.27-3.68). Similarly, the results were unaffected by starting the exposure risk period on the day of vaccination (day 0) or by censoring follow-up post-events.

---

**Figure 5.1** Schematic of the frequency and timing of events relative to study follow-up

Vaccinated girls are represented above the observation line, while unvaccinated girls are represented below. An event is considered “exposed” if it occurs within during exposed person-time; otherwise it is considered “unexposed”.

Immunization with the quadrivalent HPV vaccine was associated with a greater than four-fold increase in the risk of arthritis in the 60 days following a dose (RR 4.33, 95% CI 1.36-13.73). The risk appeared to vary over time, being inestimable between days 1 and 7 because of an absence of cases, and indicating a two-fold increase between days 8 and 21 (2 cases; RR 2.03, 95% CI 0.44-9.27) and a four-fold increase between days 22 and 60 (4 cases; RR 4.06, 95% CI 1.36-12.1) (Table 5.1).

The results of the primary analyses were essentially unchanged by the various sensitivity analyses. For example, extending the exposure risk window to 100 days yielded an overall rate ratio of 4.92 (95% CI 1.25-19.37) compared with 4.33 (95% CI 1.36-13.73) in the primary analysis. This was due to the fact that the risk was not increased between days 61-100 (RR=1.00, 95% CI 0.27-3.68). Similarly, the results were unaffected by starting the exposure risk period on the day of vaccination (day 0) or by censoring follow-up post-events.
DISCUSSION

Our study provides population-based evidence that the quadrivalent HPV vaccine may be associated with a greater than four-fold increase in the risk of juvenile arthritis in girls between the ages of 13 and 15. The risk appears to double two to four weeks post-vaccination and double again over the ensuing five weeks (i.e., weeks 4-8 post-dose). The risk returned to baseline between weeks 9 and 14 post-vaccination. The pattern of risk we observed is consistent with the putative biologic mechanism for autoimmune diseases following vaccination as one would expect a delay before symptoms became apparent, an increase in likelihood to seek medical attention as they progress over the ensuing weeks, and a return to baseline within a few months.

This is the first study to identify a possible increased risk of JA following HPV immunization with the quadrivalent vaccine. Our results are consistent with other observational studies that have linked arthritis with vaccination, most commonly with the MMR and Hepatitis B vaccine,\(^ {22,40}\) neither of which were administered within our observation period. For example, one study assessed the incidence of joint manifestations (arthralgia or arthritis) following vaccination with the MMR vaccine in 2658 immunized and 2359 non-immunized children and found an increased risk within six weeks of vaccination (RR=1.60; 95% CI 1.20-2.10).\(^ {41}\) In addition, a case-control study conducted using VAERS data found that, compared with persons exposed to the tetanus vaccine (comparator group), adults receiving the Hepatitis B vaccine had significantly higher odds of developing arthritis (OR=2.01, 95% CI 1.3-3.1) and rheumatoid arthritis (OR=9.1, 95% CI 3.1-740).\(^ {42}\)
In contrast, some studies do not find significant associations between vaccination and arthritis.\textsuperscript{22,40} For instance, a study on the safety and efficacy of the Meningococcal C vaccine in patients with juvenile idiopathic arthritis reported that vaccination was not associated with relapse of the disease.\textsuperscript{43} There are a number of reasons as to why these findings are consistent with ours. First, the study assessed a different vaccine. Second, our study evaluated incident rather than prevalent cases of JA. Finally, the analysis was based on an exposure risk window of one month that, according to our analyses, may be misclassified.

Randomized controlled trials of the quadrivalent HPV vaccine published to date have not reported on the incidence of arthritis\textsuperscript{44-48} and only one has reported on joint manifestations.\textsuperscript{44} While these trials were underpowered to detect serious adverse events,\textsuperscript{13} two were nevertheless considerable larger than our cohort.\textsuperscript{44,45} It is unclear whether this represents an absence of cases of arthritis or a failure to report such cases as being attributable to the quadrivalent HPV vaccine. On one hand, selective reporting would not be surprising given was not an uncommon practice in these trials.\textsuperscript{49} On the other hand, since the vast majority of participants in the trials were over the age of 15 (>95%) and thus had a lower baseline risk of arthritis, the rates of immune-mediated adverse events observed in these trials may simply not be generalizable to adolescent girls.

Because the quadrivalent HPV vaccine is relatively new, few observational studies have been published to date on its safety, and none have assessed the risk of autoimmune diseases following vaccination. Brotherton et al.\textsuperscript{50}, however, studied a cohort of 114,000 women over the age of 14 to evaluate Australia’s school-based publicly funded quadrivalent HPV vaccination program. Based on the number of confirmed cases
of anaphylaxis, researchers estimated that the rate of anaphylaxis following administration of the HPV vaccine was 2.6 per 100,000 doses distributed, an estimated 2.6 to 26 times higher than the baseline rate. These findings suggest that the HPV vaccine may be more immunogenic than other vaccines and may therefore have a higher propensity to cause immune-mediated adverse reactions.

The Vaccine Adverse Events Reporting System (VAERS) is a passive surveillance system designed to detect signals of possible adverse events associated with vaccines licensed in the US. Between June 1, 2006 and December 31, 2008, there were 12,424 VAERS reports of adverse events following quadrivalent HPV vaccination in the US. Of the 51 reports of autoimmune diseases identified during that time, 13 were of rheumatoid arthritis (RA). These findings represent a rate of 0.05 reports of RA per 100,000 doses distributed or 0.15 per 100,000 persons (assuming a three dose regimen for all). While this is well below the baseline incidence of juvenile arthritis, passive surveillance systems are known to significantly underestimate the true rate of adverse outcomes.

This study has a number of important limitations that must be considered. First and foremost, the present analysis is based on only 17 cases, 14 of whom received the HPV vaccine. As a result, the findings must be interpreted with particular caution and require confirmation in a larger cohort.

Another major limitation to this study is that the codes used to identify the study endpoint have not been validated. Consequently, the code could represent a misdiagnosis or miscoding, or even a suspected rather than confirmed case of JA. We would expect such errors to occur equally between vaccinated and unvaccinated time periods; therefore,
any misclassification would be non-differential, biasing the results toward the null and resulting in an underestimation of the true risk of JA. Another limitation of the diagnostic codes we used is that they do not provide specific information about the presentation of the disease. Consequently, we cannot comment on the duration or severity of symptoms. In addition, we cannot determine with certainty the onset of the JA, which theoretically could have preceded vaccination.

While the immunization data used in our study has been previously validated, it is important to consider other sources of exposure misclassification. In particular, when a risk period is too long, too short, or inappropriately placed, it can lead to misclassification of exposure and bias results toward the null. However, the results of our sensitivity analysis using a 100 day exposure risk period demonstrates that the 60 day period we used for our primary analyses did not introduce misclassification bias.

It is also necessary to consider the possibility of detection bias in studies of adverse events following immunization since heightened awareness of possible harms, particularly with new and controversial vaccines, could lead a person to seek medical care more often following vaccination. It is possible that a cautious parent may be more likely to seek care for the aches and pains of her daughter if she suspects the vaccine may be involved. However, given the nature of the symptoms of juvenile arthritis, it is unlikely that a girl would go undiagnosed for several months. Consequently, we would expect detection bias to affect the timing of the diagnosis rather than likelihood of diagnosis. The pattern of risk we observed, however, is consistent with the presumed clinical course, suggesting detection bias did not influence our results.
A major strength of this study is that we employed a self-matched approach, thereby eliminating confounding bias by time-independent factors. As a result, it is unlikely that long-standing factors like religious attitudes, genetic susceptibility, and health beliefs influenced our results. Although the possibility of residual confounding by time-dependent factors needs to be considered with a self-matched analysis, our use of a brief observation period (i.e., 16 months) and control of age effects in the analysis makes this unlikely. Of particular concern, we did not have information on influenza vaccination or influenza-like illness, both of which have been associated with autoimmune illnesses.13, 14 This is particularly important since the first two doses of the HPV vaccine may overlap with influenza vaccination. Although it is possible that influenza-like illness could overlap with the third dose of the HPV vaccine, it is less likely given that the dose is administered late in the influenza season (April-August). Since the majority of our exposed events (4/8) were observed following the third dose, our results speak against the likelihood of bias by influenza vaccination or influenza-like illness. Nevertheless, future studies are needed to model these time-dependent factors as potential confounders.

Given that we studied girls at an age when girls are both at increased risk of autoimmune diseases (such as juvenile arthritis) and undergoing immune system changes, our results may not be generalizable to girls of different ages. However, our study should be replicated in different age groups to determine if this is an age-dependent risk, as it may be possible to mitigate the risk by targeting a different age group for vaccination.

It is important to remember that not getting vaccinated also carries a risk – the risk of developing an HPV-related illness like genital warts or cervical dysplasia. The results of two randomized efficacy trials of the quadrivalent HPV vaccine indicates that, when
given as indicated, this vaccine provides sustained protection against grade 1 cervical, vulvar, and vaginal intraepithelial neoplasia and anogenital condylomas related to HPV types (6, 11, 16, and 18) through 42 months of follow-up. In addition, a recent observational study suggests that the vaccine decreases the incidence of genital warts in women. Unfortunately, however, it will be years before we know the vaccine’s impact on the burden of cervical cancer and cervical cancer mortality. Ultimately, the risk-benefit ratio of the quadrivalent HPV vaccine depends on whether it reduces the risk of cervical cancer and its overall side effect profile when used in the real world. Nevertheless, our study speaks to the importance of continuing to monitor the safety of the quadrivalent HPV vaccine using a population-based approach.

CONCLUSION

Our results provide new evidence of a possible increased risk of juvenile arthritis following quadrivalent HPV vaccination in girls aged approximately 13-15 years. The timing and pattern of risk observed is consistent with the putative biologic mechanism for autoimmune diseases following vaccination. Nevertheless, given the small sample size, these findings should be regarded as hypothesis generating and require confirmation in a larger study.
5.2 References


3. Health Canada. Summary basis of decision: GARSASIL Quadrivalent human papillomavirus (Types 6, 11, 16, 18) recombinant vaccine. 2007


CHAPTER 6: SUMMARY AND CONCLUSION
6.1 General Discussion

Surveillance of vaccine coverage and safety is critical to the success of any immunization program. It is widely recognized that an ideal way to achieve this goal is by linking records across immunization, population, and health databases. Nevertheless, the studies contained in this thesis are the first to evaluate use and safety of Ontario’s $117 million HPV vaccination program using a population-based approach. Our results speak to importance of assessing uptake and adherence at the provincial-level and confirm the need to monitor potential adverse effects of this vaccine when used in the real world.

An objective of the first study of this thesis was to evaluate vaccine coverage (uptake) in KFL&A, one of Ontario’s 36 health regions. We found that vaccine uptake in this region was higher than the provincial average, but was still well below the level needed to maximize the health benefits and cost-effectiveness of this vaccination program. The former may be attributable to the fact that the KFL&A Medical Officer of Health (Dr. Ian Gemmill) openly advocated for the vaccine and provided information sessions for parents; however, we do now yet know if these factors are related. An evaluation of Ontario’s HPV vaccination program carried out by the Ontario Agency for Health Protections and Promotion found there was a great deal of variability in endorsement of the program across health units. For example, 95% of LPHAs issued press releases, 64% paid for advertising, and 45% provided educational activities (e.g., parent information sessions). Uptake across the province has also been variable. It is important to determine whether the extra promotional efforts of any one LPHA actually improves uptake of the HPV vaccine, as it appears to have done in KFL&A. Moreover, it
is necessary to assess whether these efforts are worthwhile in terms of the time and cost they incur.

We also found that vaccine uptake in KFL&A increased significantly between the first and second campaign year, though the absolute increase was negligible. The lower uptake in the first year of the program has been attributed in part to the fact that the program’s launch coincided with a provincial election that imposed a ban on the promotion of provincially-funded programs. As such, the Ontario government was not permitted to endorse their initiative at the time it was implemented. Additionally, the time period between announcement (August 2007) and commencement (September 2007) of the program was extremely short, limiting the opportunity for individuals to seek information about the vaccine on their own. By the second campaign year, the Grade 8 HPV vaccination program was better known and information about the vaccine was readily accessible. As such, it is not surprising that uptake increased across years.

Although uptake of the HPV vaccine in KFL&A is relatively high and may be increasing, it is important to note that the rate of uptake was considerably lower than that in all other school-based HPV immunization programs in Canada.\(^4\) Moreover, uptake of the HPV vaccine in Ontario was far lower than that of other vaccines, including the hepatitis B vaccine, which is offered in Grade 7 and is also optional.\(^5\) The lower uptake of the HPV vaccine suggests there are factors specific to the HPV vaccine that are contributing to its acceptance and avoidance. In particular, worries about the potential harms of the HPV vaccine have been cited as a reason for which parents are reluctant to consent to vaccination for their daughters. If for nothing else than to try and increase uptake of this poorly accepted vaccine, it is essential to address these safety concerns.
In order to validly evaluate the safety of the HPV vaccine, it is important to recognize the potential impact of confounding factors. In fact, research on sources of confounding bias in observational studies of vaccines has demonstrated that a number of social and medical characteristics associated with vaccine avoidance are also associated with an increased risk of adverse events. Although these factors are known to be difficult to identify and measure, failing to control for them may confound the relationship between vaccination and adverse outcomes. One of the goals of Manuscript 1 (section 4.2) was to get a sense of potential predictors of HPV vaccine uptake in this population, a necessary step in identifying factors related to both HPV vaccination (exposure) and autoimmune diseases (outcome). We observed no significant differences in socio-demographics, medical history, or health services utilization between groups, suggesting these factors would not confound the relationship. Nonetheless, when interpreting null results, it is important to consider the possible influence of non-differential misclassification. For example, we used neighbourhood income quintile as a proxy for household income. Some studies show that the variability between area-based income and household-level income can be large. Accordingly, the non-significant associations that we observed between vaccine uptake and income quintiles could be partly due to misclassified data and should be verified using more a more precise measure of income.

While vaccinated and unvaccinated girls appeared similar on a number of characteristics, there were also important differences with respect to a girl’s vaccination history, whereby those who received the HPV vaccine were significantly more likely to have also received other vaccines. This tendency seems to indicate general pro- and anti-vaccine attitudes among vaccinated and unvaccinated girls, respectively. These finding
are consistent with studies on predictors of HPV vaccine acceptance that show previous vaccine use predicts subsequent use of the HPV vaccine.\textsuperscript{8-10} Moreover, an evaluation of the Ontario HPV vaccination program reflects that anti-vaccine sentiments are in fact a concern with this program.\textsuperscript{3} Nevertheless, it does not appear that anti-vaccine attitudes alone are responsible for the low uptake. This is evidenced by the fact that uptake of the HPV vaccine among eligible girls is far lower than their uptake of other vaccines. To illustrate, hepatitis B and meningococcal C vaccines are optional vaccines that were offered to cohort members just one year before the HPV vaccine. As a result, we would expect the uptake of these three vaccines to be similar. However, our assessment demonstrates that HPV vaccine uptake was 25\% lower than the uptake of the hepatitis B vaccine and 23\% lower than the uptake of the meningococcal C vaccine. These results confirm there are likely factors specific to the HPV vaccine contributing to HPV vaccine avoidance.

HPV vaccine avoidance is important to consider further since it may reflect underlying beliefs that could not be captured using these administrative data. In fact, previous studies indicate that moral concerns about sexual behaviour, low perceived risk of HPV infection, and a lack of knowledge about HPV are among the factors that predict HPV vaccine avoidance.\textsuperscript{10,11} A major limitation of these studies, however, is that they were based on the intent to vaccinate rather than actual HPV vaccine receipt. Moreover, all used survey methods and were therefore subject to reporting and recall bias. Nevertheless, surveys are evidently valuable for providing information about factors like beliefs and values, which are largely unavailable in administrative databases. Given the strengths and limitations of both administrative and survey data, ideally these sources of
information should be linked in future studies to provide individual-level data that is as comprehensive and objective as possible. A complete understanding of all of the factors associated with HPV vaccine acceptance or avoidance is essential to address the low uptake observed in this thesis and identify potential modifications that can be made to future program delivery by public health officials to optimize use of the HPV vaccine.

It is equally important that researchers understand the factors that influence HPV vaccine exposure. If these factors are also determinants of autoimmune diseases (or other adverse events), they would be important sources of confounding that would need to be taken into account in either the design or analysis of observational studies of the effects of the HPV vaccine. Although the use of administrative data limited our ability to study a range of cohort characteristics, our findings nevertheless demonstrate that there are some important differences between vaccinated and unvaccinated girls that could confound the relationship between vaccine use and health outcomes. As such, traditional cohort and case-control methodologies should not be used to study the effects of this vaccine until their potential for confounding bias is assessed.

To address the potential for confounding bias, we employed a self-matched method for the safety analysis. As such, we eliminated the potential for confounding by individual-level, time-invariant factors. Using this method, we detected an important safety signal. In particular, we found that the risk of juvenile arthritis was four times higher within 60 days of a dose of the HPV vaccine than in other study periods. Moreover, the time-varying nature of this risk was consistent with putative biologic mechanisms. Specifically, this risk was high between days 8 and 21 post-vaccination, even stronger between days 22 and 60, and returned to baseline thereafter. The pattern of
these results are clinically intuitive since, if vaccination triggered the condition, we would expect symptoms to be unperceivable at onset and to intensify over time (inevitably reaching a level of severity that would warrant medical attention), and for the risk to eventually return to normal.

Given the controversy about the safety of the HPV vaccine, these findings could have important public health ramifications. Consequently, it is especially important to consider the various strengths and limitations of this analysis.

The most important limitation of the safety analysis is that it is based on only 17 cases. As such, these results must be interpreted with due caution. In particular, the analysis of the time-varying nature of the risk, based on an even fewer cases, yielded statistically unstable risk estimates (i.e., not statistically significant); thus our interpretation of these findings was based on the observed pattern of risk estimates and their biological and clinical plausibility rather than their statistical precision. In addition, we cannot rule out the possibility of a type 1 error. Although this is true of any study, whether experimental or observation, the possibility of any one study representing a type 1 error is greater when the number of events is small. It is therefore important that these results be confirmed in a larger study.

A major strength of this study is that, because it used administrative data sources, outcome and exposure data were collected prospectively for an entire population of unselected individuals. In addition, individual consent was not required. The resulting ‘all-inclusive’ nature of the study cohort left little to no potential for selection in bias. Another common source of selection bias in cohort studies pertains to losses to follow-up. Due to the type of data utilized in this study, losses to follow-up could only have occurred
as a result of termination of health care coverage (which occurs mainly as a result of emigration from Ontario) or death. Data on deaths is contained within the RPDB and is based on a number of sources (e.g., DAD, NACRS). No cohort members died during study follow-up. Unfortunately, we did not have reliable data on the end of health insurance coverage. However, given the young age of the study population, this source of loss to follow up is expected to be low. Consequently, losses to follow-up and any resulting bias are assumed to be negligible.

As with any study that utilizes administrative data, another potential source of bias pertains to the quality of these data. For one, the codes used to ascertain cases of juvenile arthritis have not been validated. Consequently, we cannot be absolutely certain that these codes represent a diagnosis of a confirmed case. Nevertheless, we would expect any errors due to misdiagnosis or miscoding to occur equally between vaccinated and unvaccinated person-time. As a result, such errors would bias the estimate toward the null and result in an underestimation of the true risk. Another limitation of using administrative data to ascertain outcomes is that they provide no direct information about the duration or severity of symptoms. In addition, we cannot determine with certainty the date of disease onset, which theoretically could have preceded vaccination.

The potential for misclassification of exposure must also be considered. For one, misclassification could also have arisen due to coding errors in vaccination status or vaccination dates. Fortunately, these types of errors are extremely uncommon in the validated KFL&A database and are therefore not a major cause of concern. Another important strength of the IRIS database is that, unlike prescription drugs for which agreement between filled prescriptions and biological exposure is unknown, the
immunization database captures information on actual administration of the vaccine by a public health nurse. Consequently, the immunization record captures true biological exposure. Accurate dates of exposure were particularly crucial to this analysis since “exposed time” in the case series is based on well-defined exposure risk periods, defined \textit{a priori}.

The possibility of detection bias also needs to be considered. Given parental concerns about the HPV vaccine’s safety and media reports questioning this vaccine’s safety, it is possible that girls are monitored more closely following vaccination than at other times. As a result, it is possible that a vaccinated girl experiencing joint pain or discomfort would be more likely to consult a healthcare provider if she had been recently vaccinated. In the same vein, physician diagnostic behaviours can be affected by knowledge of vaccination history. In both cases, the potential for detection bias would lead to an overestimation of the event’s relative incidence. However, juvenile arthritis is a condition for which symptoms are severe and persistent enough that it is unlikely that a young girl suffering from such symptoms would not eventually seek medical care. In addition, the diagnostic criteria for this condition are relatively standard and, in this population, there are few competing diagnoses to rule out. In either case, we would not expect true cases of this disease to go undetected for the duration of the study. Our observed estimates also speak against the presence of detection bias. Conceptually, if a symptom that was temporally associated with the HPV vaccine was more likely to prompt medical care and/or diagnosis than symptoms that presented in the absence of vaccination, one would expect to observe an early risk. On the contrary, we observed no cases in the week following immunization and an increased risk in later time periods.
Moreover, since the association between any vaccination and juvenile arthritis is not well known to family physicians, the primary source of diagnosis in our study, this source of detection bias is also unlikely.

A major strength of the safety analysis is that we employed a self-matched analysis, thereby eliminating confounding by time-independent factors. As a result, we can be relatively confident that long-standing factors like religious and health beliefs, attitudes towards vaccines, and genetic susceptibility did not bias the results. In addition, follow-up time was limited to 16 months, minimizing the potential influence of time-dependent factors (i.e., time effects). Nevertheless, the possibility of residual confounding by time-dependent factors must be addressed. Of particular concern, we did not have information on influenza vaccination or influenza-like illness, both of which have been associated with autoimmune illnesses.\textsuperscript{13, 14} This is especially important since the first two doses of the HPV vaccine may overlap with influenza vaccination. On the other hand, the majority of our exposed events were observed following the third dose (administered between April and August), by which time rates of influenza immunization and influenza-like illness are relatively low.\textsuperscript{15} Although our results speak against bias by influenza vaccination or influenza-like illness, future studies are needed to model these as potential confounders. Moreover, we cannot rule out the possibility that unknown time-dependent confounders may have biased our results. Again, this raises the need for further investigation of factors that could influence HPV vaccination and the risk of adverse events following immunization.

While there are undoubtedly concerns about detection bias, small sample size, and the use of unvalidated outcomes data, this thesis benefits from validated vaccination data
that represents true biologic exposure. In addition, selection and confounding biases, which are often problematic in pharmacoepidemiology studies, were minimal to non-existent given the use of population-based data, the all-inclusive nature of the study population, and the choice of a self-matched analysis. Consequently, at a time when there is limited evidence about the potential harms associated with use of the HPV vaccine in pre-adolescent girls, this thesis contributes valuable real-world information about this issue.

Importantly, this thesis demonstrates the value of using readily available data to address pressing public health questions. However, this thesis was based on only one of Ontario’s health regions. Studying HPV vaccine use would be much more informative if we could compare results across health units. Similarly, the safety analysis would be more revealing if it were based on all girls eligible for Ontario’s program. Unfortunately, Ontario’s immunization databases are currently maintained by each of the 36 local public health agencies. If these data were centralized, they could be easily linked with population-based health and demographic databases, like those available through ICES, to create a pro-active, provincial immunization surveillance system. A database of this magnitude would be comprehensive enough to evaluate vaccine coverage and powerful enough to assess safety. Ultimately, such data could also be used to determine the cost-effectiveness and health benefits of the HPV immunization program. As it stands, researchers are limited in their ability to evaluate Ontario’s costly HPV immunization program. Similarly, it would be challenging to consolidate health and immunization data across Canada, making it extremely difficult to execute the cross-provincial comparisons. Such studies are especially important to assess the health impact of the differences
between Canadian HPV immunization programs, including differences in the number and schedule of doses administered and the targeted age groups. For example, only two doses of the vaccine are administered in Quebec. In addition, the target age group of HPV immunization programs varies across the country, ranging from girls in Grade 4 to Grade 9. Studies are needed to determine any age-effects in terms of safety and efficacy of this vaccine.

Despite the limitations of the safety analysis, the results highlight a potential safety concern. As such, they confirm the need for continued monitoring of the effects of this vaccine using a population-based approach. It is also important to note that although no cases of Guillain-Barré syndrome, multiple sclerosis, systemic lupus erythematosus, and Bell’s palsy, and few cases of type 1 diabetes were observed in this study, our sample size was not sufficiently large to study such important events. Given these autoimmune conditions have been temporally linked to the use of other vaccines, they require further study. In order to properly address safety concerns in a timely and effective manner, an active surveillance system of adverse events is needed.

It is important to remember that any adverse events detected must be considered in the context of the benefits of HPV vaccination. The results of two randomized efficacy trials of the quadrivalent HPV vaccine demonstrated that, when given as indicated, the vaccine provided sustained protection against grade 1 cervical, vulvar, and vaginal intraepithelial neoplasia and anogenital condylomas related to HPV types (6, 11, 16, and 18) through 42 months of follow-up. In addition, a recent Australian study reported a decrease in the incidence of genital warts since the implementation of their HPV vaccination program.
Ultimately, each individual is responsible for weighing the risks and benefits of the HPV vaccine for themselves. Unfortunately, it will be years before we know if this vaccine will have a positive impact on the burden of cervical cancer and cervical cancer mortality. Moreover, the vaccine’s safety profile is currently incomplete. Without accurate and comprehensive information about efficacy and safety, an individual’s ability to provide ‘informed consent’ is restricted. Providers of this vaccine therefore have an ethical responsibility to continue monitoring the vaccine’s effects in the real world and to disseminate this information to the public in real-time.

HPV vaccine providers also require accurate, up-to-date information about the safety and use of this vaccine for their own program development. In particular, the Ontario government invested $117 million dollars in its three-year HPV immunization program. However, at the current level of uptake, it is unlikely the program is cost-effective or will confer the expected health benefits to the population. Given the paucity of harms-related information for young girls, it is not surprising that safety concerns continue to be an important barrier to vaccine uptake. In this thesis, we detected an important safety signal, indicating the safety of the vaccine in this population needs to be further evaluated. In addition, this thesis provides evidence that there are other important determinants of HPV vaccine uptake and adherence that need to be considered in efforts to improve vaccine use. Since use and safety are key factors in determining and improving the overall health impact and cost-effectiveness of Ontario’s HPV vaccination program, they are issues that need to be addressed at the provincial-level in future studies.
6.2 References


BIBLIOGRAPHY


Beagley KW, Gockel CM. Regulation of innate and adaptive immunity by the female sex hormones oestradiol and progesterone. FEMS Immunology and Medical Microbiology 2003;38:13-22.


Health Canada. Summary basis of decision: GARSASIL Quadrivalent human papillomavirus (Types 6, 11, 16, 18) recombinant vaccine. 2007.


Improving health care data in Ontario. ICES investigative report. Toronto: Institute for Clinical Evaluative Sciences, 2005


Iron K. Moving toward a better health data system for Ontario. Toronto: Institute for Clinical Evaluative Sciences, 2006


Smeeth L, Donnan PT, Cook DG. The use of primary care databases: Case-control and case-only designs. Family Practice 2006;23:597-604.


APPENDICES
Appendix I  Ethics Approval

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING
HOSPITALS RESEARCH ETHICS BOARD

October 1, 2009

This Ethics Application was subject to:
☐ Full Board Review
☐ Meeting Date:
☒ Expedited Review

Dr. Linda Lévesque
Department of Community Health & Epidemiology
PHRED Unit
KFL&A Public Health
221 Portsmouth Avenue
Kingston, ON  K7M 1V5

Dear Dr. Lévesque,

Study Title:  The Short-Term Safety of the Quadrivalent HPV Vaccine in Grade 8 Girls:
The Ontario Cohort Study
Co-Investigators:  Ms. Leah Smith

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 list 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. (see
http://www.queensu.ca/vpr/reb.htm).

➢ 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.

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

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

Yours sincerely,

[Signature]
Chair, Research Ethics Board

Oct 1, 2009

ORIGINAL TO INVESTIGATOR - COPY TO DEPARTMENT HEAD - COPY TO HOSPITAL(S) / P&T (if appropriate) - FILE COPY

Study Code: EPID-298-09

➢ 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
### Appendix II  Diagnoses and corresponding diagnostic codes for baseline medical history

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>ICD-9 code</th>
<th>ICD-10 code</th>
<th>OHIP code</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Previous Diagnoses</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infectious and parasitic diseases</td>
<td>001-139</td>
<td>A00-B99</td>
<td></td>
</tr>
<tr>
<td>Intestinal infections</td>
<td>008-009</td>
<td>A08-A09</td>
<td></td>
</tr>
<tr>
<td>Chickenpox (varicella)</td>
<td>052</td>
<td>B01</td>
<td>025</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>140-239</td>
<td>C00-D48</td>
<td></td>
</tr>
<tr>
<td>Metabolic disorders</td>
<td>276</td>
<td>E87</td>
<td></td>
</tr>
<tr>
<td>Disorders involving the immune mechanism</td>
<td>279</td>
<td>D80-D89</td>
<td></td>
</tr>
<tr>
<td>Diseases of the blood and blood-forming organs</td>
<td>280-289</td>
<td>D50-D89</td>
<td></td>
</tr>
<tr>
<td>Mental disorders</td>
<td>290-319</td>
<td>F00-F99</td>
<td></td>
</tr>
<tr>
<td>Epilepsy, recurrent seizures, convulsions</td>
<td>345, 7803</td>
<td>G40-G41, R56</td>
<td>345</td>
</tr>
<tr>
<td>Non-infective gastroenteritis and colitis, unspecified</td>
<td>558</td>
<td>K52</td>
<td></td>
</tr>
<tr>
<td>Nephritis, nephrotic syndrome, and nephrosis</td>
<td>580-589</td>
<td>N00-N05</td>
<td></td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>740-759</td>
<td>Q00-Q99</td>
<td></td>
</tr>
<tr>
<td>Syncope and collapse</td>
<td>7802</td>
<td>R55</td>
<td></td>
</tr>
<tr>
<td>Other previous diagnoses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Nutritional deficiencies</em></td>
<td>260-269</td>
<td>E40-E46, E50-E64</td>
<td></td>
</tr>
<tr>
<td><em>Inflammatory diseases of the central nervous system (e.g., bacterial meningitis, encephalitis)</em></td>
<td>320-326</td>
<td>G00-G09</td>
<td></td>
</tr>
<tr>
<td>Cerebral degenerations usually manifest in childhood</td>
<td>330</td>
<td>G31-G32</td>
<td></td>
</tr>
<tr>
<td>Cerebral palsy and other paralytic syndromes</td>
<td>342-343</td>
<td>G80-G81</td>
<td></td>
</tr>
<tr>
<td>Diseases of the circulatory system</td>
<td>390-459</td>
<td>I00-I99</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>480-486</td>
<td>J12-J18</td>
<td></td>
</tr>
<tr>
<td><strong>Immune-Mediated Events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>477</td>
<td>J30</td>
<td>477</td>
</tr>
<tr>
<td>Asthma</td>
<td>493</td>
<td>J45-J46</td>
<td>493</td>
</tr>
<tr>
<td>Dermatitis and related conditions</td>
<td>691-693</td>
<td>L20-L30</td>
<td></td>
</tr>
<tr>
<td><strong>Autoimmune Diseases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>250</td>
<td>E11</td>
<td>250</td>
</tr>
<tr>
<td>Multiple sclerosis (and other demyelination diseases of the central nervous system)</td>
<td>340-341</td>
<td>G35-G37</td>
<td>340</td>
</tr>
<tr>
<td>Bell’s palsy</td>
<td>3510</td>
<td>G510</td>
<td>351</td>
</tr>
<tr>
<td>Acute infective polyneuritis (including Guillain-Barré syndrome)</td>
<td>3570</td>
<td>G610</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis and other</td>
<td>7143</td>
<td>M08</td>
<td>711, 714-716</td>
</tr>
<tr>
<td>Condition</td>
<td>Code 1</td>
<td>Code 2</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>--------</td>
<td>--------</td>
<td></td>
</tr>
<tr>
<td>inflammatory polyarthropathies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>7100</td>
<td>M32</td>
<td></td>
</tr>
<tr>
<td><strong>Risk Factors for Autoimmune Diseases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>0785</td>
<td>B25</td>
<td></td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>075</td>
<td>B270</td>
<td></td>
</tr>
<tr>
<td>Campylobacter</td>
<td>00843</td>
<td>A045</td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td>487-488</td>
<td>J09-J11</td>
<td>147, 487</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>4830</td>
<td>B960, J157, J200, P236</td>
<td></td>
</tr>
</tbody>
</table>