ASSESSING THE RISK FOR AUTOIMMUNE DISORDERS
FOLLOWING USE OF THE QUADRIVALENT HUMAN
PAPILLOMAVIRUS VACCINE: THE ONTARIO GRADE 8 HPV
VACCINE COHORT STUDY

by

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A thesis submitted to the Graduate Program in Epidemiology in the Department of Public Health
Sciences
In conformity with the requirements for
the degree of Master of Science

Queen’s University
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Abstract

**Introduction:** In 2007 Ontario implemented a grade 8 quadrivalent human papillomavirus (qHPV) vaccination program targeting the virus that causes cervical cancer. Despite being 6 years post-implementation, few post-licensure studies have assessed the safety of the qHPV vaccine in this adolescent population. Since autoimmune disorders are often targeted for post-marketing surveillance by regulatory agencies, it is important to assess the risk of developing an autoimmune disorder post-qHPV vaccination.

**Objectives:** The objectives of this thesis were to assess the risk for developing an autoimmune disorder following qHPV vaccination, assess for effect modification by the presence of predisposing risk factors, identify the period of highest risk and explore the risk for individual autoimmune disorders.

**Methods:** A population-based retrospective cohort of girls eligible for Ontario’s qHPV vaccination program was identified using population-based databases. The risk of autoimmune disorders following qHPV vaccination was ascertained using the self-controlled case series method.

**Results:** The risk of developing a new autoimmune disorder, adjusted for age, seasonality, concurrent vaccines and infections was 1.28 (95% CI: 0.87 – 1.89), and this association was independent of a history of immune-mediated disorders (p=0.39). The risk was not increased during days 7-24 post-vaccination (adjusted RR = 0.87, 95% CI: 0.43 – 1.74), but appeared to increase thereafter (adjusted RR = 1.36, 95% CI: 0.77 – 2.41 and RR = 1.62, 95% CI 0.94 – 2.78 respectively, for days 25 – 42 and days 43 – 60), although these differences were non-significant. The risk may be increased for certain disorders including Bell’s palsy (RR = 2.30, 95% CI: 0.67 –
7.95), systemic autoimmune rheumatic disorders (RR = 1.84, 95% CI: 0.42 – 8.02), Hashimoto’s disease (RR = 1.39, 95% CI: 0.46 – 4.22), and juvenile rheumatoid arthritis (RR = 1.31, 95% CI: 0.83 – 2.08), although none of these associations were statistically significant.

**Conclusion:** This thesis demonstrated that no statistically significant increased risk for autoimmune disorders following qHPV vaccination was detected. However, there remains some uncertainty about the safety of the qHPV vaccine for a subset of the autoimmune disorders. The results from this analysis need to be pooled with those of other studies to confirm whether these are true safety signals.
Co-Authorship

Yiran Erin Liu completed this thesis under the supervision of Dr. Linda Lévesque and in consultation with her thesis committee members, Dr. Barbara Law and Dr. Anne Ellis. Under guidance from Dr. Linda Lévesque, Yiran Erin Liu designed the study, completed the ethics application, prepared the datasets and performed statistical analyses. Yiran Erin Liu wrote this thesis with input from Dr. Linda Lévesque.
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There are a number of people I am grateful towards for if it was not for their help, I could not have completed this thesis. First, I would like to thank my thesis supervisor, Dr. Linda Lévesque. She is the reason I came to pursue my graduate degree at Queen’s University, where I was given the opportunity to conduct research that I am passionate about. I am forever indebted to her for helping me develop various new skills, and for strengthening my understanding of epidemiological concepts. In addition to Dr. Linda Lévesque, I am extremely grateful to everyone in her research group for their expertise and feedback during the course of conducting my thesis. In particular, I would like to thank Guoyuan Liu for helping me with my SAS programming. Also, I would like to acknowledge Leah Smith for her input on my thesis and for the invaluable feedback she provided for all of my presentations.

Secondly, I extend my gratitude to Dr. Barbara Law, Chief of Vaccine Safety in the Surveillance and Outbreak Response Division at the Public Health Agency of Canada and Dr. Anne Ellis, clinical immunologist at the Kingston General Hospital. I could not have asked for a better thesis committee, as their expertise in the area of vaccine safety and autoimmune disorders has been instrumental to this project.

In addition, I would like to thank the Institute for Clinical Evaluative Sciences (ICES) for allowing me access to the databases necessary for this thesis. Amongst the members of the ICES@Queen’s team, I would like to thank Marlo Whitehead for helping me debug my SAS program and I am forever indebted to Shari Scanlan, who prepared and distributed copies of my thesis when I was unable to.

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Rosillo and I am forever grateful to him for quickly responding to all my emails, providing me important resources, expertly coordinating my thesis defense process, and essentially helping me get through this degree. I am very thankful to the department for having hired him. Also, I want to thank my classmates for being there for me, both during the hard times and when celebrating the high points. I am glad that I had such a fantastic MSc. class.

One friend who has been there every step of the way is Melanie Cheung. I am incredibly grateful for her friendship, patience and kindness. She helped me at various points during our two years together, motivated me to keep trying when I just wanted to give up, and never ceased to teach me new things. I am glad to have had her by my side, and could not have asked for a better friend.

Finally, I must acknowledge the support of my loved ones. I am so grateful to my family for helping me in any way possible to make this process easier. If it was not for my father, I would not have even known about epidemiology, so I thank him for his advice to pursue this field of study. I have found something I love, and I hope to do this for the rest of my life. Lastly, I am thankful for my partner, Jacob Wong’s support on this journey. His encouragement never ceased and I could not have done it without his help.

Lastly, I would like to acknowledge the Ontario Graduate Scholarship and the Canadian Institute for Health Research Master’s Award for providing the financial support for this thesis.
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List of Abbreviations

ADEM: Acute disseminated encephalomyelitis
AE: Adverse event
AEFI: Adverse Events Following Immunization
AIH: Autoimmune hepatitis
AIHA: Autoimmune haemolytic anaemia
AIP: Autoimmune pancreatitis
Alum: Aluminum
CAEFISS: Canadian Adverse Events Following Immunization Surveillance System
CIHI: Canadian Institute for Health Information
DAD: Discharge Abstract Database
DM: Dermatomyositis
EN: Erythema nodosum
GBS: Guillain-Barré syndrome
GD: Grave’s disease
GWS: Gulf War Syndrome
HD: Hashimoto’s disease
HPV: Human papillomavirus
IBD: Inflammatory bowel disorder
ICD: International Classification of Diseases
ICES: Institute for Clinical Evaluative Sciences
IKN: ICES Key Number
IOM: Institute of Medicine
IRIS: Immunization Record Information System
ITP: Immune thrombocytopenia purpura
JRA: Juvenile rheumatoid arthritis
KFL&A: Kingston, Frontenac, Lennox and Addington
MMF: Macrophagic myofasciitis
MMR: Measles, mumps and rubella
MS: Multiple sclerosis
NACI: National Advisory Committee on Immunization
NACRS: National Ambulatory Care Reporting System
NMO: Neuromyelitis optica
OHIP: Ontario Health Insurance Plan
ON: Optic neuritis
PHAC: Public Health Agency of Canada
PHU: Public health unit
qHPV: quadrivalent human papillomavirus
RA: Rheumatoid arthritis
RPDB: Registered Persons Database
RCT: Randomized controlled trial
SARD: Systemic autoimmune rheumatic disorder
SCCS: Self-controlled case series
SLE: Systemic lupus erythematosus
SS: Sjogren’s syndrome
T1DM: Type 1 diabetes mellitus
TM: Transverse myelitis
UC: Ulcerative colitis
VAERS: Vaccine Adverse Event Reporting System
VICP: Vaccine Injury Compensation Program
Chapter 1

Introduction

1.1 Autoimmune Disorders

Autoimmune disorders encompass a diverse spectrum of diseases that manifest as a result of an immune system dysfunction. Autoimmune disorders are usually precipitated by an external trigger, which leads to an immune-mediated attack on host tissues and organs in genetically susceptible individuals. (Davidson & Diamond, 2001; Noel Rose, 2004a; Selmi, 2012) Since these disorders can become chronic and progressive, autoimmune disorders are particularly devastating when they occur during childhood and adolescence.

There are at least 80 disorders of autoimmune aetiology (Hayter & Cook, 2012; Noel Rose, 2004a) and females account for nearly 80% of all those affected (Fairweather & Rose, 2004). These disorders can target any organ system and their incidence and prevalence varies considerably across age groups and between diseases. For example, in those under 18 years of age, the incidence ranges from a low of 0.5-1.5/100 000 person-years (Sladky, 2004) for Guillain-barre syndrome (GBS), a disease of the peripheral nervous system, to a high of 17.8 and 24 per 100 000 person-years for juvenile rheumatoid arthritis (JRA) (Ehrmann Feldman, Bernatsky, & Houde, 2009) and type 1 diabetes mellitus (T1DM) (Karvonen et al., 2000), respectively. While autoimmune disorders are considered rare at an individual level, their combined prevalence has been estimated at 4.5% in the general population (Hayter & Cook, 2012).

1.2 Burden of Autoimmune Disorders

Due to the chronic nature of autoimmune disorders, disease burden is high at the individual level and since patients require frequent interactions with the health care system, this translates into significant direct and indirect costs for society. (Noel Rose, 2004a) For example, GBS patients suffer from the degeneration of peripheral, motor and cranial nerves, and 20-30% of
patients eventually require mechanical ventilation while 10-35% will accrue irreversible nerve damage. This translates into $1.7 billion per year in the form of direct medical costs (14%) and indirect costs (86%), based on estimates from the United States. (Frenzen, 2008) Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder that targets all major organ systems and symptoms include musculoskeletal, renal, ocular, and neuropsychiatric disorders. Paediatric SLE, which is the form of SLE that affects children younger than 16 years of age, is more aggressive, and 11% and 15% of afflicted children will suffer delayed puberty and physical growth, respectively. (Kamphuis & Silverman, 2010; Levy & Kamphuis, 2012) An economic analysis conducted in the United States estimated that compared to disease-free age and sex-matched children ages 15 and under, those with SLE incurred an extra 77.1 medical claims per year, totalling $32,919. (Karve et al., 2012) T1DM is an autoimmune disorder where the immune-mediated destruction of pancreatic cells prevents the body from producing insulin and this disorder is also associated with a significant economic burden. The annual per capita cost for medical expenditures attributed to T1DM is $6,288 per case and since this disorder is most often diagnosed in childhood and is chronic in nature, the estimated lifetime costs for all cases is $133.7 billion for medical expenses and $289.2 billion for indirect costs. (B. Tao, Pietropaolo, Atkinson, Schatz, & Taylor, 2010) Although most autoimmune disorders are rare, they nonetheless can result in significant morbidity and reduced quality of life, and place a considerable burden on society with respect to direct health care expenditures, and potential years of life lost.

1.3 Autoimmune Disorders following Vaccination

Since the aetiology of autoimmune disorders involves a combination of genetic and environmental factors, it is important to identify modifiable risk factors that may lower the risk of these disorders. Previous research has demonstrated that a number of vaccines have been found to be potentially associated with autoimmune disorders (Table 1 - 1). Although much of the
available evidence has come from case reports, where disease was found to be temporally associated with vaccination, observational studies of vaccine safety have been conducted for thirteen autoimmune disorders. Based on these studies, significantly elevated risks were detected for immune thrombocytopenia purpura (ITP), Crohn’s disease, and ulcerative colitis (UC) following the Measles, mumps, rubella (MMR) vaccine, SLE, rheumatoid arthritis (RA), multiple sclerosis (MS), and optic neuritis (ON) following Hepatitis B vaccination (HBV), and GBS and Bell’s palsy following Influenza vaccination. Although the strength of association varies between disorders, the evidence from these observational studies suggests that vaccines may increase the risk of developing certain autoimmune disorders.

There is currently insufficient evidence to either reject or accept these associations of vaccine-induced autoimmunity to be causal, based on limited evidence from case reports, and inconsistent findings from observational studies. Nonetheless, given their immune mediated aetiology, and vaccines’ role in stimulating the immune system, autoimmune disorders remain one of the most commonly targeted adverse events for the post-marketing surveillance of vaccines (Bardage et al., 2011; Black et al., 2009; Klein et al., 2010; Slade, Gee, Broder, & Vellozzi, 2011).

1.4 Biologic Plausibility and Rationale

Although the mechanism for vaccine-induced autoimmunity is not well understood, it has been proposed that exposure to vaccines may evoke an exaggerated immune system response in genetically susceptible individuals, that in turn can trigger autoimmunity because of molecular similarities between host antigens and vaccines (Albert & Inman, 1999). This mechanism of molecular mimicry provides a biological plausibility for the purported exposure-disease relationship. In addition, research has shown that adolescent girls, the age group targeted by quadrivalent human papillomavirus (qHPV) vaccination programs in Canada and elsewhere, may be particularly prone to exaggerated immune responses because of hormonal changes occurring
during puberty (Bartlett et al., 1998; Beagley & Gockel, 2003; Jaspan, Lawn, Safrit, & Bekker, 2006). Given that a number of autoimmune disorders [i.e., JRA, T1DM, Coeliac disease, acute disseminated encephalomyelitis (ADEM) and transverse myelitis (TM)] experience a peak in incidence between the ages of 0-13 years (Glinda Cooper & Stroehla, 2003; Hayter & Cook, 2012), it is important to monitor new vaccines, such as the qHPV vaccine, for their potential to trigger an autoimmune disorder among adolescent girls.

1.5 Objectives

The primary objectives of this thesis are to:

(i) Assess the risk for the development of a new autoimmune disorder following qHPV vaccination

(ii) Determine if the risk is modified by the presence of predisposing factors

(iii) Identify the period of highest risk

The secondary objective is to explore the risk for individual autoimmune conditions.

1.6 Thesis Outline

The organization of this thesis is as follows: Chapter 2 constitutes the literature review, and includes a description of the outcome and exposure, their known predictors, and previous research that has examined the association under study. Chapter 3 describes, in detail, the methods used, including the data sources, data quality and variables available, cohort formation, measurement of the exposure, ascertainment of the outcome, and covariates, and the analytical strategy. Results are provided in Chapter 4, in the form of a manuscript, and include a descriptive analysis of the cohort and the results from the primary and sensitivity analyses. Finally, Chapter 5 includes a general discussion of the results, with study implications, strengths, and limitations addressed.
1.7 References


Dooley, M. A., & Hogan, S. L. (2003). Environmental epidemiology and risk factors for autoimmune disease. *Current opinion in rheumatology*. Retrieved August 16, 2013, from http://ovidsp.tx.ovid.com/sp-3.9.1a/ovidweb.cgi?QS2=434f4e1a73d37e8e3dd5959385f5c1117b4be299f865ef190cd3e1016179c21692d5dbab64b1b8d6b414d615839dfef8754e45a188a5ab90386da66827aeef5c5d7b960d4f808bc0678ab108df24a68ecbec866d05eaa30786e507d55e573f7562c348a83a2a5689


randomized controlled trial. *Obstetrics and Gynecology*, 107(1), 18–27. doi:10.1097/01.AOG.0000192397.41191.fb


MERCK CANADA INC. (2013). GARDASIL® [Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine] Product Monograph (pp. 1–60).


1.8 Tables
Table 1-1: Autoimmune disorders potentially associated with vaccines, based on case reports, observational studies, and causality determined by the Institute of Medicine (IOM)*

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Published case reports</th>
<th>Observational studies assessing an association with at least 1 vaccine</th>
<th>Causality assessment made by IOM</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITP</td>
<td>HBV</td>
<td>MMR</td>
<td>Inadequate: DT, TT, and aP-containing vaccines</td>
</tr>
<tr>
<td></td>
<td>7 cases (Neau et al., 1998)</td>
<td>IRR = 7.06 (95% CI: 1.95–25.88) (France et al., 2008)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RI = 3.27 (1.49 - 7.16) (Miller et al., 2001)</td>
<td></td>
</tr>
<tr>
<td>Measles-containing vaccines</td>
<td>56 in VAERS (Beeler, Varricchio, &amp; Wise, 1996)</td>
<td>MMR 2nd dose RI = 1.04 (95% CI: 0.37 - 2.92) (Stowe, Kafatos, Andrews, &amp; Miller, 2008)</td>
<td></td>
</tr>
<tr>
<td>MMR</td>
<td>79 cases (Jadavji, Scheifele, Halperin, &amp; Program, 2003)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>23 cases (Nieminen, Peltola, Syrjälä, Mäkipernaa, &amp; Kekomäki, 1993)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td>1 case (Mantadakis, Farmaki, Thomaidis, Tsalkidis, &amp; Chatzimichael, 2010)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCG vaccine</td>
<td>1 case (Jakovljević &amp; Culić, 2007)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HBV OR = 2.3 (95% CI: 1.02 – 6.2) (D. Geier &amp; Geier, 2005)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Meningococcal group C conjugate RI = 1.15 (95% CI: 0.80-1.67) (Andrews, Stowe, Miller, &amp; Taylor, 2007)</td>
<td></td>
</tr>
<tr>
<td>AIHA</td>
<td>Oral polio and MMR</td>
<td>DPT</td>
<td>Not assessed</td>
</tr>
<tr>
<td></td>
<td>1 case (Seltsam, Shukry-Schulz, &amp; Salama, 2000)</td>
<td>IRR = 0.65 (95% CI: 0.19-2.24)</td>
<td></td>
</tr>
<tr>
<td>DTP, Hib, HBV, and polio</td>
<td>1 case (Seltsam et al., 2000)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTP</td>
<td>1 case (Downes, Domen, McCarron, &amp; Bringelsen, 2001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HBV IRR = 1.73 (95% CI: 0.59–5.01)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any vaccine IRR = 1.04 (95% CI: 0.46–2.32) (Naleway et al., 2009)</td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>Vaccines</td>
<td>Reference</td>
<td>Odds Ratio (95% CI)</td>
</tr>
<tr>
<td>--------------------</td>
<td>---------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>SLE</td>
<td>HBV</td>
<td>10 cases (Agmon-Levin, Zafrrir, et al., 2009)</td>
<td>OR = 9.1 (95% CI: 2.3 – 76) (D. Geier &amp; Geier, 2005)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 case (Santoro et al., 2010)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 cases exacerbation (Maillefert et al., 1999)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Routine soldier immunization</strong> Combination of Typhoid, Influenza, Meningococcal, MMR, anthrax, HAV, and TT vaccines</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 cases (Older, Battafarano, Enzenauer, &amp; Krieg, 1999)</td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>HBV</td>
<td>11 cases (Pope, Stevens, Howson, &amp; Bell, 1998)</td>
<td>OR = 18 (95% CI: 3.1 – 740) (D. Geier &amp; Geier, 2005)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 cases (Maillefert et al., 1999)</td>
<td></td>
</tr>
<tr>
<td>JRA</td>
<td>None found</td>
<td>None found</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>None found</td>
<td></td>
</tr>
<tr>
<td>Sjogren’s disease</td>
<td>BCG</td>
<td>None found</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>None found</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HBV</td>
<td>1 case (Narváez, Castro-Bohorquez, &amp; Vilaseca-Momplet, 2003)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 case (Toussirot, Lohse, Wendling, &amp; Mougin, 2000)</td>
<td></td>
</tr>
<tr>
<td>T1DM</td>
<td>MMR</td>
<td>Several cases (Sinaniotis, Daskalopoulou, Lapatsanis, &amp; Doxiadis, 1975)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Influenza vaccine</strong></td>
<td></td>
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<td></td>
<td></td>
<td>1 case (Yasuda et al., 2012)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td><strong>Case-control study:</strong></td>
<td></td>
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<td></td>
<td></td>
<td>HBV: p = 0.765</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hib: p = 0.275</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polio: p = 0.678</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>DTP: p = 0.611</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Graves et al., 1999)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Retrospective cohort study in adults:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anthrax: RR = 1.00 (95% CI: 0.85 - 1.17)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Smallpox: RR = 0.84 (95% CI: 0.70 – 1.01)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Typhoid: RR = 1.03 (95% CI: 0.87 – 1.22)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HBV: RR = 0.83 (95% CI: 0.72 – 0.95)</td>
<td></td>
</tr>
</tbody>
</table>

26
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>RR (95% CI)</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMR</td>
<td>RR = 0.71 (95% CI: 0.61 – 0.83)</td>
<td>Yellow fever vaccine: RR = 0.70 (95% CI: 0.59 – 0.80) (Duderstadt et al., 2012)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Retrospective cohort study in children:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hib: RR = 0.91 (95% CI: 0.74 – 1.12)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DTP: RR = 1.02 (95% CI: 0.75 – 1.37)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DT-aP: RR = 0.96 (95% CI: 0.71 – 1.30)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wc-P: 1.06 (95% CI: 0.80 – 1.40)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MMR: 1.14 (95% CI: 0.90 – 1.45)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polio: 1.08 (95% CI: 0.74 – 1.57) (Hviid, Stellfeld, Wohlfahrt, &amp; Melbye, 2004)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Duderstadt et al., 2012)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>OR (95% CI)</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV</td>
<td>OR = 1.23 (95% CI: 0.87-1.73)</td>
<td>(Yu et al., 2007)</td>
</tr>
<tr>
<td></td>
<td>OR = 0.90 (95% CI: 0.62-1.32)</td>
<td>(Yu et al., 2007)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>OR (95% CI)</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV</td>
<td>OR = 5.2 (1.9 – 20) (Geier et al 2005)</td>
<td>Pediatric-onset MS: Inadequate for MMR, HBV vaccines</td>
</tr>
<tr>
<td></td>
<td>OR = 0.9 (0.5-1.6) (Ascherio et al 2001)</td>
<td>MS relapse in children: Inadequate for HBV, DT-, TT- and aP-containing Vaccines</td>
</tr>
<tr>
<td></td>
<td>OR = 3.1 (1.5-6.3) (Hernán et al 2004)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR = 1.03 (0.62-1.69) (Mikaeloff et al 2008)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RR = 0.71 (0.40 – 1.26) (Confavreux et al 2001)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RR = 1.8 (0.7 – 4.6) (Touze et al 2002)</td>
<td></td>
</tr>
</tbody>
</table>

HD: None found; GD: None found; MS: HBV 2 cases (Herroelen, de Keyser, & Ebinger, 1991)
<table>
<thead>
<tr>
<th>Condition</th>
<th>Cause</th>
<th>Events</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADEM</td>
<td>H1N1 – 2009</td>
<td>None found</td>
<td>Fujii et al., 2012; Lapphra, Huh, &amp; Scheifele, 2011; Maeda &amp; Idehara, 2012</td>
</tr>
<tr>
<td></td>
<td>Previous influenza vaccines</td>
<td></td>
<td>Shoamanesh &amp; Traboulsee, 2011</td>
</tr>
<tr>
<td></td>
<td>HBV</td>
<td>15 cases since 1982</td>
<td>Shoamanesh &amp; Traboulsee, 2011</td>
</tr>
<tr>
<td></td>
<td>8 cases</td>
<td></td>
<td>Tourbah et al., 1999</td>
</tr>
<tr>
<td>TM</td>
<td>HBV</td>
<td>None found</td>
<td>Shaw et al., 1988</td>
</tr>
<tr>
<td></td>
<td>HBV, MMR/Rubella, DTP/DT, rabies, OPV, Influenza</td>
<td></td>
<td>Agmon-Levin, Kivity, Szyper-Kravitz, &amp; Shoenfeld, 2009</td>
</tr>
<tr>
<td></td>
<td>37 cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GBS</td>
<td>HBV</td>
<td>Influenza</td>
<td>Lasky et al., 1998</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RR = 1.7 (95% CI: 1.0 – 2.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(M. Geier, Geier, &amp; Zahalsky, 2003)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>RR = 4.3 (95% CI: 3.0-6.4)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>(Hughes, Charlton, Latinovic, &amp; Gulliford, 2006)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RR = 1.03 (95% CI: 0.48 - 2.18)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>(Juurlink et al., 2006a)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>RR = 1.45 (95% CI: 1.05-1.99)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RR = 0.76 (95% CI: 0.41 – 1.40)</td>
<td></td>
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</tbody>
</table>

RR = 1.68 (0.77 – 3.68) (Hocine et al 2007)

Inadequate: MMR, Varicella, Influenza, HAV, HBV, DT-, TT- and aP- containing Vaccines, Meningococcal vaccine
<table>
<thead>
<tr>
<th>Condition</th>
<th>Vaccine Type</th>
<th>Data Source</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bell’s Palsy</td>
<td>Parenteral inactivated influenza vaccine</td>
<td>197 reports from VAERS; safety signal detected (Zhou et al., 2004)</td>
<td>RR = 2.50 (95% CI: 0.42-15.0) (Yih et al., 2012)</td>
</tr>
<tr>
<td></td>
<td>Inactivated intranasal influenza vaccine</td>
<td>OR: 84.0 (95% CI: 20.1 - 351.9) (Mutsch et al., 2004)</td>
<td>RR = 1.57 (95% CI: 1.02-2.21) (Wise et al., 2012)</td>
</tr>
<tr>
<td></td>
<td>Parenteral influenza vaccine</td>
<td>RI = 0.92 (95% CI: 0.78-1.08) (Stowe, Andrews, Wise, &amp; Miller, 2006)</td>
<td>RR = 3.02 (95% CI: 1.64-5.56) (De Wals et al., 2012)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RR = 1.05 (95% CI: 0.37 - 2.24) (Andrews, Stowe, Al-Shahi Salman, &amp; Miller, 2011)</td>
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<tr>
<td>NMO</td>
<td>Japanese encephalitis vaccine</td>
<td>None found</td>
<td></td>
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</tr>
<tr>
<td>ON</td>
<td>MMR</td>
<td>3 cases (Stevenson, Acheson, Ball, &amp; Plant, 1996)</td>
<td>OR = 14 (95% CI: 2.3 – 560) (D. Geier &amp; Geier, 2005)</td>
</tr>
<tr>
<td></td>
<td>Influenza</td>
<td>5 cases (Crawford, Grazko, Raymond, Rivers, &amp; Munson, 2012; Hull &amp; Bates, 1997; Kawasaki, Purvin, &amp; Tang, 1998)</td>
<td>OR = 1.18 (95% CI: 0.74 – 1.87) (Payne et al., 2006)</td>
</tr>
<tr>
<td></td>
<td>HBV</td>
<td>6 cases (Albitar et al., 1997; Shaw et al., 1988)</td>
<td></td>
</tr>
<tr>
<td>None found</td>
<td>None found</td>
<td>Inadequate: HAV</td>
<td></td>
</tr>
<tr>
<td>---</td>
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<td></td>
</tr>
<tr>
<td>None found</td>
<td>None found</td>
<td>Not assessed</td>
<td></td>
</tr>
<tr>
<td>HBV 32 cases (Fraunfelder &amp; Suhler, 2010)</td>
<td>None found</td>
<td>Not assessed</td>
<td></td>
</tr>
<tr>
<td>MMR 2 cases (Islam, El-Sheikh, &amp; Tabbara, 2000)</td>
<td>None found</td>
<td>Not assessed</td>
<td></td>
</tr>
<tr>
<td>H1N1 2 cases (Y. Tao, Chang, Zhao, &amp; Li, 2011)</td>
<td>None found</td>
<td>Not assessed</td>
<td></td>
</tr>
<tr>
<td>BCG 1 case (Shah, Uppal, &amp; Tappin, 2011)</td>
<td>None found</td>
<td>Not assessed</td>
<td></td>
</tr>
<tr>
<td>AIP</td>
<td>None found</td>
<td>None found</td>
<td>Inadequate: HAV</td>
</tr>
<tr>
<td>AIH HAV 1 case (Berry &amp; Smith-Laing, 2007)</td>
<td>None found</td>
<td>Not assessed</td>
<td></td>
</tr>
<tr>
<td>DM / PM HBV 4 case (Altman, Szyper-Kravitz, &amp; Shoenfeld, 2008; Fernández-Fúnez &amp; Polo Romero, 1998; Ramírez-Rivera, Vega-Cruz, &amp; Jaume-Anselmi, 2003)</td>
<td>None found</td>
<td>Not assessed</td>
<td></td>
</tr>
<tr>
<td>Influenza 2 cases (Ferri et al., 2012; Jani, Gray, &amp; Lanham, 1994)</td>
<td>None found</td>
<td>Not assessed</td>
<td></td>
</tr>
<tr>
<td>Diphtheria and Scarlet Fever vaccine, DPT and Polio Various number of cases of vaccine-induced DM (Ehrengut, 1978)</td>
<td>None found</td>
<td>Not assessed</td>
<td></td>
</tr>
<tr>
<td>CD Influenza 1 case of reactivation of CD (Lisotti, Roda, Brillanti, &amp;</td>
<td>MMR RR = 3.01 (95% CI: 1.45 – 6.23)</td>
<td>Not assessed</td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td>Vaccine</td>
<td>Event Description</td>
<td>Reference</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------</td>
<td>-----------------------------------------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>UC</td>
<td>Influenza</td>
<td>Reactivation of UC</td>
<td>Kwon et al., 2007</td>
</tr>
<tr>
<td></td>
<td>MMR</td>
<td></td>
<td>Thompson et al., 1995</td>
</tr>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Davis et al., 2001</td>
</tr>
<tr>
<td>UC</td>
<td></td>
<td>None found</td>
<td>Torrelo et al., 2006</td>
</tr>
</tbody>
</table>

*The IOM conducts causality assessments for adverse events following vaccination and causality conclusions are based on epidemiologic and mechanistic evidence (Stratton, Ford, Rusch, Clayton, & Wright Clayton, 2011).*

**ITP = immune thrombocytopenia purpura, AIHA = autoimmune haemolytic anaemia, SLE = systemic lupus erythematosus, RA = rheumatoid arthritis, JRA = juvenile rheumatoid arthritis, T1DM = type 1 diabetes mellitus, HD = Hashimoto’s disease, GD = Grave’s disease, MS = multiple sclerosis, ADEM = acute disseminated encephalomyelitis, TM = transverse myelitis, GBS = Guillain-barre syndrome, NMO = neuromyelitis optica, ON = optic neuritis, AIP = autoimmune pancreatitis, AIH = autoimmune hepatitis, DM = dermatomyositis, PM = polymyositis, CD = Crohn’s disease, UC = ulcerative colitis, HBV = Hepatitis B vaccine, MMR = Measles, mumps, rubella, BCG = Bacillus Calmette–Guérin, DPT = Diphtheria, pertussis, tetanus, Hib = Haemophilus influenzae type B, HAV = Hepatitis A vaccine, TT = Tetanus vaccine, DT-aP = Diphtheria, tetanus, acellular pertussis, Wc-P = Whole-cell pertussis, OPV = Oral polio vaccine, RR = relative risk, RI = relative incidence, OR = odds ratio, IRR = incidence rate ratio, 95% CI = 95% Confidence Interval
Chapter 2

Literature Review

2.1 Background on Autoimmune Disorders

Autoimmune disorders may differ due to distinctive clinical features, but this category of diseases shares a common pathogenesis that involves the self-destruction of tissues and organs due to an aberrant immune response. (Davidson & Diamond, 2001) Since the autoimmune response may be directed at one or multiple organ systems, these disorders are usually categorized as organ-specific (e.g. multiple sclerosis affects the central nervous system) or systemic diseases (e.g. systemic lupus erythematos affects the cutaneous, cardiovascular, musculoskeletal, respiratory, renal, and nervous systems). Although there remains some debate on the exact classification of these disorders, it is accepted that there are approximately 80 disorders of autoimmune origin. Criteria such as the modified Witebsky’s postulates define a disorder to be autoimmune if a) there is presence of an adaptive immune response towards an organ or tissue, b) there is presence of autoantibodies or auto-reactive T-cells, c) the transfer of these auto-reactive T-cells or autoantibodies can induce disease in healthy animals or humans, and d) removing the autoimmune response can result in a cessation of disease progression or clinical symptoms. (Hayter & Cook, 2012; N Rose & Bona, 1993)

2.1.1 Epidemiology of Autoimmune Disorders

The epidemiology of autoimmune disorders has been investigated in a number of review papers in North America and prevalence estimates have ranged from 3.2% (Jacobson, Gange, Rose, & Graham, 1997) to 4.5% (Hayter & Cook, 2012) to 7.6 – 9.4% (Glinda Cooper, Bynum, & Somers, 2009). These estimates vary due to a number of factors, such as the number of autoimmune disorders included for study, the data sources used, the type of epidemiologic studies used for each particular disease, and adjustment for the under-ascertainment of certain diseases.
Despite the variable estimates, autoimmune disorders are fairly prevalent in the general population, although individually, their incidence rates are low. This is explained by their chronic nature, high rates of survival, and the reality that there is no cure for the majority of these disorders. (Noel Rose, 2004a) With respect to demographic trends, women are disproportionately affected, as they are 2.7 times more likely to develop an autoimmune disorder compared to men (Jacobson et al., 1997). The risk of autoimmune disorders generally increases with age, with mean age at onset for the majority of disorders occurring in the 40 – 49 age range. Seven among 80 autoimmune disorders are more commonly diagnosed in adolescence, with the most prevalent of these being type I diabetes mellitus (T1DM), juvenile rheumatoid arthritis (JRA) and Coeliac disease. (Hayter & Cook, 2012)

Accurate incidence and prevalence measures of autoimmune disorders can be difficult to ascertain because a large number of autoimmune disorders are so rare that they lack adequate epidemiologic data to produce reliable measures. Further, about a third of autoimmune disorders will develop into a relapsing-remittance form, where patients will have periods of disease flares followed by periods of disease remission (personal communication, Dr. Anne Ellis), which will likely underestimate the prevalence of these disorders at any point in time. The greatest determinant though, is the issue of case ascertainment as autoimmune disorders are difficult to diagnose and there exists variability in diagnostic criteria for many of these disorders. Given that many autoimmune disorders are progressive, initial symptoms can be non-specific and may present themselves as general malaise (e.g. muscle weakness, fatigue, tingling sensations). Further compounding the problem is that a diagnosis of an autoimmune disorder is usually exclusionary, first requiring clinical manifestations for a probable diagnosis, then confirmation via laboratory tests and/or biopsies, MRI readings, and auto-antibody tests to rule out other causes. Thus, diagnoses in primary care often require confirmation from additional tests, and/or referral to a specialist. The resultant number of unconfirmed diagnoses and misdiagnoses can affect case ascertainment and thus further impact prevalence estimates.
2.1.2 Risk Factors for Autoimmune Disorders

Although the aetiology of autoimmune disorders is not fully understood, various risk factors have been studied in relation to these disorders (Table 2-1). Established factors that are globally accepted and have demonstrated an association with numerous autoimmune disorders include genetics and infectious pathogens.

Evidence for a genetic predisposition to autoimmune disorders first came from studies of familial clustering of diseases (Anaya et al., 2006; Criswell et al., 2005; Lin et al., 1998), and twin studies, where concordance rates for diseases such as T1DM, autoimmune thyroid disease, myasthenia gravis, SLE, Coeliac disease, Crohn’s disease and ulcerative colitis (UC) were much higher for monozygotic twins than dizygotic twins (Table 2-1). Research has since expanded to examine specific genes, and has demonstrated that the human leukocyte antigen (HLA) complex, which expresses genes involved in immune function, account for about 50% of this genetic susceptibility. These HLA genes have been associated with various autoimmune disorders, and relative risks have ranged from two to greater than 150 when compared to those who do not have the corresponding alleles (Table 2 – 1). Emerging research has identified some non-HLA genes such as Protein tyrosine phosphatase, non-receptor type 22 (PTPN22) and Cytotoxic T-Lymphocyte Antigen 4 (CTLA4) that have also been found to increase risk for certain autoimmune disorders, with odds ratios ranging between 1.15 and 2 for T1DM, autoimmune thyroid diseases, rheumatoid arthritis (RA), and SLE. The specific gene-disorder associations presented in Table 2 – 1 are by no means exhaustive, and the role of genetics in autoimmune disease aetiology is complex as some alleles are associated with multiple diseases, whereas others increase the risk of one, but protect against other autoimmune disorders. Further, not all individuals who possess a susceptibility gene will develop an autoimmune disorder, suggesting interactions with other genes and exogenous factors. Thus, the prevailing theory is that overt disease will manifest as a result of an external trigger in genetically susceptible individuals, and a large portion of the risk is due to these non-inheritable factors.
Infectious pathogens are considered one of the most likely triggers for autoimmune manifestations. (Davidson & Diamond, 2001; Noel Rose, 2004b) A commonly proposed mechanism to explain the infection-autoimmune disorder association is molecular mimicry, where similar epitopes between host cells and foreign cells can lead to cross-reactivity of antigens. Even after the pathogen has been eliminated, the immune system continues its inflammatory response, damaging cells that share antigenic similarities to the pathogen. (Albert & Inman, 1999) Support for this theory comes from a variety of clinical and mechanistic evidence from animal and in vitro studies which have shown multiple infectious agents to be associated with autoimmune disorders (Table 2 -1). Although epidemiologic studies have been limited, many autoimmune disorders are preceded by infections (personal communication, Dr. Anne Ellis), and clinical studies have shown patients to have higher levels of the pathogen or antibodies to the pathogen, compared to healthy controls. Much of the evidence has implicated viral pathogens, although bacterial agents have also preceded development of certain autoimmune disorders. The results of these studies have shown that infectious agents such as Epstein-barr virus (EBV), Cytomegalovirus (CMV), Parvovirus B19, Coxsakieviruses, and Helicobacter pylori have consistently demonstrated an association with a wide range of autoimmune disorders, thus establishing them as strong risk factors for this group of diseases.

Other triggers for autoimmunity that have been identified include cigarette smoking, vitamin D status, and occupational exposure to silica, although these risk factors have only been studied for certain autoimmune disorders (Table 2 – 2). Results from several case-control and cohort studies have shown modest to strong risks (OR/RR ranging from 0.5 – 8.2) for smoking and development of RA, SLE, MS, Grave’s disease, and primary biliary cirrhosis. Although the exact biologic mechanism for this relationship is not well understood, it has been proposed that smoking-induced inflammatory processes and free radical damage with its subsequent effects on DNA gene expression could affect susceptibility for autoimmune disorders.
Lack of adequate vitamin D may also be a risk factor for autoimmune disorders, as prospective cohort studies have shown vitamin D supplementation to be protective against MS, T1DM, inflammatory bowel disease (IBD) and RA, and data from ecologic studies have demonstrated a correlation between increasing latitude and prevalence of MS and T1DM (Cantorna & Mahon, 2004). This relationship can be explained by the modulating effects of vitamin D on the immune system, and the ability of vitamin D to suppress autoimmune processes. In contrast to disorders such as MS and T1DM, which appear to derive benefit from ultraviolet (UV) radiation, autoimmune disorders such as SLE may have an inverse relationship with sunlight. A case-control study in Sweden found that women who had sun-sensitive skin (sun-reactive skin type I/II) had increased odds of developing SLE (OR = 2.9; 95% CI: 1.6 – 5.1) compared to women with sun-sensitive skin type I-II (sometimes/never burn, always tan), and that those who were sunburned more than once in their youth had 2.2 (95% CI: 1.2 – 4.1) the odds of developing SLE compared to those who were never seriously sunburned. (Bengtsson, Rylander, Hagmar, Nived, & Sturfelt, 2002) Thus, the relationship between vitamin D status and risk of autoimmune disorders may be different depending on the type of autoimmune disorder involved.

Exposure to occupational silica and silicones may increase the risk for systemic autoimmune disorders such as SLE and Scleroderma. Occupational studies have compared those working in environments with high silica exposure to other occupations and have estimated the risk of Scleroderma to be as high as 25, and a case-control study for SLE patients found increased odds of having the disease for those with medium and high exposure to silica compared to those with low exposure (Table 2 – 2). More recently, there has been concerns for the potential adverse effects of silicone breast implants, as a retrospective cohort study found that women with breast implants had almost twice the risk of developing scleroderma (RR=1.89; 95% CI: 0.98 – 3.45). Although these risks have been observed for two autoimmune disorders, it is unknown what effect silica exposure has on other systemic autoimmune disorders, or organ-specific disorders.
Although less extensively studied, other proposed risk factors for autoimmune disorders include environmental pollutants, dietary factors, history of allergies, hormonal factors, and stress (Ascherio & Munger, 2007; G Cooper et al., 1998; D’Cruz, 2000; M. Dooley & Hogan, 2003). However, the evidence is sparse, and these risk factors have not been studied across multiple autoimmune disorders, thus highlighting the considerable lack of data on causal factors for autoimmune disease. Given that there are a wide variety of risk factors that have the potential to trigger an autoimmune disorder, many of which are disease-specific or unknown, these unidentifiable determinants could be an important source of confounding bias in a traditional analysis comparing vaccinated and unvaccinated populations. Given this issue, specialized analytical techniques that control for unknown and unmeasured confounders need to be explored to increase the validity of the results.

2.2 HPV Vaccines

There are currently two human papillomavirus (HPV) vaccines available worldwide and approved for use in Canada. Both vaccines Gardasil® (Merck, Whitehouse Station, NJ, USA) and Cervarix® (GlaxoSmithKline Biologicals, Rixenstart, Belgium) are formulated to prevent infection by virus subtypes 16 and 18, which cause 70% of all cervical cancers (Clifford et al., 2005; Muñoz et al., 2009; J. Smith et al., 2007a). Gardasil, a quadrivalent vaccine, additionally protects against HPV subtypes 6 and 11, which cause 90% of genital warts (condyloma acuminata) in men and women (Wiley et al., 2002). Considering the quadrivalent vaccine has demonstrated sustained immune responses up to 5 years post-vaccination, and is highly efficacious in preventing pre-cancerous cervical lesions (L Villa et al., 2006), it has the potential to significantly reduce the burden of HPV-related diseases in Canada. As Gardasil® is used in provincially-funded immunization campaigns across Canada (Government of Canada, 2012), this literature review will focus primarily on the quadrivalent HPV (qHPV) vaccine.
The qHPV vaccine is a recombinant vaccine that relies on its L1 major capsid proteins of HPV types 6, 11, 16 and 18 to induce an antigenic response. Other vaccine constituents include an aluminum hydroxyphosphate sulfate adjuvant, sodium chloride, L-histidine, polysorbate 80, sodium borate, and water. The qHPV vaccine is generally administered in a series of three doses, given at months zero, two and six. (Merck Canada Inc., 2013)

Adjuvants are potent stimulators of the immune system and are often added to non-live vaccines to increase and sustain its immunogenic effects, reduce the amount of antigen required, and improve efficacy. (Israeli, Agmon-Levin, Blank, & Shoenfeld, 2009; Tomljenovic & Shaw, 2012) The qHPV vaccine contains a widely used aluminum salt (Alum) as its adjuvant, which is also added to several other vaccines, such as the Diphtheria-tetanus vaccine, Hepatitis A and B vaccines, and the Inactivated Polio Virus vaccine (Leventhal, Berger, Brauer, & Cohen, 2012). Despite the benefits of Alum, which facilitates an augmented antibody response in vaccinated individuals, there have been recent concerns over its safety (Exley, Swarbrick, Gherardi, & Authier, 2009; Israeli, 2012; Satoh et al., 2003; Shoenfeld & Agmon-Levin, 2011).

Hypersensitivity reactions to aluminum reported in the literature include axillary dermatitis resulting from antiperspirant use, injection-site pruritic nodules after administration of the Diphtheria-tetanus/Acellular pertussis vaccine (Bergfors, Björkelund, & Trollfors, 2005), and aluminum granuloma following qHPV vaccination (Marsee et al., 2008). This demonstrates that adjuvants can elicit an exaggerated immune response, in certain individuals, independent of the antigenic components of the vaccine.

Adjuvants have the potential to trigger an autoimmune disorder via the same mechanisms as those of vaccines and are therefore an additional safety concern for the qHPV vaccine. In animal studies, adjuvants have been shown to inflict autoimmunity via production of autoantibodies and lupus-like disease in healthy mice. (Satoh et al., 2003) In humans, repeated exposure to Alum from vaccines has been shown to lead to macrophagic myofasciitis syndrome (MMF), an autoimmune musculoskeletal disorder and chronic fatigue syndrome. (Exley et al., 2009) Gulf
War syndrome (GWS) shares clinical similarities to MMF and may also be attributed to Alum, as veterans suffering from GWS were injected with large quantities of adjuvanted vaccine during the Gulf War (Israeli, 2012). These disorders have culminated in what has recently been defined as “ASIA syndrome” (autoimmune/auto-inflammatory syndrome induced by adjuvant). (Shoenfeld & Agmon-Levin, 2011) Since the qHPV vaccine contains the adjuvant Alum, it could contribute to the biologic ability of the vaccine to trigger an autoimmune condition.

2.3 Ontario’s HPV Vaccination Program

On July 10, 2006, Health Canada licensed the qHPV vaccine Gardasil® for use in females ages 9 – 26 to reduce the burden of HPV-related diseases. Since the vaccine is most effective prior to sexual debut, the National Advisory Committee on Immunization (NACI) recommended provincial immunization campaigns targeting girls 9 – 13 years old (or alternatively, grades 4-8), with the aim of achieving 80% vaccination coverage. (Public Health Agency of Canada, 2007) Subsequently, the federal government allocated CAN$300 million to fund provincial and territorial qHPV programs for a period of 3 years. (Morris & Nguyen, 2008)

In Ontario, the publicly-funded, school-based HPV vaccination program is delivered by the province’s 36 Public Health Units (PHUs) and administered, free of charge, to grade 8 girls on a voluntary basis. (Ministry of Health and Long-Term Care, 2014) Each year, approximately 81,000 girls become eligible for this three-dose vaccine. (Wilson, Karas, Crowcroft, Bontovics, & Deeks, 2012) Despite generally high coverage rates for school-based immunization programs, as was observed for the grade 7 Hepatitis B (80%) and Meningococcal conjugate vaccine (86%) programs, vaccine coverage for the HPV program has been much lower at 51% in 2007-2008, 58% in 2008-2009 and 59% in 2009-2010 (Wilson, Harris et al. 2013). Although it is unclear the exact cause of this low uptake, research from cross-sectional and observational studies have identified a variety of factors that may influence parental acceptance or refusal of the HPV vaccine.
2.4 Determinants of HPV Vaccination

Numerous studies have investigated the determinants of HPV vaccine acceptance. Findings have shown that parental belief in vaccine efficacy and the likelihood of acquiring an HPV infection positively influenced HPV vaccination (Brewer & Fazekas, 2007; Reiter, Brewer, Gottlieb, McRee, & Smith, 2009), whereas perceived vaccine harms, belief that the vaccine is unnecessary or may influence sexual behaviour reduced vaccination rates (Brewer & Fazekas, 2007; Laz, Rahman, & Berenson, 2012; Reiter et al., 2009; Sotiriadis et al., 2012; W. Williams et al., 2013). Ethnicity is also a determinant of HPV vaccination. Results from the United States National Health Interview Survey (2010) found that Hispanics had 1.63 (95% CI: 1.22 – 2.17) the odds of receiving the HPV vaccine compared to Caucasians (Laz et al., 2012) and a retrospective cohort study revealed that girls whose parents were born outside of the Netherlands had decreased uptake as compared to those whose parents were born in the Netherlands (ranging from OR = 0.33, 95% CI: 0.31-0.37 to OR= 0.83, 95% CI: 0.75–0.93) (Rondy, van Lier, van de Kassteele, Rust, & de Melker, 2010). Other studies have shown health behaviours such as regular visits to the family physician (Remes, 2013; L. Smith et al., 2011; W. Williams et al., 2013) and receipt of other, non-HPV vaccines to increase odds of HPV vaccination (Laz et al., 2012; Rondy et al., 2010; L. Smith et al., 2011; W. Williams et al., 2013). For example, girls who previously received the Measles, mumps, rubella (MMR), Meningococcal C, and Hepatitis B vaccines had 4.89 increased odds (95% CI: 4.04 – 5.92) of initiating the HPV vaccine. (L. Smith et al., 2011) Lower and higher socioeconomic status both appear to impact HPV initiation (Brewer & Fazekas, 2007; Rondy et al., 2010; Sotiriadis et al., 2012), whereas history of serious medical conditions such as autism (OR = 0.53, 95% CI: 0.40 – 0.70) and Down’s syndrome (OR = 0.65, 95% CI: 0.42 – 0.99) decreased the odds of HPV vaccination, likely due to the fact that these girls may not be in a grade that corresponds to their age or may not be in the school system where the HPV vaccination program is offered (Remes, 2013).
These studies demonstrate that predictors of HPV vaccine acceptance and refusal are numerous, multifactorial, and complex, and involve factors such as parental beliefs and values, ethnicity and cultural factors, socioeconomic status, parental acceptance of vaccines in general, a girl’s medical history and frequency of contact with the health care system. If these factors, or others that have not yet been identified, are also associated with the risk of developing an autoimmune disorder, they could represent important sources of confounding in vaccine safety studies. In addition, a number of the above-mentioned factors, such as parental beliefs and values, ethnicity, and cultural factors are either difficult to measure or are not available in administrative databases. Further, there are likely to be other factors that contribute to a parent’s decision to vaccinate their daughters that have not yet been identified. As such, observational studies of a vaccine’s effects require the use of specialized statistical techniques to address the problem of unmeasured and unknown confounders.

2.5 Safety Evidence of the qHPV Vaccine

Evidence about the safety of the qHPV vaccine is available from systematic reviews, randomized controlled trials (RCTs), observational studies, reports from post-marketing surveillance programs, published case reports and a report from the American Institute of Medicine. Additional evidence of a possible association between HPV vaccination and autoimmune disorders will also be discussed. Presented below is a review of each source of evidence, followed by a discussion of its limitations and knowledge gaps that need to be addressed.

2.5.1 Evidence from Experimental Studies

There have been seven published RCTs (Ault & Group, 2007; Castellsagué et al., 2011; Garland et al., 2007; Future I Group, 2007; Kang et al., 2008; Li et al., 2012; Villa et al., 2006) and one non-inferiority immunogenicity trial (Block et al., 2006) assessing efficacy and safety of
the qHPV vaccine (Table 2 - 3). Most were international, multicentre studies, with sample sizes ranging from 176 to 12,167. The study populations ranged between 9 – 45 years of age, with <5% of participants under the age of 15, since most studies recruited a population at higher risk for HPV infections and related complications. For six of these studies, participants were randomized to receive either the vaccine or its aluminum adjuvant as the placebo. One placebo-controlled trial used a saline (inert) placebo and one trial did not have a placebo group, as it was an immunogenicity study comparing antibody titers between adolescent females and males. All trials administered a 3-dose regimen over 6 months and follow-up ranged from 7 to 60 months (Table 2 – 3). In the safety analyses, the risk for serious adverse events was not significantly different between the vaccine and control groups and the authors of all studies concluded that there were no serious safety concerns associated with the qHPV vaccine.

Evidence from RCTs is generally considered strong, but the qHPV vaccine trials had a number of important limitations with regards to the assessment of the safety of this vaccine. Even with a combined sample size of 26,079, the qHPV trials did not have adequate power to detect rare but important events, such as autoimmune disorders. Indeed, a study evaluating the power to detect a doubling in risk for Guillain-barre syndrome (GBS), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and multiple sclerosis (MS) in the largest RCT carried out to date, the FUTURE II study (Ault & Group, 2007) reported the power as 5.7%, 6.4%, 8.1% and 13.9%, respectively. (L. M. Smith & Levesque, 2009) Thus, even pooling the results of these RCTs would be insufficient to detect an elevated risk for these disorders. Another limitation is that the two largest trials, FUTURE I (Garland et al., 2007) and II (Ault & Group, 2007), accounting for 68% of all trial participants, had study populations with a mean age of 20 years. With such significant under-representation of those aged 9 – 13 years, the results of the qHPV trials may not be generalizable to the populations targeted for HPV vaccination programs, as these populations may have a higher risk for certain autoimmune disorders, in part due to their younger age. Additionally, the use of an adjuvant-containing placebo as the comparison group is
problematic given that Alum has been shown to trigger an autoimmune response in both animals and humans (See Section 2.2). Thus, a comparison of the risk profiles of the adjuvanted placebo and vaccine groups could have underestimated an association, if one existed.

Since the RCTs for the qHPV vaccine were underpowered to detect a risk increase for autoimmune disorders, recruited females considerably older than those targeted by vaccination programs, and did not utilize an inert placebo as the comparator, they are insufficient to establish the safety of the HPV vaccine. This highlights the need for large population-based cohort studies with appropriate comparison groups to assess the risk for rare and serious adverse events of the qHPV vaccine.

2.5.2 Evidence from Systematic Reviews

Two review papers of the efficacy and safety of the qHPV vaccine have been published to date. (Lu, Kumar, Castellsagué, & Giuliano, 2011; Macartney, Chiu, Georgousakis, & Brotherton, 2013) The study by Lu et al included data from RCTs published up until June 2009 and assessed outcomes related to both efficacy and safety of HPV vaccines. Amongst the seven included RCTs, four evaluated the quadrivalent HPV vaccine and three were of the bivalent and monovalent HPV vaccines. The meta-analysis included a total of 21,940 females ranging in age from 15 – 44 years who were administered a three dose series of either the vaccine or a placebo and were followed from 26 to 60 months. The analysis including data from all trials demonstrated an RR of 1.00 (95% CI: 0.91 – 1.09) for the composite endpoint of “any serious adverse event” (AE) and of 1.82 (95% CI: 0.79 – 4.20) for “injection-related serious AEs.” The most frequent AEs (affecting > 50% of participants) reported were pain at injection site, headache and fatigue, and the most frequent serious AE reported was adverse pregnancy outcomes (i.e. abnormal infant, spontaneous abortion). The authors concluded that further research was required for pregnancy-related outcomes. The systematic review by Macartney and colleagues (Macartney et al., 2013) included both pre-licensure and post-licensure studies of the qHPV vaccine but reached similar
conclusions with regards to there being no statistically significant differences in serious AEs between the qHPV vaccine and placebo, including for autoimmune disorders.

Although the results of meta-analyses have more statistical power than individual studies, autoimmune disorders occur so infrequently that combining the results of small trials may not overcome the power limitations. For example, although the rate of autoimmune disorders was 2.4% in both the vaccine and placebo groups when pooling data from RCTs, most individual disorders were reported at frequencies (< 5 events) too low to allow for detectable differences in risk to be detected. As such, even meta-analyses were underpowered to detect an increased risk of autoimmune disorders following qHPV vaccination. Thus, these reviews could not provide conclusive evidence on the association for qHPV vaccine-induced autoimmunity.

2.5.3 Evidence from Observational Studies

To date, there have been four observational studies published examining the association between the qHPV vaccine and outcomes that include at least one of the autoimmune disorders studied in this thesis. Three of these studies were sponsored by the vaccine’s manufacturer, Merck and Co. (Chao et al., 2012; Klein et al., 2012; Mok, Ho, Fong, & To, 2012a)

Chao et al. conducted a retrospective cohort study of the qHPV vaccine to compare the incidence of 16 pre-specified rheumatologic, endocrine, and neurologic autoimmune conditions occurring within 180 days of qHPV vaccination to that occurring in unvaccinated females between the ages of 9-26 using administrative health data from two large, managed care organizations. (Chao et al., 2012) Although the study found a statistically significantly elevated risk for Hashimoto’s disease (HD) (Incidence rate ratio = 1.29, 95% CI: 1.08 – 1.56), but not for other autoimmune disorders, the authors stated that this was unlikely to represent a true safety signal as incident cases were randomly distributed in time post-vaccination, and several of the cases were suspected to be pre-existing in nature. Thus, the study concluded that no increased risk of autoimmune conditions was detected; however, this study had a number of important
limitations. First, there was lack of adjustment for confounders such as socio-demographics and medical history. Second, the use of unvaccinated females as the comparator group could have biased the results towards the null as vaccinated individuals have been shown to be healthier than those unvaccinated as sicker persons often defer or refuse vaccination (healthy vaccinee bias). (Arrighi, Black, Shinefield, & DeStefano, 2008; Fine & Chen, 1992) Third, the study used different methods of outcome ascertainment for vaccinated and unvaccinated individuals. Vaccinated cases identified in administrative databases were reviewed by a case review committee (CRC) consisting of rheumatologists, paediatricians, endocrinologists, neurologists and ophthalmologists, whereas unvaccinated cases were subject to Rubin’s multiple imputation to estimate the background rate of autoimmune conditions. Even the authors acknowledged that this was not a standard approach for determining the rates of outcome in an unvaccinated population, and this could have biased the rate ratio estimates if the background rate was over-estimated. Finally, the use of a six-month exposure risk window may have introduced misclassification of exposed person-time. For example, if an elevated risk for the outcome was observed from days 0 – 30, but then levelled off to reflect the background rate of disease thereafter, the point estimate would be biased towards the null. Other studies of vaccine-induced autoimmunity have generally used exposure risk windows within 90 days of vaccination, to reflect the biologic mechanism.

Another study (Klein et al., 2012) by the same research group assessed the frequency of emergency department visits and hospitalizations for a cohort of 189,629 females who received at least one dose of the qHPV vaccine using hierarchical health outcome categories with varying degrees of specificity (e.g. diseases of nervous system and sense organs, diseases of skin and subcutaneous tissue). There were four levels of outcome categories, and one of them included diabetes mellitus. The OR and 95% Confidence Intervals using days 1-60 as the risk interval for the odds of developing diabetes was 2.2 (1.1 - 4.4), and for days 1-14, was 2.5 (1.0 – 6.4). Thus there was a statistically significantly elevated risk for developing diabetes mellitus in the 1-60 days period post-vaccination, compared to a control period of 180 days that began 91 days after
the last dose. However, the risk did not remain statistically significant after adjustment for multiplicity. After considering all the results, the authors concluded that qHPV vaccination was only associated with a risk of same day syncope (OR = 6.0, 95% CI: 3.9 – 9.2) and skin infections within the two weeks post-vaccination (OR = 1.8, 95% CI: 1.3 – 2.4). Although a risk for diabetes mellitus did not remain statistically significant after adjusting for multiple comparisons, the limitations of this study need to be considered. Since it is unknown what proportion of diabetes cases were type 1 (autoimmune disorder) versus type 2 (not autoimmune in nature), a non-significant association with any diabetes mellitus does not inform us on the specific association between qHPV vaccination and risk of type 1 diabetes mellitus. Further, this study only examined hospitalization and emergency department visits. This precludes cases diagnosed in an outpatient setting, which would significantly reduce the power to study rare outcomes such as autoimmune disorders. Finally, this study only examined broad disease categories, and thus did not assess the risk for the specific autoimmune disorders most likely to be triggered by vaccination. As such, the results do not provide strong evidence against a possible qHPV vaccine-autoimmune disorder association.

The third study (Mok, Ho, Fong, & To, 2012b) used a prospective study design to compare the immunogenicity and safety of the qHPV vaccine among 50 vaccinated 18-35 year-old female SLE patients, 50 vaccinated healthy participants and 50 unvaccinated SLE patients matched on disease duration. Participants were followed for 12 months and assessed for differences in adverse events between the vaccinated SLE participants and their healthy vaccinated controls. In addition, rates of symptom exacerbation between the vaccinated SLE participants were compared to their unvaccinated SLE controls. The study reported no significant differences in frequency of adverse events between the vaccinated SLE patients and their disease-free controls and no significant difference in number of disease flares compared with their unvaccinated SLE controls (p = 0.81). Unfortunately, this study was completely underpowered to
detect such differences and the participants were much older (mean age of 25.8) than the girls to whom the vaccine is being offered in Canada.

Finally, a prospective cohort study (Gee et al., 2011) using administrative health data from seven managed care organizations sought to compare, against background rates the number of new cases of GBS, stroke, venous thromboembolism, appendicitis, anaphylaxis, seizure, syncope and allergic reactions for 600, 558 doses of qHPV vaccine in a cohort of 9 – 26 year olds in the United States. For outcomes < 150/100,000 person-years, the background rate was calculated from unvaccinated historical comparison groups and for the remaining outcomes, the background rate was obtained from a concurrent unvaccinated group. Based on 416,942 administered doses of qHPV in participants aged 9 – 17, there were no cases of GBS (the only autoimmune disorder in this study) found within the 1-42 days post-vaccination risk period (compared to an expected 0.80 events). In the adult sample (ages 18 and older) of 183,616 doses of the vaccine, 1 event was observed (yielding an RR of 2.10, based on an expected 0.48 events), although upon medical record review, the authors stated that this was a pre-existing case of GBS. Thus, this study did not show a statistically significant association with GBS. Since this analysis was based on doses of qHPV administered and individuals typically receive a three-dose series of this vaccine, the number of study participants is likely less than the number of doses. As such, the study was potentially underpowered to detect a risk for GBS in this population. Even the authors acknowledged this limitation and indicated that the analyses for rare outcomes such as GBS will be repeated once the sample has increased to one million doses. Based on this likely underpowered analysis of risk for GBS, one cannot make any conclusions on the association between qHPV vaccination and autoimmune disorders.

There are few observational studies assessing the relationship between the qHPV vaccine and risk for autoimmune disorders. While these studies did not find an elevated risk of specific autoimmune disorders, the findings from these studies are limited by use of inappropriate comparators, small sample sizes and corresponding low power, lack of control for confounders,
and lack of generalizability to the younger populations targeted by HPV vaccination programs. Consequently, there is a need for large, population-based and methodologically sound observational studies to assess the risk of autoimmune diseases associated with the use of the qHPV vaccine.

2.5.4 Evidence from Post-Market Surveillance Systems

Every jurisdiction has post-marketing surveillance systems for newly marketed pharmaceuticals and vaccines, including Canada. Most are passive surveillance systems that rely on voluntary reporting of adverse events from physicians, health professionals, and individuals. The role of these adverse events surveillance systems is to detect safety signals that may not be apparent in pre-marketing trials. Canada employs the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) that is monitored by the Vaccine Safety Division of the Public Health Agency (PHAC). (Government of Canada, 2006) This is a Federal/Provincial/Territorial monitoring system that receives reports of adverse events following immunization (AEFIs) from the provinces and territories for inclusion in a national database. This then permits the computation of the frequency and severity of AEFIs for different vaccines, the identification of possible new adverse events, and the detection of safety signals that require further investigation. However, as this data is not publicly available, the following section focuses on data from a similar program in the United States known as the Vaccine Adverse Event Reporting System (VAERS).

2.5.5 Vaccine Adverse Event Reporting System (VAERS)

An analysis of qHPV vaccine related reports submitted to VAERS between June 1, 2006 and December 31, 2008, reported that 12,424 reports had been submitted during this 2½ year period, which corresponded to a reporting rate of 53.9 adverse events per 100,000 distributed doses of the vaccine. (Slade et al., 2009) Reporting rates for AEFIs of autoimmune aetiology were no higher than the background rates for these diseases (0.2/100,000 doses distributed for
autoimmune disorders, 0.2/100,000 doses distributed for GBS, 0.04/100,000 doses distributed for Transverse myelitis, and 0.009/100,000 doses distributed for motor neuron disease). However, this type of data and analysis is subject to a number of limitations, the most important being the lack of a true denominator, under-reporting of adverse events and lack of a comparison group; limitations shared by all post-marketing surveillance systems. Since these databases have no information on the number of girls vaccinated, and only a small proportion of adverse events are reported, true incidence rates of AEFIs cannot be estimated. Instead, AEFI *reporting* rates are calculated using the number of doses sold (rather than administered) in a given time period. As qHPV immunization requires three doses of the vaccine be administered to each girl, using doses sold likely underestimated the true incidence of AEFIs. Moreover, studies have estimated the proportion of adverse events reported to range from 1% to 72% (Varricchio et al., 2004) as such reports rely on someone recognizing the temporal association and then taking the time to complete a report form. The latter would further underestimate the true incidence of AEFIs.

Finally, there is the lack of an unvaccinated comparison group for the calculation of a rate ratio. As such, post-marketing surveillance systems, including VAERS, often use the *reporting* rate of other vaccines as the (active) comparator to determine if a new vaccine is associated with an increased risk of an AEFI which could also lead to an under estimation of the true risk if the comparator vaccine also carries an (unknown) risk of the adverse event.

Post-marketing passive surveillance systems play an important role with regards to monitoring unintended adverse events and early signal detection. However, given the important limitations of this monitoring system discussed above, it is clear that while such systems fulfill an important role and can generate safety signals, they cannot be used to test hypotheses of potential harms. Moreover, estimates of *incidence* rates of AEFIs obtained from *reporting* rates likely underestimate the true incidence of an AEFI.
2.5.6 Published Case Reports

There have been case reports for eight autoimmune disorders temporally associated with the receipt of the HPV vaccine published to date (Table 2 – 4). These eight case reports described five cases of MS (Sutton, Lahoria, Tan, Clouston, & Barnett, 2009), three cases of SLE (Soldevilla, Briones, & Navarra, 2012a), two cases of central nervous system (CNS) demyelinating disease (Chang, Campagnolo, Vollmer, & Bompreszzi, 2011), a case of acute disseminated encephalomyelitis (ADEM) (Wildemann, Jarius, Hartmann, Regula, & Hametner, 2009), one case of autoimmune hepatitis (AIP) (Della Corte, Carlucci, Fracalanci, Alisi, & Nobili, 2011), one of pancreatitis (Das, Chang, Biankin, & Merrett, 2008), a case of erythema nodosum (Longueville et al., 2012) and a case of immune thrombocytopenia purpura (ITP) (Pugnet, Ysebaert, Bagheri, Montastruc, & Laurent, 2009). The patients affected ranged in age from 11-58 years old, and symptoms appeared from a few days post-vaccination, up to 4 months after vaccination. Most events (11/15) occurred after the second or third dose. The authors of these reports concluded that in the absence of any other causal factor, these cases were most likely due to a vaccine-mediated immune reaction.

Similar to the limitations of the VAERS database, these case reports do not have an adequate comparison group, so it is unknown whether these cases represent a temporal relationship with the qHPV vaccine or a causal one. However, they add to the biologically plausible nature of the HPV vaccine-autoimmune disorder relationship. Therefore, safety signals such as these require confirmation in a large population-based cohort study using an appropriate comparator.

In 2009 the Institute of Medicine (IOM) of the United States assembled a scientific committee of experts to develop a scientific approach for the assessment of causality for reports of adverse events following immunization (AEFIs). (Stratton et al., 2011) The basis of this report was to assess the evidence from epidemiologic, clinical and mechanistic studies of AEFIs to
provide a causality framework for adjudicating AEFI claims submitted to the National Vaccine Injury Compensation Program (VICP), as well as those suggested by case reports and epidemiologic studies. Amongst the 13 AEFIs assessed for a causal relationship with the HPV vaccine, six were autoimmune disorders (ADEM, transverse myelitis, neuromyelitis optica, MS, Guillain Barré syndrome, and pancreatitis). However, much of the available evidence was limited to case reports, which could only provide information about a temporal association. The few epidemiologic studies conducted at the time, lacked appropriate comparison groups and, as such, were not considered for the causality assessment. Not surprisingly, the committee concluded that there was inadequate evidence to accept or reject a causal association between the qHPV vaccine and the aforementioned autoimmune disorders. As such, there is clearly a need for high quality studies of the risk of autoimmune disorders following qHPV vaccination.

In addition to the above mentioned safety data, further evidence of potential harms associated with the use of the qHPV vaccine comes from the VICP, which has compensated 35 of 192 claims for HPV vaccine associated harms submitted as of October 1, 2012 using well established causality criteria (United States Department of Health and Human Services, 2012). Although the details of these claims, such as the types of adverse events that may be related to the qHPV vaccine, are not available to the public, they nonetheless add some credence to the hypothesis that there may be serious harm following exposure to the qHPV vaccine.

2.6 Summary

There is evidence to suggest that the qHPV vaccine could increase the risk of developing certain autoimmune disorders. First, this association is biologically plausible given the immune system mediated aetiology of autoimmune disorders and vaccines’ role in stimulating the immune system. Further, the adjuvant contained in the qHPV (Alum) has been shown to induce autoimmune-like reactions in both animals and humans and vaccine-induced autoimmunity has
been reported for several other vaccines (Chapter 1, Appendix 1 – 1). Secondly, there have been a number of cases of autoimmune disorders following qHPV vaccination reported in post-market surveillance systems and in the literature. Current evidence on the association between qHPV vaccination and autoimmune disorders is lacking, and results from the few studies conducted thus far are limited by a lack of statistical power, the use of inappropriate comparator groups, an inability to control for confounders and the recruiting of participants who are much older than those targeted by most provincial immunization programs. This highlights the need for methodologically sound, large, population-based cohort studies to address this important population health question.
2.7 References


MERCK CANADA INC. (2013). *GARDASIL® [Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine] Product Monograph* (pp. 1–60).


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2.8 Tables
### Table 2-1 Established risk factors for multiple autoimmune disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>HLA Susceptibility Genes</th>
<th>Non-HLA Susceptibility Genes</th>
<th>Evidence from twin studies&lt;sup&gt;d&lt;/sup&gt;</th>
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<tr>
<td></td>
<td>RR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>RR&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Insulin gene</td>
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<td>DQ6(02)</td>
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<td>PTPN22</td>
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<td>DR3/DR4</td>
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<td>CTLA4</td>
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<td>&gt; 150</td>
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<td>Infection</td>
<td>Clinical evidence</td>
<td>Experimental evidence (animal studies)</td>
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<tr>
<td>--------------------------------</td>
<td>---------------</td>
<td>------------------------------------------------------------------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Acute anterior uveitis</td>
<td>B27</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Goodpasture’s syndrome</td>
<td>DR2</td>
<td>15.9</td>
<td></td>
</tr>
<tr>
<td>Addison’s disease</td>
<td>DR3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Behcet’s disease</td>
<td>DR3</td>
<td>33</td>
<td>12.5</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td></td>
<td>20 – 50</td>
<td>0 – 6.5</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td></td>
<td>6.3 – 18.8</td>
<td>0 – 4.5</td>
</tr>
</tbody>
</table>

2. *Infectious agents*<sup>e</sup>

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Infection</th>
<th>Clinical evidence</th>
<th>Experimental evidence (animal studies)</th>
<th>Experimental evidence (in vitro studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>EBV</td>
<td>RA patients had 10 times the EBV as controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td></td>
<td>26% of RA patients versus 4% of controls were positive for Parvo B19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td></td>
<td>Injection of <em>M. tuberculosis</em> can induce arthritis in mice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td></td>
<td>Anti-Proteus mirabilis antibodies significantly higher in RA patients versus controls (p &lt;0.0005)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Helicobacter pylori</td>
<td></td>
<td><em>H. pylori</em> antigens produced RA auto-antibodies in B lymphocyte cultures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td>Pathogen</td>
<td>Description</td>
<td>Other Infections Reported</td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------</td>
<td>---------------------------</td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>EBV</td>
<td>MS patients are 13.5 more likely to have been infected with EBV compared to controls; association increases with age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Encephalomyelitis virus</td>
<td></td>
<td>Injection of virus produced demyelinating disease in mice</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Chlamydomphila pneumonia</em></td>
<td></td>
<td>Bacteria was found in higher concentrations in the cerebral spinal fluid of MS patients, compared to patients with other neurological disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other infections reported:</td>
<td></td>
<td><em>Plasmodium malaria (infection in adolescence)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1 Diabetes Mellitus (T1DM)</td>
<td>Rubella</td>
<td>Patients with congenital rubella syndrome (12 – 20%) have high incidence of T1DM and presence of antibodies for pancreatic cells</td>
<td>Cross-reactivity between rubella viral proteins and pancreatic cells</td>
<td></td>
</tr>
<tr>
<td>Coxsackievirus B4</td>
<td></td>
<td>Viral particles from pancreas of diabetic patients can produce T1DM in mice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV</td>
<td></td>
<td>CMV-infected patients have antibodies for pancreatic islet cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mumps</td>
<td></td>
<td>Often precedes T1DM in children</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Other infections reported: HCV, *E.coli*, *M. avium*
<table>
<thead>
<tr>
<th>Disease</th>
<th>Infection</th>
<th>Description</th>
<th>Other Infections Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
<td>EBV</td>
<td>Lupus patients have increased viral load, infected peripheral B cells, impaired T cell responses, and EBV DNA compared to controls</td>
<td></td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td></td>
<td>Infection with Parvo B19 increased disease flare-ups in lupus patients and markers of acute infection (e.g. malar rash, arthralgia, arthritis and fever) are similar to symptoms of SLE</td>
<td></td>
</tr>
<tr>
<td>CMV</td>
<td></td>
<td>CMV viral material was higher in SLE patients than healthy controls (p = 0.02)</td>
<td>Immunization with the CMV antigen induced lupus autoantibodies and glomerulonephritis</td>
</tr>
<tr>
<td>Other infections reported: HCV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatomyositis / Polymyositis</td>
<td>Cocksackievirus</td>
<td>Serological evidence in patients with DM and PM</td>
<td></td>
</tr>
<tr>
<td>Trypanosoma cruzi</td>
<td></td>
<td>Induced symptoms of DM and PM in mice, when infected</td>
<td></td>
</tr>
<tr>
<td>Other infections reported: Parvovirus B19, HIV, HTLV-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>Parvovirus B19</td>
<td>Cases had increased Parvovirus B19 DNA (75%) in biopsies as compared to healthy controls (53%)</td>
<td></td>
</tr>
<tr>
<td>Entity</td>
<td>Virus</td>
<td>Notes</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>-------</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td>CMV</td>
<td>Cases had elevated antibody titers of CMV matrix proteins compared to controls</td>
<td>In vitro, CMV proteins were capable of inducing apoptosis in endothelial cells</td>
<td></td>
</tr>
<tr>
<td>H. Pylori</td>
<td>Patients with SS had higher levels of <em>H. pylori</em> in sera compared to controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sjogren’s syndrome</td>
<td>HCV</td>
<td>Co-occurrence of Sjogren’s syndrome in chronic hepatitis C patients</td>
<td></td>
</tr>
<tr>
<td>Coxsackie virus</td>
<td>Viral RNA was found in higher concentrations in the biopsies of Sjogren’s patients compared to healthy controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBV</td>
<td>Sjogren’s patients had higher titers of EBV antibodies compared to healthy controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV</td>
<td></td>
<td>Infection with murine CMV induced Sjogren’s-like disease in mice</td>
<td></td>
</tr>
<tr>
<td>Autoimmune thyroid diseases (Grave’s and Hashimoto’s disease)</td>
<td>HCV</td>
<td>Associated with patients who have chronic HCV infection</td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td></td>
<td>Infection with influenza virus can active toll-like receptors in thyrocytes in mice</td>
<td></td>
</tr>
<tr>
<td>Other infections reported: <em>Yersinia enterocolitica</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune</td>
<td>HIV</td>
<td>HIV patients have been found to have</td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>Pathogen</td>
<td>Description</td>
<td>Other noted associations</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>---------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Thrombocytopenia purpura</td>
<td>Cross-reactivity between HIV proteins and platelet proteins, leading to platelet destruction</td>
<td></td>
<td>Cross-reactivity between platelet-associated immunoglobulin and <em>H. pylori</em> proteins</td>
</tr>
<tr>
<td><em>H. pylori</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guillain-Barre syndrome</td>
<td><em>Campylobacter jejuni</em></td>
<td>Incidence of GBS in those infected with <em>C. jejuni</em> is 1.7/1000, a rate 77 times higher compared to the general population</td>
<td></td>
</tr>
<tr>
<td><em>Brucella melitensis</em></td>
<td></td>
<td>Mice infected with <em>Brucella melitensis</em> produced auto-antibodies against ganglioside structures on nerve cells</td>
<td></td>
</tr>
<tr>
<td><em>Mycoplasma pneumoniae</em></td>
<td></td>
<td>Infected patients often develop auto-antibodies prior to onset of GBS</td>
<td></td>
</tr>
<tr>
<td><em>Haemophilus influenza</em></td>
<td></td>
<td>Infection with <em>H. influenza</em> results in cross-reactivity between gangliosides on peripheral nerves and bacterial antigens</td>
<td></td>
</tr>
<tr>
<td>Other infections reported: HIV, CMV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBD (Crohn’s disease and Ulcerative colitis)</td>
<td><em>H. pylori</em></td>
<td>Association found for particular forms of CD</td>
<td></td>
</tr>
<tr>
<td><em>Yersinia enterocolitica</em></td>
<td></td>
<td>Patients with IBD 6 – 13 years later were found to still have <em>Y. enterocolitica</em></td>
<td></td>
</tr>
</tbody>
</table>
**Mycobacterium avium paratuberculosis (MAP)**

MAP infection occurs at increased frequency in patients with CD

Molecular mimicry between MAP proteins and gastrointestinal glutathione peroxidase self-peptides

**Other infections reported:** *Clostridium difficile*, CMV, *Entamoeba hystolitica*

---

a RR1 = relative risk 1: The risk of developing the disease in those who have the gene, compared to those who do not. Based on ref (Thorsby & Lie, 2005)

b RR2 = relative risk 2: Obtained from comparing the observed number of cases with the gene to the prevalence of the gene in the general population. Based on ref (Murphy, Travers, & Walport, 2008)

c OR = odds ratio. Based on ref (Gregersen & Behrens, 2006)

d The concordance rates are based on pairwise concordances, comparing the proportion of twin pairs who have the disease, to twin pairs who do not have the disease. Based on ref (Bogdanos et al., 2012)

e Results in table are based on two literature reviews assessing the association of infections and autoimmune disorders (Ercolini & Miller, 2009; Pordeus, Szyper-Kravitz, Levy, Vaz, & Shoenfeld, 2008)
### Table 2-2 Risk factors for certain autoimmune disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Type of evidence</th>
<th>Range for strength of association (OR/RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>12 case-control studies; 4 cohort studies</td>
<td>0.6 – 3.4</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>8 case-control studies; 2 cohort studies</td>
<td>0.5 – 6.7</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>3 case-control studies; 2 cohort studies</td>
<td>1.6 – 1.9</td>
</tr>
<tr>
<td>Grave’s disease</td>
<td>8 case-control studies; 1 cohort study</td>
<td>1.3 – 8.2</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>2 case-control studies</td>
<td>1.6 – 3.5</td>
</tr>
</tbody>
</table>

#### 3. Cigarette Smoking

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Type of evidence</th>
<th>Strength of Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>12 case-control studies; 4 cohort studies</td>
<td>Women with sun-sensitive skin had 2.9 odds (95% CI: 1.6 – 5.1) of developing SLE compared to those with skin less prone to burn. Also, having been sunburned more than once in youth was associated with higher SLE risk (OR = 2.2, 95% CI: 1.2 – 4.1)</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>3 case-control studies; 2 cohort studies</td>
<td>RR = 0.67 (95% CI: 0.40 - 1.12) for vitamin D supplementation and risk of developing MS</td>
</tr>
<tr>
<td>Type I diabetes mellitus</td>
<td>4 case-control studies; 1 cohort study</td>
<td>RR = 0.47 (95% CI: 0.26 – 0.84) for MS patients who spent an average 2 hours in the sun compared to those who spent &lt; 1 hour</td>
</tr>
<tr>
<td>Grave’s disease</td>
<td>8 case-control studies; 1 cohort study</td>
<td>RR = 0.47 (95% CI: 0.26 – 0.84) for MS patients who spent an average 2 hours in the sun compared to those who spent &lt; 1 hour</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>2 case-control studies</td>
<td>Inverse correlation between sunlight and prevalence of MS</td>
</tr>
</tbody>
</table>

#### 4. UV Radiation / Vitamin D status

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Type of evidence</th>
<th>Strength of Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
<td>1 case-control study</td>
<td>Women with sun-sensitive skin had 2.9 odds (95% CI: 1.6 – 5.1) of developing SLE compared to those with skin less prone to burn. Also, having been sunburned more than once in youth was associated with higher SLE risk (OR = 2.2, 95% CI: 1.2 – 4.1)</td>
</tr>
<tr>
<td>Type I diabetes mellitus</td>
<td>4 case-control studies; 1 cohort study</td>
<td>Pooled OR = 0.71 (95% CI: 0.60 - 0.84) for vitamin D intake in infancy and risk of T1DM in childhood</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>1 prospective cohort study (Nurse’s Health Study)</td>
<td>RR = 0.67 (95% CI: 0.40 - 1.12) for vitamin D supplementation and risk of developing MS</td>
</tr>
<tr>
<td></td>
<td>1 case-control study</td>
<td>RR = 0.47 (95% CI: 0.26 – 0.84) for MS patients who spent an average 2 hours in the sun compared to those who spent &lt; 1 hour</td>
</tr>
<tr>
<td></td>
<td>Several ecologic studies</td>
<td>Inverse correlation between sunlight and prevalence of MS</td>
</tr>
</tbody>
</table>
Ulcerative colitis  2 placebo-controlled, double-blind RCTs  Fish oil significantly decreased disease activity index for the treatment group (56%) versus placebo (4%) (p <0.05)

Rheumatoid arthritis  1 prospective cohort study (Iowa Women’s Health Study)  RR = 0.67 (95% CI: 0.44–1.00) for dietary and supplemental vitamin D

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Type of Evidence</th>
<th>Association with Drug/Toxins</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLE</td>
<td>1 case-control study (The Carolina Lupus Study)</td>
<td>Occupational exposure to silica (medium versus low: OR = 2.1; 95% CI: 1.1 – 4.0; high versus low: OR = 4.6; 95% CI: 1.4 – 15.4)</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>Occupational studies</td>
<td>Silica dust (RR ~ 25 for working in an environment with silica exposure)</td>
</tr>
<tr>
<td></td>
<td>Retrospective cohort study (Women’s Health Study)</td>
<td>Silicone breast implants (RR = 1.89; 95% CI: 0.98 – 3.45)</td>
</tr>
</tbody>
</table>

aData obtained from (Costenbader & Karlson, 2006)

bData obtained from (Ascherio & Munger, 2007; Cantorna & Mahon, 2004; Zipitis & Akobeng, 2008)

cData obtained from (G Cooper et al., 1998; D’Cruz, 2000; M. A. Dooley & Hogan, 2003)
### Table 2-3 Study characteristics of the RCTs for the qHPV vaccine

<table>
<thead>
<tr>
<th>Study</th>
<th>Protocol/Trial Registry number</th>
<th>Study type</th>
<th>Phase</th>
<th>Placebo</th>
<th>N</th>
<th>Age Range</th>
<th>Study duration (months)</th>
<th>Risk for serious adverse events [95% Confidence Interval]</th>
<th>Risk for injection-related serious adverse events [95% Confidence Interval]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Villa et al., 2006</td>
<td>Protocol 007 NCT00365716</td>
<td>International, multicentre, double-blind</td>
<td>II</td>
<td>225 µg aluminum hydroxyphosphate sulfate adjuvant</td>
<td>552</td>
<td>16-23</td>
<td>60</td>
<td>1.01 [0.14, 7.10]</td>
<td>Not estimateable</td>
</tr>
<tr>
<td>Garland et al. 2007 (FUTURE I)</td>
<td>Protocol 013 NCT00092521</td>
<td>International, multicentre, double-blind</td>
<td>III</td>
<td>225 µg aluminum hydroxyphosphate sulfate adjuvant</td>
<td>5,455</td>
<td>16-24</td>
<td>48</td>
<td>1.07 [0.71, 1.60]</td>
<td>3.00 [0.12, 73.58]</td>
</tr>
<tr>
<td>Ault et al., 2007 (FUTURE II)</td>
<td>Protocol 015 NCT00092534</td>
<td>International, multicentre, double-blind</td>
<td>III</td>
<td>225 µg aluminum hydroxyphosphate sulfate adjuvant</td>
<td>12,167</td>
<td>15-26</td>
<td>48</td>
<td>0.83 [0.56, 1.24]</td>
<td>1.50 [0.25, 8.99]</td>
</tr>
<tr>
<td>Munoz et al. 2009 Castellsague et al. 2011</td>
<td>Protocol 019 NCT00090220</td>
<td>International, multicenter, double-blind</td>
<td>III</td>
<td>225 µg aluminum hydroxyphosphate sulfate adjuvant</td>
<td>3,819</td>
<td>24-45</td>
<td>48</td>
<td>0.43 [0.11, 1.65]</td>
<td>Not estimateable</td>
</tr>
<tr>
<td>Li et al. 2012</td>
<td>Not reported</td>
<td>Randomized, double-blind safety and immunogenicity study</td>
<td>--</td>
<td>225 µg aluminum hydroxyphosphate sulfate adjuvant</td>
<td>600</td>
<td>9 – 45</td>
<td>7</td>
<td>Vaccine: 0% Placebo: 0.3%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Kang et al., 2007</td>
<td>Not reported</td>
<td>Randomized, double-blind safety and immunogenicity study</td>
<td>I</td>
<td>225 µg aluminum hydroxyphosphate sulfate adjuvant</td>
<td>176</td>
<td>9 - 23</td>
<td>7</td>
<td>Vaccine: 0% Placebo: 1.7%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Block et al., 2006</td>
<td>Protocol 016</td>
<td>International, multicenter, non-inferiority</td>
<td>--</td>
<td>No placebo group</td>
<td>1,016</td>
<td>10 – 15</td>
<td>7</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

83
<table>
<thead>
<tr>
<th>Study</th>
<th>Protocol</th>
<th>Design</th>
<th>Target</th>
<th>Age</th>
<th>Follow-up</th>
<th>Vaccine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reisinger et al., 2007</td>
<td>Protocol 018</td>
<td>International, multicenter, double-blind</td>
<td>III</td>
<td>Saline</td>
<td>1,781</td>
<td>9 – 16</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11.8</td>
<td>(1.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Vaccine: 0.4%</td>
<td>Vaccine: 0.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo: 0%</td>
<td>Placebo: 0.0%</td>
<td></td>
</tr>
</tbody>
</table>

**Immunogenicity study (sub-study of RCT)**
Table 2-4 Case reports of autoimmune aetiology following uptake of the HPV vaccine

<table>
<thead>
<tr>
<th>Outcome (Country)</th>
<th>Age</th>
<th>Dose of HPV preceding event</th>
<th>Symptom onset post-vaccination (days)</th>
<th>Clinical Information/Symptoms</th>
<th>Sequelae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sutton et al., 2009</td>
<td>16</td>
<td>3</td>
<td>21</td>
<td>CIS</td>
<td>All patients experienced complete or partial recovery</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>2</td>
<td>4</td>
<td>CDMS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>2</td>
<td>1</td>
<td>CDMS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>2</td>
<td>16</td>
<td>CIS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>3</td>
<td>4</td>
<td>CDMS</td>
<td></td>
</tr>
<tr>
<td>Della Corte et al., 2011</td>
<td>11</td>
<td>?</td>
<td>5 weeks</td>
<td>Patient was naïve for SLE</td>
<td>Patient stabilized after treatment for 4 weeks</td>
</tr>
<tr>
<td>Soldevilla et al., 2012</td>
<td>17</td>
<td>2</td>
<td>2 months</td>
<td>Patient has had RA for 11 years and been in clinical remission for 1 year Their RA turned into SLE</td>
<td>Patient achieved clinical and renal remission after treatment</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>N/A</td>
<td>4 months</td>
<td></td>
<td>Patient improved after therapy and has since been maintained on meds</td>
</tr>
<tr>
<td></td>
<td>58</td>
<td>2</td>
<td>3 months</td>
<td>Patient had SLE and has been in remission for 8 years Patient experienced a severe SLE flare</td>
<td>Patient died 1 day after hospitalization</td>
</tr>
<tr>
<td>Wildemann et al., 2009</td>
<td>20</td>
<td>2</td>
<td>28 days</td>
<td>Medication did not help the patient’s symptoms, even with corticosteroids, immune suppression, etc.</td>
<td>Doctor noted this “suggests an aggressive form of ADEM possibly induced by Gardasil mediated immune activation”</td>
</tr>
<tr>
<td>Das et al., 2008</td>
<td>26</td>
<td>1</td>
<td>4</td>
<td>Doctor noted “an autoimmune mechanism is possible” And “pancreatitis was secondary to vaccination”</td>
<td>After 10 days of treatment, patient became well</td>
</tr>
<tr>
<td>Chang et al., 2011</td>
<td>18</td>
<td>1</td>
<td>6 weeks</td>
<td></td>
<td>- received a lot of meds but over next few months showed she had</td>
</tr>
<tr>
<td>Location</td>
<td>Condition</td>
<td>Age</td>
<td>Onset</td>
<td>Duration</td>
<td>Treatment Details</td>
</tr>
<tr>
<td>-----------------------</td>
<td>----------------------------------</td>
<td>-----</td>
<td>-------</td>
<td>-----------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>United States</td>
<td>After treatment with methylprednisone, patient improved</td>
<td>19</td>
<td>2</td>
<td>1 month</td>
<td></td>
</tr>
<tr>
<td>(France)</td>
<td>Erythema nodosum (France)</td>
<td>16</td>
<td>2</td>
<td>15 days</td>
<td></td>
</tr>
<tr>
<td>(France)</td>
<td>Immune thrombocytopenia purpura</td>
<td>16</td>
<td>2</td>
<td>3 months</td>
<td>Patient confirmed to have ITP by antiplatelet autoantibodies</td>
</tr>
</tbody>
</table>

*CIS = clinically isolated syndrome (could convert to Multiple Sclerosis), CDMS = clinically definitive MS*
Chapter 3

Methods

3.1 Overview of Study Design

This was a population-based retrospective cohort study carried out using Ontario’s administrative health databases. A copy of these databases are housed at the Institute for Clinical Evaluative Sciences (ICES) and anonymously linked at the individual level using an encrypted unique identifier. The cohort was assembled using birth year to identify all grade 8 girls eligible for Ontario’s school-based HPV vaccination program between 2007/2008 -2010/2011 and a girl’s vaccination status was obtained from the immunization databases of the province’s health units. Outcome ascertainment was based on physician diagnoses, emergency department visit discharge diagnoses, and hospitalization discharge diagnoses. Data analysis employed the self-controlled case series (SCCS) method, which is a self-matched, case-based method used to control all time-fixed confounders, whether measured or unmeasured. Thus, this method was used to address some of the challenges of evaluating associations between vaccines and potential adverse events using an observational design.

3.2 Data Sources and Data Quality

3.2.1 Overview of Health Care Databases

This study used four of Ontario’s health care databases: (i) the Registered Persons Database (RPDB), (ii) the Ontario Health Insurance Plan (OHIP), (iii) the National Ambulatory Care Reporting System (NACRS), and (iv) the Canadian Institute for Health Information’s (CIHI) Discharge Abstract Database (DAD) (Table 3 - 1). In addition, the Immunization Record Information System (IRIS) database was also used.
The RPDB is a database of all Ontario residents who has ever received a health card number and contains information such as sex, date of birth, date of death, and health service eligibility status. (Iron, Zagorski, Sykora, & Manuel, 2008) An ICES Key Number (IKN), which is an encrypted form of each individual’s OHIP number, allows for record linkage between the RPDB and all other ICES databases. Thus, the health information of individuals who are insured under the publicly funded system can be record-linked to assess their medical histories, use of health services and health outcomes over time. Since ICES receives regular updates for each of its health service databases, it can supplement any missing or out-dated information in the RPDB to create an enriched version of the RPDB that provides more accurate information on vital statistics. In this thesis, the RPDB database was used for the selection of cohort members, and the identification of socio-demographic information.

The OHIP database contains information on all fee-for-service claims that are insured under the publicly-funded system, and this includes services provided by physicians. (ICES: Institute for Clinical Evaluative Sciences, 2005) Submitted claims correspond to 94% of all physician billings, and services include in-hospital and out-of-hospital services and diagnostic tests. However, some services such as certain lab services, and services provided by health service organizations under alternate funding plans are not be captured under OHIP. As a result of quality control measures undertaken by ICES, the percentage of valid records in OHIP is quite high (e.g., very little to no missing data for the variables IKN, physician specialty, diagnostic code, and date of service). (J. Williams & Young, 1996) The OHIP database was used to capture both inpatient and outpatient physician diagnoses of autoimmune disorders in this study. However, there are limitations to studying rare outcomes using physician claims data. First, coding errors are possible as certain of these diseases are particularly difficult to diagnose. Second, OHIP diagnostic codes are typically truncated at the third position making them non-specific. For example, the International Classification of Diseases, 9th Revision (ICD-9) code for
immune thrombocytopenia purpura (ITP) is 287.3, but OHIP uses code 287, which includes other hemorrhagic conditions and is therefore non-specific for ITP. Finally, the appearance of a diagnostic code may not correspond to an actual diagnosis as physicians may use the disease code to represent their differential or suspected diagnosis. Given the above limitations, and the limited number of validation studies performed for OHIP-based diagnoses, there is the potential for misclassification of the outcomes under study. As such, diagnostic algorithms were developed in consultation with a Clinical Immunologist (Dr. Anne Ellis, Queen’s University), a Rheumatologist (Dr. Sasha Bernatsky, McGill University), and the Chief of Vaccine Safety in the Surveillance and Outbreak Response Division at the Public Health Agency of Canada (Dr. Barbara Law, Paediatric Infectious Diseases Specialist) to maximize the sensitivity and specificity of the outcomes identified using the OHIP database (Table 3 – 2).

The National Ambulatory Care Reporting System (NACRS) or Emergency Department (ED) visits database includes information on diagnoses and interventions performed during a patient’s visit to the ED. A CIHI re-abstraction study of NACRS data from 2004-2005 found 78.5% (± 2.3) agreement for International Classification of Diseases, 10th Revision (ICD-10) diagnostic codes and an additional 10.3% agreement for category matching. (Canadian Institute for Health Information, 2008). Thus, outcomes identified in this database are likely to be valid and this database was used to identify autoimmune disorders and infections diagnosed during emergency department visits.

The Discharge Abstract Database (DAD) or hospitalizations database captures data on inpatients and contains information on clinical data (e.g. diagnoses and procedures), patient demographics (e.g. sex, date of birth, postal code), and administrative data (e.g. dates of admission and discharge). The Ontario-specific results from the CIHI Data Quality Study of the 2009–2010 Discharge Abstract Database found 89.8% (95% CI: 88–92) agreement of ICD-10 codes when compared to chart review. (Canadian Institute for Health Information, 2012) As such,
this database was used to ascertain autoimmune conditions diagnosed during acute-care hospital visits (i.e., discharge diagnoses). This database was also used for the identification of hospital-confirmed infections, a covariate in this study.

The IRIS database is maintained by each of Ontario’s 36 Public Health Units (PHUs) and under the Day Nurseries Act (“Day Nurseries Act - Revised Regulations of Ontario 1990, Reg. 262,” 2013) and the Immunization of School Pupils Act (“Immunization of School Pupils Act, Revised Statute of Ontario 1990, c. I.1,” 2010), IRIS captures the immunization status of all mandatory and most voluntary vaccines, including the qHPV vaccine, for school-aged children. If children receive their vaccine at the family physician’s office, the physician is obligated to inform their PHU for reimbursement purposes; the PHU then updates their IRIS records accordingly. A validation study performed on all 2158 girls eligible for the 2007 and 2008 HPV vaccination program in the Kingston, Frontenac, Lennox and Addington (KFL&A) PHU found that doses of the HPV vaccine were captured with a sensitivity of 99.8% (95% CI: 99.34-99.95) and a specificity of 95.4% (95% CI: 93.7 – 96.8). (Smith LM, Lévesque L, Nasr M, 2010) In this thesis, the IRIS database was used to determine qHPV vaccination status and covariate information (receipt of non-HPV vaccines).

A limitation of using IRIS to ascertain qHPV vaccination status is that immunization data is not available beyond the date on which IRIS data was transferred to ICES (transfer date). Thus, transfer date was used as a variable for censoring follow-up. Another potential limitation was that, at the time of the current study, IRIS data was available for only 22 of 36 PHUs. Thus, this may introduce some misclassification of vaccination status if an unvaccinated girl from one of the 22 PHUs for which data was available were to move to a PHU for which data was not available, and subsequently received the qHPV vaccine. However, since the percentage of movers is likely to be small over the course of the study period, and moving is unlikely to be associated with
qHPV vaccination, or development of an autoimmune disorder, any misclassification would be non-differential.

3.3 Cohort Assembly

Since information on grade status is not available in the RPDB or IRIS, birth year was used as a proxy for grade to identify all grade 8 girls eligible for Ontario’s publicly funded, school-based qHPV immunization program between 2007/2008 and 2010/2011. Girls entering grade 8 typically turn 13 by December 31st of that year, therefore in 2007, most girls entering grade 8 would have been born in 1994. Thus, to identify girls who were eligible for the qHPV immunization program between 2007 – 2011, birth years of 1994-1997 were used. A data re-abstraction study carried out in a medium size health unit found that this approach correctly identified approximately 96.4% of eligible girls. (L. M. Smith, Levesque, Nasr, & Perry, 2010)

For each birth cohort, cohort entry (t0) began on September 1st of their grade 8 year, and cohort members were followed until the earliest of a) their date of death b) last date of known qHPV immunization status (transfer date), or c) end of study (March 31, 2012).

3.3.1 Inclusion/Exclusion Criteria

Eligible grade 8 girls whose immunization data were unavailable at the time of the study were excluded from the birth cohorts. As such, the cohort represented approximately 40% of all eligible girls in the province. Amongst these girls, they were further excluded if their immunization data was inactive. Inactive data applied to cohort members whose latest update of their immunization history occurred prior to cohort entry. These individuals likely moved out of province, or into a PHU for which data was not available. In addition, girls who received the qHPV vaccine prior to cohort entry were also excluded.
3.4 Ascertainment of HPV Vaccination Status

Information on qHPV vaccinations was obtained from the IRIS database. Any cohort member who received at least 1 dose of the qHPV vaccine was considered to be vaccinated, whereas those who did not receive any doses of qHPV were considered to be unvaccinated.

3.5 Ascertainment of Outcomes

The primary outcome of interest was the first diagnosis of any of the 12 autoimmune disorders listed in Table 3 – 2, under “Primary Composite Endpoint”. An additional six autoimmune disorders including type 1 diabetes mellitus (T1DM), Hashimoto’s disease (HD), Grave’s disease (GD), autoimmune haemolytic anemia (AIHA), ulcerative colitis (UC) and Crohn’s disease were assessed in an expanded definition of the composite endpoint for the sensitivity analysis (See Section 3.8, Sensitivity Analysis). An initial list of autoimmune disorders was generated based on biologic plausibility, as evidenced by case reports of adverse events following qHPV vaccination, post-market safety studies of the qHPV vaccine, their consideration in studies of other vaccines and their inclusion in the Institute of Medicine (IOM)’s report on the adverse effects of vaccines, (Table 3 – 3). This list was then finalized after consultation with Dr. Barbara Law (Chief of Vaccine Safety in the Surveillance and Outbreak Response Division at the Public Health Agency of Canada). However, due to the rarity of many of these disorders (rates of < 10/100,000 person-years in this age group), the resulting 12 autoimmune disorders selected for study were evaluated as a composite endpoint. Autoimmune disorders were ascertained using the physician services claims, emergency department visits, and hospitalizations databases (OHIP, NACRS, and DAD, respectively) and their corresponding diagnostic codes (Table 3 – 2). To ensure that only incident cases were included in the analysis, cases were excluded if they had a diagnostic code for any autoimmune disorder (Table 3 – 4) prior to cohort entry given that certain autoimmune conditions may be the early manifestation of other autoimmune disorders. For
example, optic neuritis (ON), a demyelinating disorder of the optic nerve often precedes multiple sclerosis (MS). (Shams & Plant, 2009)

Since autoimmune disorders are complex and require multiple tests to confirm a diagnosis, there is the potential for misdiagnosis in general practice. A study examining the diagnostic accuracy for systemic lupus erythematosus (SLE) found that this disease is over-diagnosed by family physicians, and that rheumatologists had higher odds of making a correct diagnosis compared to non-rheumatologists (OR = 3.9; 95% CI, 1.6 – 9.4). (Narain et al., 2004)

Further, a study assessing the validity of ICD-9 codes for identifying Guillain-barre syndrome (GBS) was associated with a high sensitivity (90.6%) but also a high rate of false positives (PPV = 54.8%). (Bogliun, Beghi, & Group, 2002) Another study assessing the diagnostic code for ITP in the paediatric population found a sensitivity ranging from 63 – 73% and a PPV of 65%, with PPV improving to 72% when restricting the diagnoses to haematologists. (Terrell et al., 2012)

These findings suggest that for complex outcomes such as autoimmune disorders, use of only one diagnostic code may introduce high rates of false positives, and that the additional use of physician specialty may increase specificity. For this thesis, the objective for the case definition was to achieve high sensitivity, while maximizing positive predictive value (PPV). Thus, the use of diagnostic algorithms was necessary to minimize the potential for misclassification of outcomes (Table 3 – 2).

3.5.1 Algorithms for Outcome Ascertainment

There have been relatively few studies assessing the validity of diagnostic codes for identifying autoimmune disorders, and even fewer using Ontario’s administrative health databases. The results from two Canadian database studies that have used validated algorithms for specific autoimmune disorders will be presented here.

A validation study using physician billing (the equivalent of the OHIP database) and hospitalization data conducted in Nova Scotia compared the accuracy of ICD-9 codes for
systemic autoimmune rheumatic diseases (SARDs) to medical chart review. To increase disease specificity, researchers used the following algorithm: a) \( \geq 2 \) diagnostic codes by any physician within 2 years, or b) \( \geq 1 \) diagnostic code made by a specialist such as a rheumatologist or internist, or c) \( \geq 1 \) hospitalization discharge diagnosis code. The results found an overall sensitivity of 83% for SARDs, while specificity ranged from 72.5 – 96.4% for the six diseases under study. (Bernatsky, Linehan, & Hanly, 2011b) Since the other autoimmune disorders in the composite endpoint are similar to SARDs in that they are also rare and difficult to diagnose, this validated algorithm, with the additional use of \( \geq 1 \) emergency department visit diagnostic code was applied to all outcomes except T1DM.

For diagnoses of T1DM, a disease-specific validated algorithm for physician-made diagnoses was used. (Walsh, 2012) This algorithm, which constitutes four OHIP diagnostic codes or one of three fee codes within two years, is associated with a sensitivity of 83% and a specificity of 99%. Fee codes were used because they included services specifically performed in the management of diabetes (e.g., insulin therapy support and diabetes management assessment). Thus, the case definition for a diagnosis of T1DM constituted: a) \( \geq 4 \) diagnostic codes by any physician within 2 years, or b) \( \geq 1 \) fee code within 2 years, or c) \( \geq 1 \) hospitalization discharge diagnosis code, or d) \( \geq 1 \) emergency department diagnosis code.

3.6 Ascertainment of Covariates

3.6.1 Baseline Covariates

To detect differences between HPV vaccinated and unvaccinated girls, a comparison of baseline characteristics such as socio-demographics, vaccination history, health care utilization and medical history was undertaken. Socio-demographic variables were extracted from the RPDB database, and included age at cohort entry, urban/rural status, and neighbourhood income quintile. Health care utilization was measured by the frequency and duration of hospitalizations,
emergency department visits, and outpatient physician visits in the year prior to cohort entry. Vaccination history was based on the receipt of at least one dose of a mandatory (Measles, mumps, and rubella or Diphtheria, pertussis, and tetanus vaccines) and optional (Meningococcal C or Hepatitis B) vaccine prior to cohort entry. Medical history was based on the presence of serious medical conditions such as asthma, atopy, respiratory disorders, any autoimmune disorders, HIV, cancer, hemorrhagic conditions, neurodevelopmental disorders, chronic renal failure or congenital anomalies and were ascertained from birth until cohort entry.

3.7 Statistical Analysis

3.7.1 Descriptive Analysis

A descriptive analysis was conducted to compare the baseline characteristics of vaccinated and unvaccinated girls. For all factors, means or proportions were compared, depending if the variable was continuous or categorical.

3.7.2 Primary Analysis

Cohort studies are generally analyzed using Cox proportional hazard models comparing exposed and unexposed individuals, however, it can often be difficult to adequately control for confounding bias in such analyses. For the qHPV vaccine-autoimmune disorders association, this is especially problematic given that many of the determinants of vaccination and of the outcomes are either unknown, difficult to measure, or unavailable in administrative databases. As previously mentioned, predisposing factors to vaccine avoidance, such as health status (Dahlström et al., 2010), personal beliefs and values and socioeconomic status (Kahn et al., 2009; Marlow, Waller, & Wardle, 2007; Ogilvie et al., 2007) could also be associated with the risk of developing an autoimmune disorder. Further, known risk factors for development of autoimmune conditions, such as genetic susceptibility, cannot be easily quantified and, therefore, controlled for using statistical modelling. As such, the presence of potential unmeasured and unknown
confounders justifies the use of self-matching methods, such as the self-controlled case series (SCCS) analysis.

The SCCS analysis was developed specifically to address the challenges inherent in the assessment of vaccine safety, as it is best applied to study associations from transient exposures and acute outcomes. (Whitaker, Farrington, Spiessens, & Musonda, 2006a) Vaccines are an example of a transient exposure because they are administered at single points in time, and the initial process of immunogenicity, whereby the immune system becomes stimulated after vaccination, is acute. For the SCCS, cases serve as their own controls and, therefore, their follow-up time is divided into (biologically or etiologically) exposed and unexposed intervals (Figure 3 – 1). As such, the SCCS inherently controls for all time-independent confounders including ethnicity, genetic susceptibility, health status, and personal beliefs and values. Rate ratios, calculated as the number of events during exposed person-time divided by the number during unexposed person-time and 95% confidence intervals were estimated using conditional Poisson regression to account for individual level matching.

Since the SCCS cannot implicitly control for time-dependent confounders, such as age, the presence of concomitant infections, and the receipt of concurrent vaccines, the Poisson model was adapted to control for these. Non-HPV vaccination and certain infections are risk factors for the development of autoimmune disorders and if they occurred in close proximity to the receipt of a qHPV vaccine dose, could introduce confounding. To control for confounding by age, the analysis was stratified by one-year age group and unvaccinated cases were included in the analysis as the age distribution of these cases contributed information on the age-specific incidence of autoimmune disorders, without affecting the exposure-specific point estimate. (Farrington & Whitaker, 2006) The analysis was also stratified to account for the presence of recent infections and concurrent non-qHPV vaccinations. Infections were ascertained using the corresponding diagnostic codes found in OHIP, NACRS and CIHI-DAD. These infections of
interest, Cytomegalovirus, Parvovirus B19, Hepatitis B and C, Cocksakievirus B, Influenza Type A, Campylobacter jejuni, Staphylococcus aureus and Haemophilus influenza, were chosen based on their association with multiple autoimmune disorders (see Chapter 2, Table 2-1). However, non-specific codes for “other” bacterial and viral infections were also included since many of the above-mentioned infections may not be captured by administrative databases. To control for the potentially confounding effects of non-qHPV vaccinations, information on all other vaccines received between cohort entry and cohort exit was extracted from the IRIS database. Since some vaccines (e.g. flu vaccine) are not recorded in IRIS, seasonality (stratified by period, for January – February, and March – August, and by month, from September to December) was used as a proxy for flu vaccination.

For the SCCS analysis, the period of person-time immediately following each dose of the qHPV vaccine during which the occurrence of an autoimmune disorder was considered biologically attributable to the effects of the vaccine, was taken as the “exposure risk window.” The duration of the exposure risk window was based on: (i) the underlying pathophysiology and clinical manifestation of autoimmune diseases (personal communication, Dr. Anne Ellis), (ii) the risk periods used in other studies of autoimmune disorders and vaccines (Figure 3–2), (iii) data on the time-to-onset of autoimmune disorders following qHPV vaccination obtained from the VAERS database (CDC & FDA, 2012), and (iv) a recognition that health databases capture ‘time-to-medical contact’ rather than to onset of symptoms.

Numerous studies have employed a risk-interval design, similar to that proposed in this thesis, to investigate the potential for vaccine-induced autoimmunity (Figure 3–2). Of these, six (29%) used an exposure risk window of 0–42 days post-vaccination, three (14%) used 0–60 days, one (5%) used 0–30 days, one (5%) used 0–90 days, another (5%) used 0–180 days, and the remaining studies excluded either the first day following vaccination (day 0) or the first week from the aforementioned exposure risk windows. In addition, a recent study of the risk for
juvenile rheumatoid arthritis (JRA) following qHPV vaccination found the period of highest risk to be between days 8 and 60 post-vaccination. (L. M. Smith et al., 2012) These findings are supported by the results of an analysis of the ‘time-to-symptom onset’ of the 893 case reports for qHPV-associated autoimmunity submitted to VAERS between 2006 and 2012 (Figure 3 – 3). The latter analysis found that, after an initial peak on day 0, which is most likely due to reporting bias where events occurring immediately after an immunization are more likely to be reported, an elevated rate of autoimmune disorder reports is sustained until day 60 post-vaccination. Although there appears to be no information available for days 61-90, an increased rate is also observed between days 91 to 120, albeit at a much lower rate.

Although the exposure risk window corresponding to symptom manifestation was the period of interest for the analysis, administrative databases capture the time at first contact with the health care system. As such, the primary exposure risk window that defined the period of follow up during which a case was considered attributable to the qHPV vaccine (i.e., ‘exposed person-time’) needed to account for delays that arose from the time needed to see a health provider. In addition, the duration of the exposure risk window needed to account for the time required for a clinical diagnosis to be made after symptom presentation, especially since some conditions will require a visit to a specialist. For the aforementioned reasons, and to account for any potential latent symptoms that may manifest, the exposure risk window for the primary analysis was chosen to be 7 - 60 days following each dose of the qHPV vaccine. Further justification for excluding the days immediately post-vaccination comes from the eligibility criteria outlined in the Vaccine Injury Table of the USA National Vaccine Injury Compensation Program (VICP), where the autoimmune disorder ITP is presumed to be caused by a vaccine if it occurs 7-30 days post-vaccination (United States Department of Health and Human Services).

3.7.3 Secondary Analyses
To identify the period of highest risk following vaccination, assess for effect modification, and explore the risk for individual autoimmune disorders, the following analyses were performed. To test the possibility that the risk for autoimmune disorders may vary over the 7 – 60 day primary exposure period, a time-stratified analysis was undertaken. Thus, the 7 – 60 day exposure risk window was stratified into the following periods: (i) 7 – 24 days, (ii) 25 – 42 days, and (iii) 43 – 60 days. Secondarily, to identify girls who may be at higher risk for developing an autoimmune disorder following qHPV vaccination, the primary analysis was repeated by stratifying cohort members according to predisposing risk factors indicative of a history of immune-mediated diseases (i.e. asthma, anaphylaxis and other forms of atopy). Finally, the primary analysis was repeated for the individual autoimmune disorders included in the composite endpoint, to explore whether individual disorders were influencing the overall point estimate.

3.7.4 Sensitivity Analysis

The robustness of the results to assumptions made in the execution of this thesis was tested in sensitivity analyses. First, to determine if any aetiological-relevant outcomes were excluded from the primary composite endpoint, the primary analysis was repeated using an expanded composite endpoint of all autoimmune disorders outlined in Table 3 – 2. Second, to address the possibility of misclassification of exposure, the primary risk period of 7 – 60 days was widened to a) 0 – 60 days, b) 7-90 days, and c) 7-180 days. These exposure risk windows have been used in previous studies and thus may be biologically relevant for autoimmune diseases.

All statistical analyses were conducted using SAS version 9.3 (SAS institute Inc., USA) and STATA version 11 (Statacorp, USA).
3.8 Ethics

All IRIS data from Ontario’s public health units and ICES data accessed at Queen’s University were rendered anonymous using a unique encrypted identifier. Further, potentially identifying information such as dates of birth and postal codes were removed from all data sets. No individuals were contacted in the execution of this thesis, and all results were disseminated in aggregate form. This thesis was approved by the Research Ethics Board of Queen’s University.
3.9 References


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3.10 Tables and Figures
<table>
<thead>
<tr>
<th>Name of database</th>
<th>Description</th>
<th>Source</th>
<th>Variables within database</th>
<th>Variables extracted</th>
<th>Diagnostic record</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPDB (Registered Persons Database)</td>
<td>Registry of all Ontarians eligible for health services insured under OHIP</td>
<td>MOHLTC (Ministry of Health and Long-Term Care)</td>
<td>- health card number&lt;br&gt;- sex&lt;br&gt;- date of birth&lt;br&gt;- date of death&lt;br&gt;- postal code&lt;br&gt;- health service eligibility status&lt;br&gt;- IKN</td>
<td>- demographic information</td>
<td>N/A</td>
</tr>
<tr>
<td>IRIS (Immunization Recording Information Systems)</td>
<td>Database of the immunization status of all school-aged children for mandatory and voluntary vaccines</td>
<td>Each of Ontario’s 36 Public Health Units</td>
<td>- immunization status&lt;br&gt;- vaccination history&lt;br&gt;- date of vaccination&lt;br&gt;- number of doses received&lt;br&gt;- demographics&lt;br&gt;- school</td>
<td>- demographic information for probabilistic record linkage&lt;br&gt;- vaccination status (for qHPV and non-HPV vaccines) and date of vaccination</td>
<td>N/A</td>
</tr>
<tr>
<td>OHIP (Ontario Health Insurance Plan)</td>
<td>Administrative database for billing of services that are insured under the publicly funded system</td>
<td>MOHLTC</td>
<td>- service provided&lt;br&gt;- diagnostic code&lt;br&gt;- fee code&lt;br&gt;- date of service&lt;br&gt;- patient and physician identifiers (encrypted)&lt;br&gt;- IKN</td>
<td>- diagnostic codes and date of diagnosis for primary care consultations&lt;br&gt;-physician specialty</td>
<td>dxcode: 3-digit diagnostic code (based on ICD-9)&lt;br&gt;- type: 1 character “type of diagnosis” code&lt;br&gt;- suffix: 1 character suffix code&lt;br&gt;- must contain all 3 elements for a unique diagnosis</td>
</tr>
</tbody>
</table>
| NACRS (National Ambulatory Care Reporting System) | Database of ambulatory and care use | CIHI (Canadian Institute of Health Information) | - demographics  
| - diagnoses and procedures made during emergency room visits, day surgery visits, diagnostic procedures and outpatient services  
| - administrative data  
| - financial data  
| - IKN | - diagnostic codes and date of diagnosis for emergency room visits | - 1 – 10 diagnoses  
| - ICD-9 codes used prior to 2002, ICD-10 now used  
| - 1 character for associated type of dxcode (dxtype) |

| DAD (Discharge Abstract Database) | Database of acute-care hospital usage | CIHI | - demographics (sex, DOB, postal code, etc.)  
| - administrative data (institution, length of stay, etc.)  
| - clinical data (diagnoses, procedures, physician)  
| -IKN | -diagnostic codes and date of diagnosis for acute-care hospitalizations | Since 2002:  
| - 1 diagnosis  
| - each record contains 1 – 25 fields for diagnoses (dx10code1 – dxcode25)  
| - ICD-9 codes used prior to 2002, ICD-10 now used  
| - 1 character for associated type of dxcode (dxtype) |
### Table 3-2 Autoimmune Disorders included in the Composite Endpoint and the associated OHIP and ICD-10 codes for Case Ascertainment

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>Physician Billing Data</th>
<th>Hospitalizations and Emergency Department Visits</th>
<th>Primary Composite Endpoint</th>
<th>Expanded Composite Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>i) ≥ 2 OHIP diagnostic codes within 2 years (any physician diagnosis) or</td>
<td>i) ≥ 2 OHIP diagnostic codes within 2 years (any physician diagnosis) or</td>
<td>≥ 1 ICD-10 diagnostic code (in any of the</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ii) ≥ 1 OHIP diagnostic code diagnosed by a specialist</td>
<td>ii) ≥ 1 OHIP diagnostic code diagnosed by a specialist</td>
<td>diagnostic fields)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disorder</td>
<td>Disorder</td>
<td>Disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune thrombocytopenia purpura</td>
<td>287</td>
<td>D69.3, D69.4</td>
<td>(Stowe et al., 2008)</td>
<td>X</td>
</tr>
<tr>
<td>SARDs (includes SLE, Scleroderma, Sjogren’s syndrome, Dermatomyositis and</td>
<td>710</td>
<td>M32.1, M32.8, M32.9, M34.0, M34.1, M34.8, M34.9, M35.0, M33.0, M33.1, M33.9, M33.2</td>
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*Type 1 Diabetes fee code Q040 is for diabetes management incentive, K029 is for insulin therapy support, and K030 is for diabetes management assessment*
Table 3-3 Justification for the inclusion of certain autoimmune disorders* in the composite endpoint

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<th>Outcome is of interest to CDC, FDA, and UK Health Protection Agency for H1N1 vaccine (Black et al., 2009)</th>
<th>Outcome is of interest to USA regulatory agency (Institute of Medicine) for the HPV vaccine (Stratton et al., 2011)</th>
<th>Outcome is of interest and/or reported to USA Postlicensure Safety Surveillance for qHPV (Slade et al 2009)</th>
<th>Outcome is of interest to pharmaceutical companies for qHPV (Chao et al 2012)</th>
<th>Outcome was reported after enrollment in Gardasil clinical trials (Tomljenovic et al 2012)</th>
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*These autoimmune outcomes have the biologic potential to be associated with the qHPV vaccine, as determined by government regulatory agencies, pharmaceutical companies, passive surveillance systems, clinical trials and published case reports*
Table 3-4 Diagnostic codes used to identify a history of any autoimmune disorder in the OHIP, NACRS and CIHI-DAD databases

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**Other Autoimmune Disorders**

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<td>Optic neuritis</td>
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Primary Analysis

Cohort entry: September 1, 2007/08/09/10

End of Study: March 31, 2011

Exposed time during follow-up

Unexposed time during follow-up
**Figure 3-2 Exposure risk windows used in other observational studies employing a risk interval design assessing for vaccine-induced autoimmunity**

<table>
<thead>
<tr>
<th>Outcome</th>
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<td>multiple</td>
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<td>ITP</td>
<td>France et al 2008</td>
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<tr>
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<td>Miller et al 2001</td>
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<td>Slowe et al 2006</td>
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<tr>
<td>ON</td>
<td>Payne et al 2006</td>
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*ITP = Immune thrombocytopenia purpura, ADEM = Acute disseminated encephalomyelitis, MS = Multiple Sclerosis, GBS = Guillain-barre syndrome, AIHA = Autoimmune haemolytic anemia, ON = Optic neuritis*
Figure 3-3 Results from the Vaccine Adverse Event Reporting System (VAERS) database for adverse events of autoimmune aetiology following qHPV vaccination (July 25, 2012)

*Days 60 – 90 had missing data for all outcomes related to the qHPV vaccine; from Day 15 and onwards, the numbers are average daily reporting rates*
Chapter 4

Assessing the Risk for Autoimmune Disorders Following Use of the Quadrivalent Human Papillomavirus Vaccine: The Ontario Grade 8 HPV Vaccine Cohort Study

4.1 ABSTRACT

**Introduction:** In 2007 Ontario implemented a quadrivalent human papillomavirus (qHPV) vaccination program targeting grade 8 girls to prevent infection by the virus that causes cervical cancer. Despite being 6 years post-program implementation, few post-licensure studies have assessed its safety among adolescent girls. Thus, it is important to evaluate the safety of the qHPV vaccine particularly with regards to serious adverse events following vaccination that are targeted by regulatory agencies.

**Objectives:** To assess the risk of autoimmune disorders following qHPV vaccination of adolescent girls.

**Methods:** This was a population-based retrospective cohort study using information from Ontario’s administrative health and immunization databases. Statistical analyses employed the self-controlled case series method, comparing event rates during days 7-60 post-dose (exposed follow-up) to that at any other time (unexposed). Rate ratios (RR) and 95% confidence intervals (CI) were estimated using conditional Poisson regression.

**Results:** The rate ratio (RR) for developing a new autoimmune disorder following qHPV vaccination, adjusted for age, seasonality, other vaccines and infections was 1.28 (95% CI: 0.87 – 1.89), and this association was independent of a history of immune-mediated diseases (p=0.39).
These data suggested the possibility of a small increased risk for Bell’s palsy (RR=2.30; 95% CI, 0.67-7.95), systemic autoimmune rheumatic disorders (RR=1.84; 95% CI, 0.42-8.02), Hashimoto’s disease (RR=1.39; 95% CI, 0.46-4.22), and juvenile rheumatoid arthritis (RR=1.31; 95% CI, 0.83-2.08), however these analyses were based on a small number of exposed cases.

**Conclusion:** Overall, there was not a statistically significant risk for autoimmune disorders following qHPV vaccination. However, since the results from the exploratory analysis indicate that a possible elevated risk may exist for a subset of these disorders, the results from this analysis need to be pooled with those of other studies to confirm whether these are true safety signals.
4.2 INTRODUCTION

The human papillomavirus (HPV) types 16 (HPV-16) and 18 (HPV-18) are responsible for 70% of cervical cancers (J. Smith et al., 2007b). Two HPV vaccines have been developed to date to prevent infection by these oncogenic strains, including the bivalent vaccine Cervarix® (GlaxoSmithKline Biologicals, Rixenstart, Belgium), and a quadrivalent HPV (qHPV) vaccine Gardasil® (Merck, Whitehouse Station, New Jersey, USA), which additionally protects against two non-oncogenic strains that cause 90% of genital warts. Since the qHPV vaccine has, in clinical trials, demonstrated 99% and 44% efficacy for the prevention of potential pre-cancerous cervical lesions in per-protocol and intention-to-treat populations, respectively (Ault & Group, 2007), its use in population-based immunization programs can significantly reduce the burden of HPV-related diseases; particularly in developing countries, where rates of cervical cancer are the highest (Clifford et al., 2005). As such, over 100 countries have approved the use of these vaccines. Canada, by recommendation of the National Advisory Committee on Immunization (NACI) (Government of Canada, 2012), implemented a national HPV immunization strategy in 2007, allocating over $300CAD million in federal funds to provinces and territories to deliver the qHPV vaccine through school-based clinics (Colucci, Hryniuk, & Savage, 2008). However, despite the anticipated 90% coverage rates needed to achieve cost-effectiveness (Brisson, Van de Velde, De Wals, & Boily, 2007), uptake of the qHPV vaccine has been low in Canada (50 – 80%) and elsewhere (53% in the United States) ((CDC), 2013). This low uptake has been attributed, in part, to parental concerns over safety (Trim, Nagji, Elit, & Roy, 2012). Thus, it is important to assess the safety of the qHPV vaccine so that parents and policymakers have the data needed to make informed decisions about use of this vaccine.

Autoimmune disorders are a group of over 80 diseases that result from an aberrant immune response that leads to the self-mediated destruction of tissues and organs (Davidson & Diamond, 2001; Noel Rose, 2004a). Although the cause of these disorders remains largely unknown, it is
believed that they are the result of an external trigger that can induce disease in those who are genetically susceptible (Albert & Inman, 1999; Selmi, 2012). Vaccines have been studied as a purported trigger for autoimmunity due to their immune-system stimulating effects. The biologic plausibility of this association is supported by a number of observational studies demonstrating significantly elevated risks for autoimmune disorders following vaccination with the Measles, mumps, rubella (MMR) vaccine (France et al., 2008; Miller et al., 2001), the Hepatitis B vaccine (Hernán, Jick, Olek, & Jick, 2004), and the Influenza vaccine (Juurlink et al., 2006a; Mutsch et al., 2004). Moreover, government regulatory agencies (Bardage et al., 2011; Black et al., 2009; Slade et al., 2009; Stratton et al., 2011) and pharmaceutical companies (Chao et al., 2012) have targeted autoimmune disorders as potential adverse events following vaccination within their post-market surveillance programs of all vaccines, including the HPV vaccine.

The association between the qHPV vaccine and autoimmune disorders has not been studied extensively. Randomized controlled trials of the HPV vaccine had less than 15% power to detect a doubling of the risk of autoimmune disorders, (L. Smith & Levesque, 2009) and the few post-marketing studies published to date have either had important methodological limitations or studied populations much older than adolescent girls targeted by qHPV immunization campaigns in most countries. Thus, we undertook a population-based, retrospective cohort study to assess the risk of autoimmune disorders following use of the qHPV vaccine among grade 8 girls eligible for Ontario’s HPV vaccination program.

### 4.3 METHODS

#### 4.3.1 Study population and data sources

We identified a population-based cohort of all girls eligible for Ontario’s grade 8 HPV vaccination program between 2007 and 2011 using the province’s administrative health and immunization databases. The administrative health databases used included the: (i) Registered Persons Database (RPDB) which contains demographic information on all residents who hold or
have held a valid health card in the province, (ii) Ontario Health Insurance Plan (OHIP) database for information on physicians’ services and procedures claims, (iii) National Ambulatory Care System (NACRS) for information on emergency department visits, and (iv) Canadian Institute for Health Information’s Discharge Abstract Database (CIHI-DAD) which contains detailed information on all hospitalizations. Generated by Ontario’s universal health care programs, an anonymized copy of these databases are housed at the Institute for Clinical Evaluative Sciences (ICES), and have been used extensively for research purposes (ICES: Institute for Clinical Evaluative Sciences). All databases were linked using an encrypted unique identifier, thus allowing for the follow-up of cohort members at the individual-level.

The Immunization Record Information System (IRIS) database, maintained by each of Ontario’s 36 public health units (PHUs), was originally developed by the Ministry of Health and Long-Term Care to enable PHUs to track and record vaccinations mandated under the Immunizations of School Pupils Act ("Immunization of School Pupils Act, Revised Statute of Ontario 1990, c. I.1,” 2010) and the Day Nurseries Act ("Day Nurseries Act - Revised Regulations of Ontario 1990, Reg. 262,” 2013). IRIS is also used to record detailed information on optional vaccines (including the qHPV vaccine) administered under the province’s publicly funded vaccination programs. At the time of the current study, a copy of IRIS from 32 PHUs had been transferred to ICES under data sharing agreements, and 22 of them had been record-linked and anonymized, and were available for use. A validation study performed using the IRIS records of all 2158 girls residing in the Kingston, Frontenac, Lennox and Addington (KFL&A) PHU and eligible for the 2007/08 and 2008/09 HPV vaccination program found that doses of the qHPV vaccine were captured with a sensitivity of 99.8% (95% CI: 99.34-99.95) and a specificity of 95.4% (95% CI: 93.7 – 96.8). (L. M. Smith et al., 2010)

4.3.2 Ontario’s HPV vaccination program
Ontario’s publicly funded HPV vaccination program, first introduced in September 2007, provides the qHPV vaccine free of charge to all grade 8 girls through school-based clinics administered by the province’s 36 PHUs. (Ministry of Health and Long-Term Care, 2014) This optional vaccine usually requires parental consent and is typically administered in September/October, November/December, and March/April of each year, corresponding to the recommended 0, 2 and 6-month dosing interval for the 3-dose series. Eligible girls also have the option of obtaining the vaccine at their PHU or physician’s office, although the vast majority of them receive it at school. Prior to September 2012 (i.e., during the study period), eligible girls had until the end of August of their grade 8 year to initiate the qHPV vaccine series and until the end of grade 9 to complete it in order to receive the vaccine free of charge. All doses of the HPV vaccine given to eligible girls are documented in the IRIS database regardless of where they were administered.

4.3.3 Study cohort

Girls eligible for Ontario’s HPV vaccination program between 2007 and 2011 were identified using birth year as information on school grade was not available. Since the majority of girls entering grade 8 turn 13 by December 31st of that year, girls eligible for the HPV vaccination program for the academic years 2007/08 – 2010/11 were born in 1994 – 1997. Girls who either died or received ≥1 dose of the HPV vaccine prior to program eligibility (i.e., grade 8) were excluded from the cohort. In addition, girls whose immunization records were either not available (i.e., not yet transferred to ICES or record-linked) or inactive (i.e., moved out-of-province or to a PHU whose IRIS records were unavailable at the time of the analysis) were also excluded. Cohort members were followed from September 1st of their grade 8 year (cohort entry), until the earliest of one of the following dates: death, transfer of IRIS database to ICES (beyond which information on immunizations was unavailable), or study end (March 31, 2012).

4.3.4 HPV vaccination status
HPV vaccination status and dates of vaccination were determined using the IRIS database. Cohort members who received at least one dose of the qHPV vaccine during study follow-up were classified as “vaccinated.”

4.3.5 Study outcomes

The primary outcome was a first diagnosis for any of 12 autoimmune disorders included in the composite endpoint of ‘any autoimmune disorder’ (Chapter 3, Table 3-2). The autoimmune disorders included in the composite endpoint were those: (i) targeted for post-marketing surveillance by regulatory agencies (Bardage et al., 2011; Black et al., 2009) and manufacturers (Chao et al., 2012), (ii) identified in case reports, (Chang et al., 2011; Das et al., 2008; Della Corte et al., 2011; Longueville et al., 2012; Pugnet et al., 2009; Soldevilla, Briones, & Navarra, 2012b; Sutton et al., 2009; Wildemann et al., 2009), and (iii) reported to the US Vaccine Adverse Event Reporting System (VAERS) (CDC & FDA, 2013; Slade et al., 2009) as being temporally associated with qHPV vaccination. A composite endpoint was chosen as the primary outcome since many of these autoimmune disorders are rare.

Autoimmune disorders were ascertained using the physician services claims, emergency department visits, and hospitalizations databases (OHIP, NACRS, and CIHI-DAD, respectively) and the corresponding OHIP and International Classification of Diseases version 10 (ICD-10) diagnostic codes. Only incident cases were included; therefore cohort members with a diagnostic code for any autoimmune disorder prior to cohort entry were excluded from the analysis. Since few of the autoimmune disorders included in the composite endpoint have been validated, a validated algorithm for identifying systemic autoimmune rheumatic disorders (SARDs) using administrative health data was adapted for this study. This algorithm is associated with a sensitivity of 83% and a specificity ranging from 72.5 – 96.4% for individual SARDs. (Bernatsky, Linehan, & Hanly, 2011a) Thus, we identified cases according to the fulfillment of at least one of the following criteria: a) ≥ 2 diagnostic codes by any physician within two years, b) ≥
1 diagnostic code made by a specialist, c) ≥ 1 hospitalization with a corresponding discharge diagnosis code, or d) ≥ 1 emergency department visit with a corresponding diagnostic code.

4.3.6 Statistical Analysis

Cohort studies are typically analyzed using Cox proportional hazard regression comparing exposed and unexposed individuals. However, it can often be difficult to adequately control for confounding in such analyses. (Fine & Chen, 1992) This is especially problematic for the qHPV vaccine-autoimmune disorder association since many of the determinants of vaccination and of autoimmune disorders are either unknown, difficult to measure, or unavailable in administrative databases. As such, this study employed the self-controlled case series (SCCS) analysis, which is a self-matched, case-based method specifically developed for vaccine safety research. (Whitaker et al., 2006a) With this method, vaccinated cases serve as their own controls because their follow-up time is divided into (biologically) exposed and unexposed intervals. As such, the SCCS implicitly controls for all time-independent confounders such as ethnicity, genetic susceptibility, personal beliefs and values and health behaviours.

For this study, the period of follow-up during which the occurrence of an event was considered biologically attributable to the effects of the qHPV vaccine (i.e., exposed follow-up time or exposure risk window) was days 7-60 post-vaccination. This exposure risk period was based on: (i) the underlying pathophysiology and clinical manifestation of autoimmune diseases, (ii) the risk period used in studies of other vaccines, (France et al., 2008; Hernán et al., 2004; Juurlink et al., 2006a; Mutsch et al., 2004) (iii) data on the time-to-onset of autoimmune diseases following qHPV vaccination obtained from the VAERS database, and (iv) a recognition that health databases capture time-to-medical contact rather than time-to-onset of symptoms. All other follow-up time was considered unexposed. The incidence rate for “exposed” follow-up time was compared to that for “unexposed” follow-up, and rate ratios (RRs) and 95% confidence intervals
(CIs) were estimated using conditional Poisson regression to account for the self-matched nature of the data.

The potentially confounding effects of time-dependent risk factors for autoimmune disorders, such as age (by year), seasonality as a proxy for flu vaccination (September to December individually, January-February, March-August), recent infections (within 7-60 days of developing the outcome), and receipt of concurrent vaccines which may overlap the risk period of qHPV vaccination (within 7-60 days of developing the outcome) were controlled for by stratifying the follow-up time accordingly. To further control for the potentially important confounding effects of age, unvaccinated cases were included in a subsequent analysis as the age distribution of these cases contributed information on the age-specific incidence of autoimmune disorders, without affecting the exposure-specific rate ratios (Whitaker, Farrington, Spiessens, & Musonda, 2006b).

To identify subgroups who may be at higher risk of autoimmune disorders, the primary analysis was repeated according to a history of immune-mediated diseases (i.e. asthma, anaphylaxis and other manifestations of atopy). Secondarily, since the risk for autoimmune disorders following qHPV vaccination may not be constant over time, the primary exposure risk window of 7 – 60 days was time-stratified into the periods 7-24, 25-42, and 43-60. Finally, the primary analysis was repeated for individual autoimmune disorders to explore whether any one of these strongly influenced the overall rate ratio.

The robustness of our results under the assumptions made was tested in planned sensitivity analyses. First, to determine if any aetiologically-relevant outcomes were excluded from the primary composite endpoint, the primary analysis was repeated using an expanded composite endpoint of all autoimmune disorders outlined in Table 3-2. Second, to address the concern that the symptoms of some autoimmune disorders are insidious and thus disease onset may precede qHPV vaccination, the analysis was repeated on a subset of cases that excluded those occurring ≤30 days of vaccination. Finally, to address the possibility of misclassification of exposure due to
mis-specified exposure risk windows, the primary risk period of 7 – 60 days was widened to 0–60, 7-90, and 7-180 days; these exposure risk periods have been used in previous vaccine safety studies.

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

4.4 RESULTS

The cohort consisted of 125,575 girls eligible for Ontario’s HPV vaccination program between 2007-2011 (Figure 4-1). Eligible girls were on average 13.2 years of age (range = 12.7 – 13.7) at cohort entry, and were followed-up for a mean of 2.5 years (SD = 1.09). A total of 72,397 (57.7%) girls received at least one dose of the qHPV vaccine, most of whom received all 3 doses of the vaccine (86.0%).

Amongst the 361 incident cases of the composite endpoint of autoimmune disorders identified during study follow-up, 212 (58.7%) occurred among vaccinated girls (Table 4-1), with 39 (18.4%) of them occurring during the primary exposure risk period of 7–60 days following vaccination (i.e., “exposed” cases) (Figure 4-2). Exposed cases were just as likely to be diagnosed after the first dose of the vaccine (n = 13), as the second (n = 16) or third dose (n = 10), and the majority (77.5%) of exposed cases received all 3 doses of the HPV vaccine. The composite endpoint consisted primarily of cases of juvenile rheumatoid arthritis (JRA), followed by immune thrombocytopenia purpura (ITP), Bell’s palsy, and SARDs (Table 4-1).

Receipt of the qHPV vaccine was not associated with a statistically significant risk of developing an autoimmune disorder (RRadj. = 1.28, 95% CI: 0.87 – 1.89), and this association was independent of a girl’s history of immune-mediated diseases (p = 0.39) (Table 4-2). Age at onset of outcome was not a significant determinant of autoimmune disorders, as the risk did not change significantly for 13 – 17 year-olds, compared to those 12 years of age. Seasonality was also not a significant predictor of autoimmune disorders, and although receipt of other vaccines was
associated with a 37% increased risk of developing an autoimmune disorder, this was not statistically significant (95% CI: 0.81 – 2.31). Having a recent infection, however, was associated with an almost twofold increased risk of developing an autoimmune disorder (RR_{adj} = 1.96, 95% CI: 1.03 – 3.71).

For the analysis stratifying the primary exposure risk window of 7 – 60 days to determine the period of highest risk (Table 4 – 3), results showed that for the periods 7 – 24 days, 25 – 42 days, and 43 – 60 days post-vaccination, the adjusted point estimates ranged from 0.87 to 1.62, thus suggesting the risk of autoimmune disease following qHPV vaccination appeared to increase as a function of time since vaccination. However, these risks were statistically indistinguishable, as shown by their overlapping 95% confidence intervals (Table 4 – 3).

The analysis of individual autoimmune disorders included in the composite endpoint showed non-statistically significant elevated risks for Bell’s palsy, SARDs, and JRA following qHPV vaccination, whereas the associations for ITP was associated with a non-significant decreased risk following HPV vaccination (Figure 4-3). However, with the exception of JRA, these analyses were based on a very small number of cases.

The results of the primary analysis using an expanded outcome definition of the composite endpoint (Table 3-2) and excluding cases occurring within 30 days of qHPV vaccination were essentially unchanged (RR_{adj} = 1.11, 95% CI: 0.83 – 1.48 and RR_{adj} = 1.44, 95% CI: 0.95 – 2.19). The qHPV vaccine-autoimmune disorder association was also unaffected by the inclusion of the seven days immediately following qHPV vaccination (RR_{adj} = 1.20, 95% CI: 0.82-1.76) or the addition of 30 days to the primary exposure risk window (RR_{adj} = 1.24, 95% CI: 0.86-1.77). However, the rate ratio approached unity when the risk period was expanded to 180 days post-vaccination (RR_{adj} = 1.05, 95% CI: 0.75 – 1.46).
4.5 DISCUSSION

This is the first observational study of the safety of the qHPV vaccine to use a self-matched analysis that implicitly controls for all time-independent confounders, including those that are unknown and unmeasured. This population-based study found no statistically significant increased risk for the composite endpoint of twelve autoimmune disorders in a cohort of adolescent girls aged 12-17 years. Moreover, this association was independent of a history of immune-mediated diseases. However, we cannot rule out the possibility of a small increased risk for certain autoimmune disorders. For example, the results suggested the possibility of a small increased risk for juvenile rheumatoid arthritis (JRA), Hashimoto’s disease (HD), Bell’s palsy, and systemic autoimmune rheumatic disorders (SARDs), although none of these associations were statistically significant given the small number of exposed cases observed for each.

These findings are, for the most part, consistent with those of two recently published cohort studies which reported no increased risk of autoimmune disorders following qHPV vaccination. (Arnheim-Dahlström, Pasternak, Svanström, Sparén, & Hviid, 2013; Chao et al., 2012) While our results suggest the possibility of an increased risk for HD, Chao et al., found a statistically significant increased risk for this disorder (RR 2.02; 95% CI 1.65-2.60) (Chao et al., 2012). However, these authors concluded that this was unlikely to represent a true safety signal since i) autoimmune thyroid conditions post-vaccination have not been consistently reported in the literature, ii) no clustering of cases around the time of vaccination was detected, and iii) many of the cases were suspected to be new-onset prior to vaccination. Moreover, their analysis was based on a significantly larger number of cases than ours. Similar to our findings, the other two studies also found no risk increase for Grave’s disease, despite using different statistical analyses and exposure risk periods. In contrast to our findings of no association for TIDM, Arnheim-Dahlström et al., reported a significantly increased risk (RR 1.29; 95% CI 1.03-1.62), whereas Chao and colleagues found an inverse association (RR 0.54; 95% CI 0.45-0.70). However, these two studies compared vaccinated and unvaccinated girls, an approach that is susceptible to
confounding bias. As it is improbable that qHPV vaccination results in a 46% risk reduction for TIDM, this association is most likely the result of an underestimation of the risk of events among unvaccinated girls given that this rate was derived through Rubin’s multiple imputations rather than being estimated directly from the study population (Chao et al., 2012). The latter likely explains the 64% significant risk reduction for JRA also reported by Chao and colleagues. On the other hand, Arnheim-Dahlström and colleagues suggested that the increased risk of TIDM in their study was likely due to a type I error. However, it is also possible that this positive association was the result of confounding bias, which in our study was implicitly controlled for. Finally, although the rate ratio for SARDs or systemic lupus was elevated in our study and that of Arnheim-Dahlström et al., (RR 1.35; 95% CI 0.69 – 2.67), both were based on a small number of exposed cases and thus, statistically non-significant.

Although there is still some uncertainty about the true nature of the association between qHPV vaccination and a few rare autoimmune disorders, as discussed above, such associations are nonetheless biologically plausible. First, certain autoimmune disorders including GBS (De Wals et al., 2012; Juurlink et al., 2006b; Wise et al., 2012), ITP (France et al., 2008; Miller et al., 2001), SLE (D. Geier & Geier, 2005), MS (D. Geier & Geier, 2005; Hernán et al., 2004), Bell’s palsy (Mutsch et al., 2004), ON (D. Geier & Geier, 2005), Crohn’s disease and ulcerative colitis (Thompson et al., 1995) have, in rare circumstances, been associated with the use of other vaccines (Chapter 1, Table 1-1). Second, the qPHV vaccine contains an aluminum salt (Alum) as an adjuvant, which is a potent stimulator of the immune system that can elicit an exaggerated immune response in certain genetically predisposed individuals, independent of the antigenic component of the vaccine. Animal studies have demonstrated that aluminum-based adjuvants can produce autoantibodies and lupus-like disease in healthy mice, (Satoh et al, 2003), and macrophagic myofaciitis and chronic fatigue syndromes have been reported in humans (Exley et
al., 2009). However, assessing vaccine-induced autoimmunity is difficult for these rare disorders and even large studies may have limited ability to study such outcomes.

This study has a number of limitations that need to be considered. First, there is the potential for misclassification of exposure status due to the choice of the exposure risk window. Although the exposure risk window of 7-60 days was based on the underlying pathophysiology and clinical manifestation of autoimmune disorders, the risk period used in other vaccine studies, and data on time-to-onset of autoimmune disorders obtained from the VAERS database, the results of the time-stratified analysis suggest that cases of autoimmune disorders may have presented later than anticipated since the rate ratio was not elevated for days 7-24 post-dose, but appeared to increase after day 25 and was highest for days 43-60. These findings suggest that including days 7-24 in our primary exposure risk window may have biased the results towards the null. Second, it is possible that the primary composite endpoint missed autoimmune disorders that are aetiologically associated with the qHPV vaccine, thus biasing the results towards the null. However, a sensitivity analysis that included an additional six aetiologically relevant autoimmune disorders yielded similar results, thereby suggesting that the definition of the composite endpoint was not a major source of bias. In addition, only the diagnostic algorithms for TIDM and SARDs have been previously validated. As such, it is possible that other autoimmune disorders identified using administrative diagnostic codes may have missed cases or included cases that were not autoimmune disorders. Indeed, Chao et al., reported that, depending on the disorder, only 20-60% of cases identified by diagnostic codes could be confirmed by chart review. (Chao et al., 2012) However, as such errors are independent of exposure status, they are expected to bias the results towards the null. Consequently, we cannot rule out the possibility that a small risk increase for some disorders was missed. Third, the date of symptom onset was not available for this study. To address the concern that disease onset may have preceded qHPV vaccination, the analysis was repeated excluding diagnoses occurring within 30 days of the first dose and found similar results.
Nevertheless, we cannot rule out the possibility that symptom onset preceded the first qHPV vaccine dose in some cases. Fourth, the possibility of confounding needs to be considered. Although our use of a self-matched analysis implicitly controlled for all time-independent confounders, we cannot rule out the possibility of confounding due to unknown or unmeasured time-dependent factors such as environmental triggers. However, as none of the time-dependent factors tested in this study were confounders, it is unlikely that confounding bias explains our results. Fifth, although the analysis of the primary endpoint was based on 212 vaccinated cases, fewer than 20% of these occurred during a time period aetiologically attributable to the qHPV vaccine (i.e., exposed cases). While this suggests a lack of association, it also resulted in some imprecision for the overall point estimate. In addition, the analysis of individual autoimmune disorders was based on a small number of exposed cases, and therefore, was intended to be exploratory in nature. Finally, the results of this study may not be generalizable to other age groups.

Overall, the results of this study are reassuring in that no statistically significant increases for the risk of autoimmune disorders following qHPV vaccination were detected. This implies that the qHPV vaccine is safe for the vast majority of adolescent girls eligible for this vaccination program. However, there remains some uncertainty about the safety of the qHPV vaccine for a small subset of adolescent girls who may be genetically predisposed to particularly rare autoimmune disorders. Given the rarity of a number of autoimmune disorders, future studies will need to pool all available data using a self-matched analysis that better controls for confounding.
4.6 REFERENCES


Dooley, M. A., & Hogan, S. L. (2003). Environmental epidemiology and risk factors for autoimmune disease. Current opinion in rheumatology. Retrieved August 16, 2013, from http://ovidsp.tx.ovid.com/servlet/SearchServlet?N=6871447760152995&SO=Loc&SF=all&SD=0&SY=2000&ST=1&PM=1&PT=1&G=0&MD=1&NR=391&RS=434f4e1a73d37e8c3dd5959385fb5c117b4be299f865ef190cd3e1016179c21692dd5dab64d18b66da41d615839def8574e45a188a5ab90386daa66827aee5f5c5d7b960d4f808bc0678ab108df24a68c8ee6b66d05ceaa30786e507d55c573f7562e348a83a2a5689

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4.7 TABLES AND FIGURES
Figure 4-1 Study Population

N = 368,430

Study Cohort  
N = 125,575

Vaccinated  
N = 72,397 (57.7%)

Unvaccinated  
N = 53,178 (42.3%)

Exclusions

Deaths before cohort entry  
N = 75 (0.0%)

Immunization data not yet available  
N = 223,181 (60.6%)

Inactive immunization records  
N = 18,601 (5.1%)

Received qHPV before cohort entry  
N = 1,080 (29.3%)

Data entry error  
N = 1 (0.0%)
Table 4-1 Incident cases of autoimmune disorders included in the composite endpoint

<table>
<thead>
<tr>
<th>Autoimmune Disorders</th>
<th>Vaccinated Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
</tr>
<tr>
<td>Juvenile rheumatoid arthritis</td>
<td>130 (58.6)</td>
</tr>
<tr>
<td>Immune thrombocytopenia purpura</td>
<td>28 (12.6)</td>
</tr>
<tr>
<td>Bell’s palsy</td>
<td>18 (8.1)</td>
</tr>
<tr>
<td>Systemic autoimmune rheumatic disorders**</td>
<td>16 (7.2)</td>
</tr>
<tr>
<td>Multiple sclerosis,</td>
<td>8 (3.6)</td>
</tr>
<tr>
<td>Optic neuritis,</td>
<td>8 (3.6)</td>
</tr>
<tr>
<td>Acute disseminated encephalomyelitis</td>
<td>6 (2.7)</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>6 (2.7)</td>
</tr>
<tr>
<td>Guillain-barre syndrome</td>
<td>≤ 5</td>
</tr>
<tr>
<td>Neuromyelitis optica</td>
<td>---</td>
</tr>
<tr>
<td>Transverse myelitis</td>
<td>≤ 5</td>
</tr>
<tr>
<td>Autoimmune pancreatitis</td>
<td>---</td>
</tr>
</tbody>
</table>

*Proportions are among all vaccinated cases. Column total for vaccinated cases is greater than 212 because some individuals developed two or more autoimmune disorders

**Systemic autoimmune rheumatic disorders (includes systemic lupus erythematosus, scleroderma/systemic sclerosis, Sjogren’s syndrome, dermatomyositis and polymyositis)
Figure 4-2 Distribution of cases following each dose of the qHPV vaccine, during exposed and unexposed person-time

- Days 7 - 60
- Days 68 - 121
- Days 190 - 243

19 13 11 16 24 10 114

- qHPV dose 1
- qHPV dose 2
- qHPV dose 3

- Unexposed person-time, where the occurrence of an event would not be attributable to the qHPV vaccine
- Unexposed person-time (days 0 – 6 post-dose), to account for the time it takes for symptoms to develop before medical care is sought
- Exposure risk window (days 7 – 60 days post-dose), where events occurring during this time period are attributable to the effects of the qHPV vaccine
### Table 4-2 Rate ratios for autoimmune disorders following quadrivalent HPV vaccination

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted* RR (95% CI)</th>
<th>Adjusted† RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>qHPV vaccine (overall)</td>
<td>1.28 (0.89 – 1.83)</td>
<td>1.28 (0.87 – 1.89)</td>
</tr>
<tr>
<td><strong>History of immune-mediated diseases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.44 (0.89-2.33) ‡</td>
<td>1.44 (0.85-2.43) ‡</td>
</tr>
<tr>
<td>No</td>
<td>1.20 (0.71-2.02) ‡</td>
<td>1.14 (0.64-2.01) ‡</td>
</tr>
<tr>
<td><strong>Age at outcome development (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>13</td>
<td>0.75 (0.38 – 1.49)</td>
<td>0.87 (0.43 – 1.78)</td>
</tr>
<tr>
<td>14</td>
<td>0.79 (0.39 – 1.59)</td>
<td>0.95 (0.45 – 1.97)</td>
</tr>
<tr>
<td>15</td>
<td>0.72 (0.35 – 1.49)</td>
<td>0.87 (0.41 – 1.87)</td>
</tr>
<tr>
<td>16</td>
<td>0.81 (0.38 – 1.72)</td>
<td>0.99 (0.45 – 2.21)</td>
</tr>
<tr>
<td>17</td>
<td>0.77 (0.27 – 2.17)</td>
<td>1.04 (0.35 – 3.10)</td>
</tr>
<tr>
<td><strong>Seasonality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>September</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>October</td>
<td>0.93 (0.52 – 1.83)</td>
<td>1.11 (0.69 – 1.77)</td>
</tr>
<tr>
<td>November</td>
<td>1.07 (0.61 – 1.89)</td>
<td>1.09 (0.68 – 1.75)</td>
</tr>
<tr>
<td>December</td>
<td>0.73 (0.39 – 1.35)</td>
<td>0.81 (0.49 – 1.35)</td>
</tr>
<tr>
<td>January - February</td>
<td>0.68 (0.39 – 1.16)</td>
<td>1.00 (0.65 – 1.53)</td>
</tr>
<tr>
<td>March - August</td>
<td>0.67 (0.42 – 1.07)</td>
<td>0.81 (0.54 – 1.19)</td>
</tr>
<tr>
<td>Other vaccines</td>
<td>1.24 (0.62 – 2.45)</td>
<td>1.37 (0.81 – 2.31)</td>
</tr>
<tr>
<td>Recent infections</td>
<td>2.12 (0.94 – 4.78)</td>
<td>1.96 (1.03 – 3.71)</td>
</tr>
</tbody>
</table>

RR = Rate Ratio; CI = confidence interval
* Unadjusted RR estimates were derived from self-matched models that only included the HPV vaccine
† Adjusted for age at diagnosis, seasonality (as depicted in table), receipt of non-HPV vaccines (within 7 – 60 days of developing outcome), and recent infection (within 7 – 60 days of developing outcome) in addition to being self-matched (i.e., time-fixed confounders implicitly adjusted)
‡ P-value = 0.392 (two-sided test of interaction comparing those with and without a history of immune-mediated diseases at a significance level of α = 0.05)
*History of immune-mediated diseases encompasses girls who have had a diagnosis of asthma, anaphylaxis, urticarial, angioneurotic oedema, eczema, dermatitis, rash, allergic rhinitis or hay fever, prior to cohort entry
Table 4-3 Rate ratios for the risk of autoimmune disorder following quadrivalent HPV vaccination according to time since vaccination

<table>
<thead>
<tr>
<th>Exposure risk period*</th>
<th>Exposed cases (n)</th>
<th>Unadjusted RR** (95% CI)</th>
<th>Adjusted*** RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 – 24 days</td>
<td>9</td>
<td>0.87 (0.45 – 1.72)</td>
<td>0.87 (0.43 – 1.74)</td>
</tr>
<tr>
<td>25 – 42 days</td>
<td>14</td>
<td>1.38 (0.79 – 2.39)</td>
<td>1.36 (0.77 – 2.41)</td>
</tr>
<tr>
<td>43 – 60 days</td>
<td>16</td>
<td>1.59 (0.94 – 2.66)</td>
<td>1.62 (0.94 – 2.78)</td>
</tr>
</tbody>
</table>

* The duration of time following qHPV vaccination, summed across all doses, during which the occurrence of an event is attributable to the effects of the vaccine.

** Unadjusted RR estimates were derived from self-matched models that only included the HPV vaccine

***Adjusted for age at diagnosis (by year), seasonality (as depicted in Table 4-2), receipt of non-HPV vaccines during study follow-up, and recent infection (within 7 – 60 days of developing outcome)
Figure 4-3 Adjusted* rate ratios for individual autoimmune disorders** following quadrivalent HPV vaccination

<table>
<thead>
<tr>
<th>Autoimmune Disorder</th>
<th>Adjusted IRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bell's palsy</td>
<td>2.30 (95% CI: 0.67-7.95)</td>
</tr>
<tr>
<td>Systemic autoimmune rheumatic disorders</td>
<td>1.84 (95% CI: 0.42-8.02)</td>
</tr>
<tr>
<td>Hashimoto's disease</td>
<td>1.39 (95% CI: 0.46-4.22)</td>
</tr>
<tr>
<td>Juvenile rheumatoid arthritis</td>
<td>1.31 (95% CI: 0.83-2.08)</td>
</tr>
<tr>
<td>Type I diabetes mellitus</td>
<td>1.07 (95% CI: 0.51-2.24)</td>
</tr>
<tr>
<td>Grave's disease</td>
<td>1.03 (95% CI: 0.42-2.56)</td>
</tr>
<tr>
<td>Crohn's disease</td>
<td>0.95 (95% CI: 0.37-2.45)</td>
</tr>
<tr>
<td>Immune thrombocytopenia purpura</td>
<td>0.45 (95% CI: 0.10-2.01)</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>0.40 (95% CI: 0.08-1.91)</td>
</tr>
</tbody>
</table>

* Adjusted for age at diagnosis, seasonality (as depicted in Table 4-2), receipt of non-HPV vaccines (within 7 – 60 days of developing outcome), and recent infection (within 7 – 60 days of developing outcome) in addition to being self-matched (i.e., time-fixed confounders implicitly adjusted)

** Only autoimmune disorders with ≥ 10 vaccinated cases were analyzed individually, for reasons of statistical power. Results are for the primary exposure risk window (7 – 60 days post dose)

***Systemic autoimmune rheumatic disorders (includes systemic lupus erythematosus, scleroderma/systemic sclerosis, Sjogren’s syndrome, dermatomyositis and polymyositis)
Chapter 5

General Discussion and Conclusion

5.1 Summary of Results

5.1.1 Objective 1

In this study we did not detect a statistically significant risk of autoimmune disorders following use of the qHPV vaccine (IRR = 1.28, 95% CI: 0.89 – 1.83) (Chapter 4, Table 4 – 2). This association did not change when adjusted for time-dependent factors such as age, seasonality, concurrent vaccines and infections. Moreover, none of the aforementioned factors were significant predictors of the outcome, with the exception of infections. The almost two-fold increased risk (IRR = 1.96, 95% CI: 1.03 – 3.71) of developing an autoimmune disorder within 7 – 60 days post-infection is consistent with current knowledge, as infections are accepted risk factors for the outcome. Further, the infections we studied are ones that have been associated with several autoimmune disorders from the primary composite endpoint, thus increasing the validity of these results.

The non-significant effects for age, seasonality and other vaccines are also expected. The difference in mean age at diagnosis between exposed (13.8 years) and unexposed cases (14.9 years) is approximately one year (Table 5-1), suggesting the baseline risk for these autoimmune disorders does not change significantly between ages 13 and 14. This finding is consistent with what is known about the age-dependency of autoimmune disorders. With the exception of Juvenile rheumatoid arthritis (JRA), which has a peak in incidence between ages 10 – 19, the age at onset for the remaining autoimmune disorders is 20 – 39 years (Hayter & Cook, 2012). Seasonality is a time-dependent covariate that was chosen as a proxy for flu vaccination, which has been associated with Guillain-barre syndrome (GBS) and Bell’s palsy in several observational studies (De Wals et al., 2012; D. Geier & Geier, 2005; Juurlink et al., 2006a; Mutsch et al., 2004;
Wise et al., 2012). However, seasonality was not found to be a determinant of autoimmune disorders, which could be explained by it being an imperfect proxy for flu vaccination, or the small number of GBS and Bell’s palsy cases, accounting for less than 10% of all autoimmune outcomes. Receipt of concurrent non-HPV vaccines also did not have an independent association with autoimmune disorders. This may seem contrary to what is expected, given the associations that have been demonstrated between other vaccines and autoimmune disorders (Chapter 1, Table 1 – 1). However, in Table 5-2, which shows the distribution of other vaccines by vaccine type, it can be seen that during study follow-up, most cases (93.36%) received the Diphtheria, pertussis, and tetanus (DPT) vaccine as their non-HPV vaccine. Since the majority of safety concerns of autoimmunity have arisen for the Measles, mumps, rubella (MMR), Hepatitis B and Influenza vaccines, it is possible that DPT is not associated with these specific autoimmune disorders.

5.1.2 Objective 2

The relationship between qHPV vaccination and risk of developing an autoimmune disorder was not modified by a history of immune dysregulation (Chapter 4, Table 4 – 2). The effect estimate for girls who had a prior diagnosis of asthma, anaphylaxis or other atopy (IRR = 1.44, 95% CI: 0.85 – 2.43) did not differ significantly from girls who did not have these diagnoses prior to cohort entry (IRR = 1.14, 95% CI: 0.64 – 2.01). We chose to study history of immune-mediated disorders as a potential predisposing factor for autoimmunity because individuals who are susceptible to developing allergies may possess a hypersensitive immune system, and thus may be more prone to autoimmunity (personal communication, Dr. Anne Ellis). Additionally, there have been some evidence linking allergies to development or exacerbation of autoimmune thyroid diseases (Prummel, Strieder, & Wiersinga, 2004), although this relationship has not been extensively studied for other autoimmune disorders. In this thesis, it was demonstrated that having a history of immune-mediated disorders did not modify the relationship
between qHPV vaccination and risk of the autoimmune disorders, at least for those included in the composite endpoint.

5.1.3 Objective 3

To address the third objective of identifying the period of highest risk within the 7 – 60 day exposure risk window, we repeated the analysis using a time-stratified approach. The adjusted point estimates for the three intervals of 7-24 days, 25-42 days, and 43-60 days (0.87, 1.36 and 1.62 respectively) suggest that the risk may be higher in the latter part of the 7-60 day exposure risk window (Chapter 4, Table 4 – 3). This observation is biologically plausible, given the latency period between autoimmunity and development of symptoms severe enough to seek medical care, as well as the difficulty in confirming a diagnosis for some of these disorders. For some autoimmune disorders such as Type I diabetes mellitus (T1DM), it requires a significant amount of time until the insulin-producing pancreatic cells become destroyed, thus rendering it unlikely for symptom manifestation to occur immediately after vaccination. Our attempt to address this latency period using a seven-day window post-vaccination may have been too short a duration of time to allow for clinical manifestations of autoimmunity. Thus, if certain disorders in the composite endpoint presented later than expected, it could explain why the risk appears to increase with time from vaccination. However, we cannot form any conclusions because the point estimates across the risk stratified analyses were statistically indistinguishable.

5.1.4 Objective 4

To determine the effect of each autoimmune disorder on the overall point estimate, an exploratory analysis was conducted for each outcome within the primary and expanded composite endpoints. Only disorders with ≥ 10 cases were analyzed to ensure a sufficient number of cases for the Poisson model. The results from the individual disorders analysis showed Bell’s palsy, Systemic autoimmune rheumatic disorders (SARDs), Hashimoto’s disease (HD) and JRA to have elevated IRRs, while others such as Immune thrombocytopenia purpura (ITP) and Ulcerative
colitis appeared to be protective (Chapter 4, Figure 4-3). However, with so few exposed cases for most of the disorders, any differences observed cannot be estimated with any precision. Since JRA was the most prevalent outcome in this composite endpoint, accounting for almost 60% of all vaccinated cases, it seems the overall point estimate of 1.28 (95% CI: 0.87 – 1.89) for the primary composite endpoint was large influenced by the association between qHPV and JRA (IRR=1.31, 95% CI 0.83 – 2.08).

In summary, the results from the individual disorders analysis have implications. First, the main finding of a non-significant elevated risk (IRR = 1.28) for any autoimmune disorder in the primary composite endpoint was largely contributed by JRA due to its high prevalence amongst the outcomes. Thus, we cannot conclude that the overall point estimate may be applicable to all other autoimmune disorders. Although the results from this exploratory analysis have demonstrated increased risks for Bell’s palsy, SARDs, JRA, and HD, these results were not statistically significant, and thus can only be considered weak safety signals that would require confirmation in larger studies. Finally, the association between qHPV vaccination and risk of Multiple sclerosis (MS), Acute disseminated encephalomyelitis (ADEM), Transverse myelitis (TM), GBS, Neuromyelitis optica (NMO), Optic neuritis (ON), Autoimmune pancreatitis (AIP) and Autoimmune hepatitis (AIH) remain inconclusive due to too few cases to produce estimates of risk.

5.2 Biologic Plausibility

Due to the rarity of the outcomes under study in this thesis, the results from the exploratory analysis have demonstrated an unclear association between the qHPV vaccine and certain autoimmune disorders. This is especially true for Bell’s palsy, SARDs, HD and JRA, which have point estimates suggestive of a potential safety signal. Nevertheless, these signals are biologically plausible, given structural similarities may be present between the antigenic components of the vaccine, and antigenic structures on certain cells in the body (Wraith et al., 2003). For example,
studies have demonstrated that the sugar molecules on the *Campylobacter jejuni* bacteria bear resemblance to surface molecules present on peripheral nerves. Thus for those who are genetically susceptible, their immune system may mistakenly attack its peripheral nerve cells, even after the pathogen has been eliminated. This explains why cases of GBS, a peripheral nerve autoimmune disorder, are often preceded by infections. This mechanism of molecular mimicry, often attributed to infection-induced autoimmunity, is also applicable to vaccine-induced autoimmunity since vaccines often contain the same antigens as its infectious agent. Thus, this mechanism may explain why elevated risks for certain autoimmune disorders was detected in this thesis.

**5.3 Comparison of Results with Other Studies**

To the best of our knowledge, there have been two qHPV observational studies specifically targeting autoimmune disorders as its safety endpoint. The following section will compare the results from the individual disorders analysis (Objective 4) with findings from these other observational studies.

The findings from this thesis were, for the most part, consistent with Chao et al and Arnheim-Dahlström et al’s results. Chao et al had detected a statistically significant two-fold increased risk of developing HD (IRR = 2.02, 95% CI: 1.65 – 2.60) when comparing confirmed cases of HD with expected rates in an unvaccinated population. This was similar to our finding of an elevated risk for HD (IRR = 2.30, 95% CI: 0.67 – 7.95), although given the small number of exposed cases (n = 5), this point estimate could not be estimated with precision. Grave’s disease was not associated with the qHPV vaccine, and this result was consistent across all three studies. Although slight elevated risks (albeit not statistically significant) for ITP were detected in Chao et al and Arnheim-Dahlström et al’s studies (IRR = 1.24, 95% CI: 0.91 – 2.02, IRR = 1.18, 95% CI: 0.65 – 2.17 respectively), this thesis did not produce a similar finding (IRR = 0.45, 95% CI: 0.10-2.01). However, the small number of exposed cases (n = ≤ 5) indicates that this analysis was
clearly underpowered to warrant a proper comparison. Another disorder that was studied is Systemic lupus erythematosus (SLE), although in this thesis, it was included in the broader category of Systematic rheumatic disorders (SARDs). All three studies detected increased risk of SLE/SARDs, with point estimates ranging from 1.10 (95% CI: 0.71-1.66) (Chao et al., 2012) to 1.35 (95% CI: 0.69-2.67) (Arnheim-Dahlström et al., 2013) and 1.84 (95% CI: 0.42-8.02). However, with so few exposed cases across these studies (n = ≤ 11), one cannot be certain whether these non-statistically significant risks represent a true safety signal. The associations for T1DM and JRA were less consistent, as this thesis found a non-significant elevated risk for JRA (IRR = 1.31, 95% CI: 0.83-2.08), whereas Arnheim-Dahlström et al found no association (IRR = 0.99, 95% CI: 0.78-1.26), and Chao et al demonstrated a protective effect (IRR = 0.36, 95% CI: 0.14-0.71). As it is improbable that qHPV vaccination reduces the risk of JRA by 64%, this significant result is most likely due to an overestimation of the incidence of JRA in the unvaccinated population. Even the authors acknowledged that their use of multiple imputation to estimate this background rate is not a standard approach. T1DM was not associated with the qHPV vaccine in this thesis (IRR = 1.07, 95% CI: 0.51-2.24). In contrast, Arnheim-Dahlström et al detected a significant risk (IRR = 1.29, 95% CI: 1.03-1.62) whereas Chao et al found an inverse association (IRR = 0.54, 95% CI: 0.45-0.70). The elevated risk found in Arnheim-Dahlström et al’s study could be due to confounding from comparing vaccinated and unvaccinated girls directly, or as a result of a type I error from multiple comparisons. Similar to the case of JRA, Chao et al’s implausible protective effect could be from their overestimate of the baseline risk of JRA in the unvaccinated population.

The results from this thesis indicate that overall, there is no significant risk of autoimmune disorders following qHPV vaccination, and this is supported by two other observational studies which did not find elevated risks for the majority of their autoimmune outcomes. However, potential safety signals were identified for a few autoimmune disorders. This
is particularly true for the association between qHPV vaccination and HD, which was significantly elevated in Chao et al’s study. The results for ITP and SARDs suggest they may also be a safety concern for this vaccine, although the non-significant elevated risks across studies would require confirmation in a pooled analysis. Finally, the inconsistent results for T1DM and JRA were most likely due to type 1 error, or methodological issues. An additional reason for any difference in results observed across studies is that this thesis used a self-matched analysis, thereby controlling for all time-independent confounders. Alternately, the remaining two studies could have introduced confounding bias by directly comparing vaccinated and unvaccinated populations, which may be systematically different populations. Further, their use of a 180-day exposure risk period may have misclassified unexposed person-time as exposed person-time. This is possible, given that Chao et al’s study measured the median time until disease onset from qHPV vaccination, and the majority of autoimmune disorders presented 36 – 65 days post-vaccination. Thus, this differential misclassification may have biased point estimates towards the null. Future studies assessing this association should employ self-matched designs using proper exposure risk windows that accurately reflect the biologic mechanism for vaccine-induced autoimmunity.

5.4 Strengths

This is the first post-license safety study for the qHPV vaccine using a self-matched analysis. Use of a self-matched analysis strengthens the validity of the findings as it can control all time-independent confounders, including those that are unknown and unmeasured. In this thesis, there was some confounding by these factors, as illustrated by the comparison of a crude IRR and the unadjusted IRR obtained from the Poisson model. The crude IRR of 1.47 (Table 5-3) was calculated by dividing the rate of events during exposed person-time (39/31,536 person-days), by the rate of events that occurred during unexposed person-time (173/204,997). Since these rates are compared between individuals, it cannot control for within-individual
characteristics such as genetic susceptibility, ethnicity, and personal beliefs and values that may have confounded the relationship. By contrast, the unadjusted IRR estimate from the Poisson model (IRR = 1.28) is matched on the individual, and thus controls for the aforementioned factors. Due to differences in these two IRR estimates, it seems there was likely some confounding by these within-individual characteristics and this supports our choice of using the SCCS method.

Another strength is that the use of population-based health data reduced the potential for selection bias. Selection-in bias is generally not a concern for cohort studies, unless individuals who choose to participate in the study are systematically different from the target population. This study used data sources that included everyone who is eligible for health services coverage in Ontario. Thus, all eligible individuals were enrolled into the study by the notion of passive consent, thereby eliminating any volunteer bias. Selection bias in the form of loss-to-follow-up may be another potential concern of cohort studies since those who drop out of a study may do so for reasons related to their probability of exposure and developing the outcome. In this thesis, loss to follow-up can only occur if participants became ineligible for health care coverage via emigration from the province. It is unlikely, though, that cohort members who moved did so for reasons related to their probability of developing an autoimmune disorder. Additionally, given the relatively short follow-up, the percentage of movers is likely to represent a small proportion of the entire cohort. Given the use of a population-based sample, there is very low potential for selection bias in this thesis.

A final strength of this thesis is that the results are generalizable to other girls in this age group, since we sought to examine a biologic relationship between qHPV vaccination and risk of autoimmune disorders. Despite these overall strengths, there are inevitably some limitations that need to be considered.
5.5 Limitations

5.5.1 Misclassification of Exposure

In this thesis, there are two potential sources of misclassification of exposure. First, there is the possibility that a small proportion of cohort members may have had their qHPV vaccination status misclassified. The reason for this potential measurement error is that at the time of this analysis, immunization data was available for only 22 of the 36 Public health units (PHU) in the province. Thus, if a girl living in one of these 22 PHUs did not receive the qHPV vaccine (and was thus considered unvaccinated), but then moved to one of the 14 PHUs which data was not available for, and subsequently received a dose of the vaccine, she would thus be misclassified as unvaccinated. However, since the percentage of movers is likely to be small over the course of the study period, this misclassification would not significantly impact the results of this study.

Another form of misclassification is that of exposed and unexposed person-time. If the chosen exposure risk window did not accurately represent the true biologically exposed time period and some exposed person-time were misclassified as unexposed-person time (with the alternative just as likely to occur), it would lead to non-differential misclassification. From the time-stratified analysis (Chapter 4, Table 4-3), it appears there may have been some misclassification, as the rate ratio was not elevated 7-24 days post-vaccination (IRR = 0.87, 95% CI: 0.43 – 1.74), but increased from 25-42 days (IRR = 1.36, 95% CI: 0.77 – 2.41), and approached significance from 43 – 60 days post-vaccination (IRR = 1.62, 95% CI: 0.94 – 2.78). This misclassification is possible since the pre-specified exposure risk period of 7 – 60 days was chosen based largely on safety evidence for other vaccines, while the qHPV vaccine may require a delayed time frame for induction of autoimmunity. This is further relevant, given the use of a composite endpoint, where certain disorders may have longer latency periods, depending on the disease-specific pathogenesis. Further, it may require some delay before a patient is diagnosed by a physician, which could explain why the risk may not appear until one to two months after
vaccination. The results from the time-stratified analysis indicate that the pre-specified exposure risk window of 7 – 60 days may have misclassified days 7 – 24 as exposed person-time, which would have biased the point estimate towards the null. However, this time interval warrants further investigation before any conclusions can be made.

5.5.2 Misclassification of Outcome

There are three forms of measurement error with respect to outcome status that could have affected our study results. One potential source of outcome misclassification is from the use of a composite endpoint. The decision to use a composite endpoint was to achieve sufficient statistical power to detect an association with “any autoimmune disorder”, in contrast to studying these rare disorders individually. If aetiologically-relevant autoimmune disorders were not included in this outcome definition, the risk could have been under-estimated. However, the addition of six more autoimmune disorders to the composite endpoint in a planned sensitivity analysis yielded similar results, thus suggesting this was not a significant source of bias.

An additional form of outcome misclassification in this thesis is through the use of un-validated diagnostic codes for autoimmune disorders. Since there is limited data on the validity of using these codes for outcome ascertainment, and even fewer validation studies conducted using Ontario’s administrative databases, this thesis applied an algorithm that was developed for SARDs to all the outcomes in the primary composite endpoint (Bernatsky et al., 2011a). This algorithm is associated with a sensitivity of 83% and a specificity ranging from 72.5 – 96.4% for SARDs, and is expected to produce similar values for the other autoimmune disorders, since they are also rare and complex outcomes subject to misdiagnoses. The rationale for using an algorithm is that administrative data are generally highly sensitive for the detection of chronic disorders, but the diagnostic codes obtained from the physicians billing database may represent mere suspected cases of the outcome. Thus, use of an algorithm that requires more than one diagnostic code or accounting for physician specialty would provide additional confirmation. Despite the use of
algorithms though, there is still the potential for misdiagnoses to occur and thus error in the ascertainment of outcomes. However, this misclassification is unlikely to occur differentially with respect to exposed and unexposed person-time; therefore the effect of this non-differential misclassification would underestimate the true risk.

Finally, there is a potential concern for detection/reporting bias if cases occurring in close proximity to vaccination may have been diagnosed earlier, as compared to cases occurring long after vaccination. In this instance, someone who developed symptoms suggestive of an autoimmune disorder immediately after vaccination may believe their symptoms are vaccine-induced, and thus could potentially present to the family physician’s office earlier. The effect would over-estimate the incidence of disease during exposed person-time. However, the results from the time-stratified analysis demonstrated that the relative incidence of autoimmune disorders was less than one during the 24 days period following vaccination and did not increase until almost one month after vaccination. Thus, any potential for detection bias is very low in this study.

5.5.3 Confounding bias

Due to the self-matching of the self-controlled case series (SCCS) method, it implicitly controls for all time-independent confounding factors, such as genetic susceptibility, ethnicity, cultural factors, and personal beliefs and values. Thus, in this thesis, the only factors that may have introduced confounding bias are the time-dependent factors associated with both the outcome (e.g. other vaccines and infections) and timing of qHPV vaccination; therefore we may have incorrectly attributed the cause of the autoimmune disorder to the qHPV vaccine. Nonetheless, the results from this thesis did not show any confounding by age, seasonality (as a proxy for flu vaccination), receipt of non-HPV vaccines and acquirement of infections, since the point estimate did not change after adjusting for these factors (Table 4-2). Although confounding bias does not appear to be a major limitation in our study, there is still the potential for some
residual confounding. The use of seasonality as a proxy for flu vaccination may be a crude measure, and there may be other non-HPV vaccines that were not recorded in the IRIS database. Further, infections are often transient or under diagnosed in a medical care setting. Thus, the imperfect measurement of covariates in this analysis may have resulted in some residual confounding, thus biasing the point estimate towards the null.

Another source of confounding bias is the potential for unmeasured or unknown time-dependent confounders, which is plausible given our incomplete understanding of what causes autoimmune disorders. However, it is improbable that these factors associated with autoimmune disorders could align with the timing of qHPV vaccination. Rather, if these factors are not unequally distributed between exposed and unexposed time periods, they cannot confound the association under study. All things considered, our inability to control for these unmeasured confounders was unlikely to impact the results significantly, especially considering none of the known time-dependent factors in this study (age, seasonality, receipt of non-HPV vaccines, and infections) were found to be confounders.

A final limitation in this study is that the last birth cohort (girls born in 1997 and thus entered the cohort in September of 2010) may not have had complete follow-up since the transfer date of their immunization records was in the summer of 2011. Thus, it would have precluded cases that took over one year to confirm their diagnosis, since our algorithm for case ascertainment required at least two OHIP diagnostic codes within two years. However, since there were most likely very few of these cases, and it is highly improbable that cases occurring during exposed time would have taken more or less time to diagnose than cases during unexposed time, this would only affect sample size and not the point estimate.

5.6 Public Health Importance and Contribution to the Field

The findings from this thesis have implications for the HPV vaccination program, and need to be considered in view of the benefits of this vaccine. Since a statistically significant elevated risk
of autoimmune disorders was not found in this thesis, and these results were, for the most part, consistent with two other studies, this means that the qHPV vaccine appears to be safe for the vast majority of adolescent girls eligible for the vaccination program. Subsequently, we do not propose any changes to the current HPV Vaccination program, based on safety concerns. While it appears that certain autoimmune disorders such as HD, ITP and SARDs may be potential safety signals, the data is not yet conclusive to warrant a change in the safety profile of this vaccine. This recommendation is formed in the context of the benefits of this vaccine, given its potential to reduce the incidence of cervical cancer and genital warts in the population.

5.7 Conclusion and Future Directions

In summary, this thesis did not detect a statistically significant risk of a composite endpoint of twelve autoimmune disorders following qHPV vaccination in a cohort of adolescent females. These results are consistent with other observational studies that also studied this association. However, due to limitations of statistical power, one cannot rule out a possibility that for certain rare autoimmune disorders there may be a potential risk. To address this limitation, this analysis will be repeated on the entire cohort of eligible girls for the Ontario HPV Vaccination program (n = ~300, 000), once the immunization data has been record-linked. Future research assessing the qHPV vaccine for risk of autoimmune disorders will need to pool the results across studies to determine if the few elevated risks that we identified in this thesis represent true safety signals.
5.8 References


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Appendix A

Ethics Approval

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD-DELEGATED REVIEW
September 23, 2013

Dr. Linda Levesque
Department of Public Health Sciences
Centre for Health Services & Policy Research (CHSPR)
Queen's University

Dear Dr. Levesque

Study Title: EPID-442-13 Assessing the Risk for Autoimmune Disorders Following Uptake of the Quadrivalent Human Papillomavirus Vaccine: The Ontario Grade 8 HPV Vaccine Cohort Study
File # 6010774
Co-Investigators: Miss Y.E. Liu

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

Reporting of Amendments: If there are any changes to your study (e.g. consent, protocol, study procedures, etc.), you must submit an amendment to the Research Ethics Board for approval. Please use event form: HSREB Multi-Use Amendment/Full Board Renewal Form associated with your post review file # 6010774 in your Researcher Portal (https://eservices.queensu.ca/romeo_researcher/)

Reporting of Serious Adverse Events: Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other serious adverse events must be reported within 15 days after becoming aware of the information. Serious Adverse Event forms are located with your post-review file 6010774 in your Researcher Portal (https://eservices.queensu.ca/romeo_researcher/)

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

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

Yours sincerely,

[Signature]
Chair, Health Sciences Research Ethics Board
September 23, 2013

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 B

Additional Analyses and Results

This table compares the mean age of exposed and unexposed cases, to determine if age could be a confounder for the association under study. See Chapter 5, General Discussion for an explanation.

Table 5-1 Age at diagnosis according to exposure* status

<table>
<thead>
<tr>
<th></th>
<th>Exposed case (N = 39)</th>
<th>Unexposed case (N = 173)</th>
<th>All Exposed and Unexposed Cases (N = 212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>13.8 (0.5)</td>
<td>14.9 (1.1)</td>
<td>14.6 (1.1)</td>
</tr>
<tr>
<td>Range</td>
<td>12.9 – 15.3</td>
<td>12.8 – 17.3</td>
<td>12.8 – 17.3</td>
</tr>
<tr>
<td>Median</td>
<td>13.7</td>
<td>14.8</td>
<td>14.6</td>
</tr>
</tbody>
</table>

*Exposed cases are those that occurred during the primary exposure risk window of 7 – 60 days post-vaccination, whereas unexposed cases are cases that occurred during all other follow-up time
This table depicts the types of non-HPV vaccines that cases received during the follow-up period. Knowing the distribution of these vaccine types could inform how likely it is for receipt of other vaccines to be a significant predictor of the outcome. See Chapter 5 General Discussion for an explanation.

Table 5-2 Cases that received a non-HPV vaccine, by vaccine type

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
</tr>
<tr>
<td>DPT</td>
<td>197 (93.36)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>28 (13.27)</td>
</tr>
<tr>
<td>MMR</td>
<td>15 (7.11)</td>
</tr>
<tr>
<td>Meningococcal C</td>
<td>13 (6.16)</td>
</tr>
<tr>
<td>Received Other vaccines</td>
<td>18 (8.53)</td>
</tr>
</tbody>
</table>

*DPT = Diphtheria, pertussis, tetanus, MMR = Measles, mumps, rubella
This table shows how a crude rate ratio (RR) was calculated for the risk of autoimmune disorders following qHPV vaccination. It is higher than the Adjusted RR obtained from the conditional Poisson regression, thus demonstrating that there was some confounding by time-independent factors. See Chapter 5, General Discussion for a more detailed explanation.

Table 5-3 Calculation of a crude rate ratio, across individuals

<table>
<thead>
<tr>
<th></th>
<th>Exposed cases</th>
<th>Unexposed cases</th>
<th>Duration of exposed person-time (days)</th>
<th>Duration of unexposed person-time (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>39</td>
<td>173</td>
<td>31,536</td>
<td>204,997</td>
</tr>
</tbody>
</table>

Calculated RR

\[
RR = \frac{\text{total no. of exposed cases/exposed person–time}}{\text{total no. of unexposed cases/unexposed person–time}}
\]

\[
= \frac{39/31,536}{173/204,997}
\]

\[
= 1.47
\]