DETERMINANTS OF NON-UPTAKE OF THE QUADRIVALENT HPV VACCINE; THE ONTARIO GRADE 8 HPV VACCINE COHORT STUDY

by

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Abstract

Background: In 2007, the Canadian federal budget provided \$300 million over three years to the provinces and territories to implement publicly-funded HPV immunization programs. Current estimates indicate that HPV vaccine uptake varies significantly across Canada and is reported to be lowest in Ontario at 53%. There is a paucity of literature on the determinants of HPV vaccine uptake in the Canadian context, therefore further research is needed.

Objectives: To describe the patterns of HPV vaccine non-uptake across health units in Ontario, and identify the individual- and health unit (ecologic)-level factors that influenced HPV immunization decision-making between 2007 and 2011.

Methods: The study linked administrative health and immunization databases to identify a retrospective population-based cohort of 144,047 girls eligible for Ontario's schoolbased HPV immunization program between 2007 and 2011. In this study a girl was considered vaccinated if she received at least 1 dose, otherwise she was considered unvaccinated. Ecologic or health unit-level factors that may have influenced HPV vaccine decision-making were assessed, as well as individual-level predictors including clinical characteristics and sociodemographics. A population-average model based on generalized estimating equations was used to identify determinants associated with nonuptake. **Results:** In all, 49.3% of girls from 21 public health units refused HPV immunization between 2007 and 2011. Non-uptake varied across health units, from 41.82% to 60.30%. In multivariate analyses, non-uptake was strongly associated with a history of autism (OR=1.60; 95% CI 1.34, 1.90) and Down's syndrome (OR=1.37; 95% CI 1.16, 1.63), refusal of mandatory and optional vaccines (OR=2.23; 95% CI 2.07, 2.4, and OR=3.96; 95% CI 3.87, 4.05, respectively), and infrequent physician visits (OR=1.45; 95% CI 1.35, 1.55). Contextual or health unit-level characteristics appeared to have a weak influence on vaccine decision-making.

Conclusions: HPV immunization could lead to a lower risk of developing and dying from HPV-related cancers; however, non-uptake of this vaccine is high. Concerted efforts are needed to reduce missed opportunities during medical consultations, to refine communication strategies and activities to address the information needs of special groups, as well as to develop cross-sectoral collaborations to support the delivery of publicly-funded HPV immunization to schools across Canada.

Co-Authorship

This thesis represents the work of Olivia R. Remes which was completed under the guidance of Dr. Linda Levesque and Dr. Beatriz Alvarado. The statistical analysis and drafting of the thesis sections was done by Ms. Remes under the guidance of her supervisors. Ms. Lindsey Colley assisted with the data set creation and provided feedback on record linkage.

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List of Abbreviations

- DAD Discharge Abstract Database
- (q)HPV (quadrivalent) Human Papillomavirus
- ICD International Classification of Diseases
- ICES Institute for Clinical and Evaluative Sciences
- IKN ICES Key Number
- IRIS Immunization Record Information System
- KFL&A Kingston, Frontenac, Lennox, and Addington
- LPHA Local Public Health Agency
- MOHTLC Ministry of Health and Long-Term Care
- NACRS National Ambulatory Care Reporting System
- OHIP Ontario Health Insurance Plan
- **RPDB** Registered Persons Database
- VPD Vaccine Preventable Disease
- WHO World Health Organization

Chapter 1

INTRODUCTION

1.1 The burden of HPV infections and cervical cancer

The World Health Organization estimates that 493,243 women worldwide acquire cervical cancer each year and 273,505 die from this disease. Cervical cancer is the second most common cancer among women 20 to 44 years of age, and prior infection with oncogenic human papillomavirus (HPV) is a necessary cause for the development of this disease.^{1,2,3} Over 200 HPV genotypes have been identified and classified into lowand high-risk groups according to their carcinogenic potential, and 30 of these are capable of infecting the genital mucosa. Low-risk types can lead to the development of benign genital warts^{3,4} or low-grade intraepithelial lesions, whereas persistent infection with high-risk oncogenic types can cause high-grade pre-cancerous cervical intraepithelial lesions and cancer.^{5,6,7} Approximately 3-9 million Canadians are HPVpositive and current estimates indicate that almost half of sexually active females have been infected with at least one cervical HPV type.^{8,9} This infection is transmitted by skin-to-skin contact and infection usually occurs soon after sexual debut.¹⁰ Although the majority of HPV infections resolve spontaneously within two years¹¹, persistent infection with high-risk types in the cervix is the first step in changing cervical cytology and triggering a potentially progressive carcinogenic process leading to carcinoma in situ and invasive cervical cancer.^{5-7,11-20} The incidence rate for acquiring a high-risk type is somewhat higher than that for acquiring a low-risk type (14 cases / 1000 women-months versus 12.4 cases / 1000 women-months), with HPV 16 being the most persistent. Prevention strategies against HPV infections include Pap screening and HPV immunization.¹¹

1.2 HPV prevention strategies

Although cervical cancer rates have decreased substantially in the last 50 years due to the advent of cytology screening for cervical abnormalities, Pap tests have been shown to be highly specific (98% for cervical intraepithelial neoplasia [CIN] grade I or higher) but only moderately sensitive (51% for grade I (CIN1) or higher) and errors in the interpretation of Pap specimens oftentimes results in the failure to detect precancerous changes. Two prophylactic HPV vaccines have been developed to protect against infection with high-risk types 16 and 18; one of which also protects against low-risk types 6 and 11.^{21,22,23,24}

1.3 Rationale for the Ontario Grade 8 HPV Vaccine Cohort Study

In 2007, the provinces and territories received 300 million dollars from the Canadian government to develop and implement free, publicly-funded, HPV immunization programs²⁵. Despite efforts by public health authorities and health providers to increase HPV immunization rates, current estimates indicate that vaccine uptake varies significantly across Canada from a low of 49-53% in the Territories and Ontario to a high of 87% in Quebec²⁴. Given the negative public health and cost-effectiveness implications of low coverage, it is necessary to provide insight into the factors contributing to the high levels of HPV vaccine refusal in Canada.

The current study aimed to provide insight into the ecologic factors associated with vaccine non-initiation measured at the level of the health unit. A secondary analysis was undertaken to provide a better understanding of personal characteristics associated with HPV vaccine refusal, while considering the influence of ecologic or health unit factors on immunization decision-making. Findings can be used to direct interventions, as well as to inform policy developers and regional immunization coordinators about priority groups that are not accessing the vaccine.

1.4 Study Objectives

The aim of the study was to provide an understanding of determinants of non-uptake of school-based HPV immunization offered to grade 8 girls in Ontario. The study objectives were:

- To identify the prevalence of non-uptake from 2007-08 to 2010-11, as well as the health unit-level factors that influenced HPV immunization refusal during this time period; and
- 2. To determine the factors associated with non-uptake at two levels of analysis: the individual and the health unit.

1.5 Thesis Outline

The remainder of this thesis is organized into five sections. Chapter 2 presents a literature review on: 1) HPV infections and prevention strategies, 2) HPV immunization coverage in Canada with an international comparison, and 3) the individual- and

ecologic-level factors associated with HPV vaccine decision-making at the intrapersonal, interpersonal, and the ecologic level using the eco-social conceptual framework. Chapter 3 provides an overview of the study methods, as well as descriptions on the study design, cohort formation, study data sources, data access and record linkage, and the statistical analysis. Chapters 4 and 5 present the results of the analysis on determinants associated with HPV vaccine non-uptake in Ontario over the first four years of the program. Chapter 6 is a discussion of the thesis results within the context of published literature, as well as the study limitations and strengths. Finally, thesis implications are addressed and recommendations for future research are made.

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Chapter 2

LITERATURE REVIEW

The scope of this review is to 1) provide a brief overview of HPV infections and prevention strategies; 2) organize existing published literature findings according to an evidence-based theoretical framework; 3) present a comprehensive overview of factors that influenced initial intention to immunize prior to HPV vaccine availability - in the prelicensure period; 4) synthesize the determinants of actual vaccine uptake after HPV immunization was made available to the public – in the post-licensure period; and 5) summarize major gaps and the contribution of this thesis. This literature review provides an overview of the factors related to HPV vaccine uptake between 2006 and 2012 (capturing both pre- and post- licensure vaccine data) and includes HPV immunization studies conducted in the United States, the United Kingdom, and the Netherlands where National HPV vaccination programs are in place.

2.1 Brief overview of HPV infections and prevention strategies

The Society of Obstetricians and Gynaecologists of Canada estimates that approximately 10% to 30% of the Canadian population is infected with sexually transmitted human papillomavirus (HPV), and 1% to 2% of those infected with a high-risk, oncogenic type develop cervical cancer. Males and females between the ages of 15 and 24 years are susceptible to infections with HPV. Strategies to prevent infection-related sequelae include routine Pap screening and HPV immunization.¹⁻⁸ In July 2006, Health Canada

approved the quadrivalent HPV vaccine Gardasil[®] for use in females and males ages 9 to 26 years and in 2010, the bivalent Cervarix[®] vaccine for females between the ages of 10 and 25 years. Furthermore, the provinces and territories (P/T) received \$300 million dollars from the federal budget to establish publicly funded free HPV immunization programs before March 2010.¹⁻⁸

Despite federal efforts to increase immunization rates, current estimates indicate that vaccine uptake in most P/Ts is well below the national target of 80% and is reported to be lowest in Ontario at 53%.⁹

Provinces/Territories	Programs
Alberta	Started in Sept 2008 Females Gr.5;
British Columbia	Started in Sept 2008 Females Gr.6 & 9
Manitoba	Started in Oct 2008 Females Gr.6
New Brunswick	Started in Sept 2008 Females Gr.7;
Newfoundland and Labrador	Started in Sept 2007 Females Gr.6;
Northwest Territories	Started in Sept 2009 Females Gr.4;
Nova Scotia	Started in Sept 2007 Females Gr.7
Nunavut	Started in winter 2009 Females Gr.6
Ontario	Started in Sept 2007 Females Gr.8
Prince Edward Island	Started in Sept 2007 Females Gr.6
Québec	Started in Sept 2008 Females Gr.4 & 9
Saskatchewan	Started in Sept 2008 Females Gr.6;
Yukon	Started in fall 2009 Females Gr.6;

Table 2-1 Grades targeted by the school-based HPV vaccination programs

2.2 HPV vaccination coverage – international comparison

To provide international context, Canadian findings are compared with those of other western regions with similar population health status and robust health care systems. In the U.K., the Joint Committee on Vaccination and Immunization (JCVI) recommended the bivalent Cervarix vaccine for routine vaccination of schoolgirls ages 12 to 13 vears.¹⁰ U.K. Department of Health records suggest that broad coverage was achieved during the first two roll-out years, with 60% of girls born between 1990 and 1997 immunized with the full series. In 2009/10, 76.4% of eligible females reported completion of the threedose regimen. School-based vaccination programs have been successful in achieving high coverage in parts of Australia, with over 80% of female students ages 12 to 18 years initiating the series in the first year of the HPV immunization program.¹¹⁻¹³ In contrast, the U.S. reports coverage of less than half of the eligible female population. There are several factors that may have contributed to this issue. The American health care delivery system is fragmented and difficult to navigate, access barriers such as cost are common, and the quality of school-based health care varies significantly across and within states.¹⁴⁻¹⁶ Despite the provision of free HPV vaccination in Canadian schools, rates vary substantially across provinces (Table 2-1).

2.3 Conceptual framework for vaccine uptake

To better understand the myriad of personal, organizational, and broader societal determinants of HPV vaccine acceptability and uptake, an integrated evidence-based approach is needed. A conceptual framework that guides the analysis of predictors of

uptake across theoretical models of vaccination behaviour can elucidate individual and contextual barriers to HPV immunization.

There are several studies on individual and healthcare system predictors of HPV vaccine uptake; however, conceptual frameworks are seldom used to guide the research and analytical process.¹⁷ Pre-licensure vaccine studies on immunization acceptability were primarily based on constructs from the Health Belief Model¹⁸, Social Cognitive Theory¹⁹, and the Theory of Reasoned Action (Planned Behaviour)²⁰. Under these models, the intentions of vaccine uptake predominantly studied included personal beliefs and experiences, and family influences. There has been increasing interest, however, in examining broader levels of influence, such as those related to the social context. In recognizing that individuals' characteristics and the environment interact to produce health behaviours such as immunization, social epidemiologists have proposed an integrated approach to guide health research – the eco-social model.^{17,21}

Disparities in the uptake of health interventions in Canada persist with significant social and economic consequences. These disparities may be caused by facets of the environment that affect the distribution of resources for public health care. To acquire a more complete understanding of how to reduce inequities, it is futile to examine a singular determinant. Approaches that examine the influence of eco-social levels on health disparities are needed. The eco-social perspective integrates the interaction between individual, community, institutional, and sociocultural factors or *levels*, and can be used as a theoretical framework for understanding health differences between population sub-groups that are attributable to specific determinants.

To provide a comprehensive overview of complex individual and contextual factors associated with HPV vaccination, the eco-social model was also used to frame this literature review (see Figure 2-1). The eco-social model nests three levels of influence: the intrapersonal, interpersonal, and environmental levels.

1) The intrapersonal level of influence describes personal factors that impact decisionmaking for oneself (or other family members), and is subdivided into attitudinal and behavioural categories. Attitudinal measures refer to beliefs, attitudes and perceptions that shape current health behaviours, whereas behavioural measures refer to past actions as predictors of current or future behaviour patterns. For example, history of routine vaccination against the seasonal flu (past behaviour) positively influenced receipt of the H1N1 vaccine during the 2009 pandemic.^{21,22} In addition, behavioural measures, such as, caregiver attitudes towards prevention have a major impact on children's acceptability of therapies.

2) The interpersonal level refers to the influence of social networks, as well as the norms and mores within those networks, on individual behaviour patterns. For example, adolescents are more likely to get vaccinated if they perceive their peer groups and health care providers to be supportive of this practice. As the proportion of vaccine recipients increases in one's environment and immunization becomes a social norm, uptake in the community subsequently rises.¹⁷

3) The last level is the environmental level. This level refers to the influence of the social context on health outcomes. People living in the same health region are more homogeneous, are exposed to the same environment, and tend to share similar health experiences in comparison with people living elsewhere. Results from multi-level analyses conducted in the U.S. indicate that those living in deprived regions have poorer health status and more frequent contact with the health care system than those in wealthier regions, regardless of individual-level socio-economic status.²³⁻²⁵ Further, neighbourhood characteristics influence health behaviours independently of individuallevel factors, such as age, marital status, employment, and education level. Older published studies suggest residential context as a key avenue of influence on health behaviours, whereby environmental constraints or opportunities to engage in particular actions are created through social norms, psychosocial stress, and media advertising.²³⁻²⁵ Although political and administrative policies and regulations can impact decisionmaking, individual behaviours are also shaped by local norms.¹⁷ Some health behaviours are more sensitive to environmental contexts above and beyond the influence of personal traits. This has been elucidated through studies on smoking patterns, whereby higher smoking rates have consistently been reported for poorer communities²³⁻²⁵ in the United States.

Figure 2-1 Conceptual framework



2.4 Pre-licensure Research

Knowledge, attitudes and awareness related to the HPV vaccine will be presented in the following section, bringing into sharper focus: 1) personal factors related to HPV immunization, such as parental acceptability, and acceptability of receiving the vaccine for oneself; and 2) environmental or societal factors associated with this therapy. Some intrapersonal-level factors identified during the vaccine pre-licensure period were found to have minimal influence on actual receipt of the vaccine after it was made available to the public (as will be evident later), while others had a profound impact on receptivity to HPV immunization after it was approved for use.

2.4.1 Intrapersonal level

Pre-licensure studies of the determinants of HPV vaccination have focused primarily on beliefs related to vaccine acceptability. Insights into personal beliefs towards the HPV vaccine offer potentially modifiable targets for interventions aimed at increasing HPV immunization rates, and the Health Belief Model is the theoretical framework commonly used to explain and understand behaviour patterns and attitudes leading to the uptake of such health interventions. Parental attitudes towards HPV immunization have an impact on children's acceptability of the vaccine and willingness to become vaccinated. Although a negligible proportion of Canadian parents in 2006-2007 worried that HPV vaccination could promote promiscuity in children and contribute to a potential decline in cervical cancer screening rates, caregivers generally demonstrated high levels of interest in an STI/HPV vaccine.²⁶⁻²⁸ This is important because positive attitudes among parents have been shown to translate into therapy receptivity among children. HPV knowledge in the general population was very low prior to the availability of the HPV vaccine, and this lack of awareness contributed to reluctance among some caregivers to support children's immunization against HPV.

Before the vaccine was available to the public, only 37% of parents in the U.S. intended to immunize their daughters against HPV and approximately half (44.6%) were uncertain.²⁹ A systematic review²⁶ of 28 cross-sectional studies conducted in urban regions of the U.S. from 1995 to 2007 indicated that the single most important factor influencing vaccine acceptability among caregivers of children eligible for HPV immunization was perceived vaccine effectiveness. Parents rated this attribute as the most important characteristic in reducing the likelihood of HPV infections and related sequelae. Other factors that positively influenced caregivers in their support for vaccination included school requirements for HPV immunization, Catholic religion, and having sexually active children. Conversely, parents who were evangelical or born-again Christians or who were politically conservative were less likely to endorse use of the HPV vaccine. Socio-economic status was also associated with vaccine acceptability in that parents with a higher income but a lower level of education were more supportive of HPV immunization.²⁶ Although this review is the most thorough to date on HPV vaccine acceptability, some important limitations were noted. The findings were primarily based on small cross-sectional surveys consisting of predominantly non-Hispanic White respondents living in urban regions, hence introducing volunteer bias. Few studies focused on ethnically diverse subgroups of women, and even fewer reported whether vaccine information was provided to participants prior to data collection. As HPV vaccine cost represents a significant barrier in U.S. studies of vaccine acceptability, it may be inappropriate to generalize these findings to the Canadian context where the vaccine is offered free of charge.

In Canada, only one population-based study²⁸ has been published on personal factors related to HPV vaccine acceptability. Findings revealed that approximately 74% of Canadian parents intended to have their daughters vaccinated, with intention varying nationally from 63% in British Columbia and the Yukon Territory to 83% in Atlantic Canada. Factors contributing to immunization intention among Canadian caregivers in the year preceding vaccine licensure included: having a positive attitude towards vaccines in general and HPV immunization specifically; having received a recommendation to vaccinate their daughters from family and/or friends; believing that HPV immunization

does not condone sexual activity; and having a friend or relative at risk for cervical cancer.²⁸ Limitations of this research included a low response rate of 55% and selection bias.

2.4.2 Interpersonal level

Almost all studies indicated that receiving a recommendation for immunization from a clinician was one of the most important determinants of a parent's decision to vaccinate his or her daughter.^{26,28-30} A population-based study²⁸ conducted in Canada revealed that caregivers had significantly greater intentions of immunizing their daughters against HPV if they received recommendations to vaccinate from physicians. Before the vaccine was licensed for use, physicians were generally in favour of the HPV vaccine and intended to recommend it to older individuals as well as to females, as they perceived women to derive a greater health benefit than their male counterparts. In pre-licensure research, physicians who were supportive of immunizing pre-adolescents believed that the HPV vaccine should be offered before sexual debut, whereas those who preferred to immunize older adolescents did not perceive their patients to be at high risk of HPV infections or were reluctant to discuss sexual health with children or young adolescents.¹⁷

2.4.3 Environmental /societal level

There were no societal or contextual factors reported in the literature as determinants of vaccine acceptability in the pre-licensure years.

2.5 Post-licensure Research: Determinants of actual HPV vaccine receipt / uptake

Given the high cost of this therapy and disappointing results with respect to uptake, further Canadian research is needed on this issue. Most of the research on HPV immunization was undertaken before the vaccine was publicly available. There are only two published population-based studies on the determinants of actual HPV vaccine uptake in Canada.^{31,32} Although post-licensure research is limited, a review of the literature on actual HPV vaccine receipt is necessary to provide a better understanding of the factors that caused individuals to engage in vaccine preventative behaviours and endorse HPV immunization.

Some factors associated with intention to vaccinate in pre-licensure research differed from those associated with actual receipt of the vaccine. Although empirical research suggests a fairly strong correlation between intention and behaviour, post-licensure studies showed that only a small proportion of caregivers followed through on their initial intentions to immunize children.³⁰ In the pre-licensure period, attitudes and beliefs were important determinants of acceptability, with perceived vaccine efficacy, safety and access, and perceived susceptibility to HPV infections as common determinants of intention to vaccinate. Parental concerns over sexual promiscuity following STI vaccination were identified as possible barriers to the uptake of the HPV vaccine. In the post-licensure period, the latter two factors were not associated with actual vaccine receipt.

Modifiable factors that influenced uptake are of great public health interest as they offer an opportunity for public health authorities to intervene and design targeted interventions.³⁰ The following section will provide further insight into the determinants of immunization uptake at all eco-social levels in the post-licensure period.

2.5.1 Intrapersonal level

Acceptability of HPV vaccination among adolescents and young adults is influenced to a large extent by social and subjective norms. Adolescents who perceive their parents, clinicians, and friends to be supportive of preventive health measures are more likely to receive immunizations. Mothers' health behaviours are important predictors of daughters' attitudes towards HPV immunization.^{33,34} U.S. data from 2006-2007 indicated that young girls were 1.47 times more likely to receive the HPV vaccine and 1.42 times more likely to complete the series if their mothers reported a history of Pap testing. Maternal attitudes towards prevention were stronger among caregivers with a history of STIs and who routinely presented for cervical cytology. Mothers' testing history influenced vaccine initiation and regimen completion among daughters, and this finding was consistent across ethnic and socio-economic strata. Girls with health-conscious mothers who missed a dose of the vaccine regimen were more inclined to return to the clinic for series completion. Also, daughters were somewhat more likely to engage in preventative health behaviours if their mothers had been previously diagnosed with an STI, however this varied by ethnicity.³⁴ In contrast to non-Hispanic white individuals, Black children were less likely to undergo vaccination if their mothers reported a history of STIs.³⁴ This finding may be influenced by social disadvantages among Black subgroups in the U.S. rather than maternal health consciousness. A more recent published study of a racially and geographically diverse population living in North Carolina counties with high cervical cancer rates showed that parents who lived in urban areas, believed their daughters to be sexually active, were non-Hispanic white, and had overall greater knowledge about HPV immunization were more likely to initiate conversations about this topic with their girls. In contrast to the previous studies (which often focused on potentially non-modifiable determinants of uptake, such as personal traits), this survey emphasized that mother-daughter communication on sexual health may be an effective means of prompting girls to undergo HPV therapy.²¹ Previous research has shown that parent-child conversations about STIs and health are associated with decreased sexual risk taking and positive attitudes towards prevention among adolescents.

Additional determinants of initiation documented in other U.S. studies, included having fewer health-care related perceived barriers (e.g., ease of finding a health care provider who offers the vaccine), fewer perceived potential harms (ex. adverse events) related to vaccination, as well as having anticipated regret of not vaccinating one's daughters against HPV to prevent sequelae.^{21,35} The U.S. health care system is more fragmented than that of Canada, and access barriers, such as insurance costs, have a large influence on willingness to become vaccinated in the American context.

National policies and public health infrastructure influence health-care decision-making among parents.¹⁷ Therefore it is necessary to explore determinants of vaccine initiation

in other countries where publicly funded programs are available. Similar to Canada, the Netherlands offers free HPV immunization to eligible girls and reports similarly low vaccination rates. Dutch girls born between 1993 and 1996 who received two doses of the MMR vaccine had at least 6 times the odds of being HPV vaccinated compared with girls who did not received the MMR vaccine (OR=6.26, 95% CI: 5.87-6.68).³⁶ This finding underscores the importance of vaccination history as a predictor of uptake of new vaccines. Furthermore, girls born in the Netherlands were almost twice as likely to be vaccinated as girls who were ethnic minorities in this region (i.e. of Moroccan or Turkish origin). The importance of disseminating culturally-sensitive health promotion information has been reiterated in previous research as a means of reducing health disparities among vulnerable sub-groups, but remains to be widely implemented.

To date, there are only two published population-based studies on the determinants of HPV vaccine uptake in Canada. The first, surveyed 2,025 parents in British Columbia with grade six girls from 2008 through to 2009³⁷. Consistent with American research, results showed that parents with a higher level of education who reported a need for more information on the safety of the HPV vaccine were least likely to immunize their daughters. ³⁷ A qualitative study of young adults living in the National Capital Region of Canada further showed that those with feelings of skepticism or uncertainty regarding the efficacy of the therapy were least likely to accept HPV immunization.³⁸ Common reasons for therapy refusal among this group included novelty of the treatment and perceived insufficient research on adverse events associated with the HPV vaccine. The

B.C. survey provided new and important insights including the association between stable family structure and refusal of childhood HPV immunization.³⁷ Findings were limited by a low response rate (50%), the inability to recruit participants from two Health Service Areas in BC accounting for 15% of the provincial population (generalizability issues), and recruitment bias towards English-speaking participants.³⁷ The second, more recent study, used Ontario's administrative health databases to evaluate, among of other things, the influence of medical history and history of health care utilization on the uptake of the HPV vaccine in grade eight girls living in the Kingston region.³¹ Individuals with a history of medical diagnoses and frequent contact with the health care system appeared less likely to undergo HPV immunization.³¹ The authors of the Kingston study speculate that chronically ill girls (as evidenced by frequent health care system encounters) may be less likely to undergo HPV vaccination to avoid post-treatment adverse events, such as autoimmune disorders. This conflicts with the B.C. survey which showed that 8% of caregivers with girls predisposed to ill health requested HPV vaccination as a prophylactic measure for their daughters.³⁷ Further research is needed to confirm these findings.

2.5.2 Interpersonal-level

Health care provider recommendation to vaccinate has the greatest influence on parents with respect to immunization acceptability.^{17,30,35,37} This underscores the impact of health care providers in addressing patient concerns about the HPV vaccine and in influencing caregivers' attitudes and behaviours related to vaccination decision-making. In a cross-sectional study of caregivers with girls ages 10 to 18 years living in North Carolina,

physician recommendation to immunize predicted initiation of at least one of the three HPV vaccine doses.³⁰

To enhance public health programs, it is worthwhile to compare clinicians' intentions to recommend this therapy to patients with actual recommendations made. Before the vaccine was licensed for use, physicians were generally in favour of the HPV vaccine, however, some believed it should be offered to patients at a later age than that recommended by national guidelines. Post-vaccine licensure research indicated that physicians and parents supported the delay of HPV immunization until children were at least 12 years of age.¹⁷ The reluctance to offer prophylactic vaccination before grade 9 may be problematic given that almost a third of children are sexually active by this time. Factors that predicted whether a physician was supportive of the HPV vaccine included HPV knowledge, perceived susceptibility of patients to HPV-related disease, perceived severity of infections, and believing that professional organizations endorsed this practice.^{17,30,37}

2.5.3 Community / societal level

Literature on the influence of the community on health decision-making is scarce. Challenges encountered in elucidating behaviours solely through the modelling of individual-level variables have called for ecologic analyses and the examination of how neighbourhood characteristics can shape health behaviours. Literature on multi-level modelling abounds in the education and health fields and proponents of this approach have used it to explore the cross-level interactions between the individual and the context in greater depth.^{17,25}

Only one published study conducted in the Netherlands exists on the influence of the environment on HPV vaccine uptake. Program implementation results of developed countries provide important directions for future research in regions such Canada and warrant further investigation. In the Netherlands, a catch-up campaign using the bivalent HPV vaccine was organized for girls born between January 1, 1993 and December 31, 1996. As in Canada, HPV immunization was offered free of charge and personal invitation letters were sent to the eligible girls. HPV vaccine uptake, captured in national centralized databases, varied from 31% to 61% across Community Health Service (CHS) regions responsible for the implementation of the immunization program at the local level.³⁶ Although socio-economic status and race/ethnicity were important determinants of HPV vaccine uptake in multi-level analyses, CHS-level characteristics had a significant impact on regional vaccination rates. For example, the use of local media to promote the HPV vaccine negatively influenced immunization rates, whereas discussions between CHS immunization program coordinators and schools, pupils, family physicians and gynecologists positively influenced local uptake. Further, areas with lower socioeconomic status and higher regional percentages of anti-vaccination groups represented by Christian Union voters were associated with lower HPV immunization rates³⁶.
Although there exists no research on the influence of social context on HPV vaccine uptake in Canada, a program evaluation study was conducted in Ontario to assess the challenges associated with HPV vaccine delivery and acceptance by health unit stakeholders and students. This evaluation was particularly important for two reasons. The Ontario Ministry of Health and Long-Term Care received 117 million dollars from the federal budget to fund the first 3 years of a publicly-funded, school-based HPV immunization program, with the aim of achieving 80% uptake.^{32,39} Despite initial optimism in this therapy, results were disappointingly low with approximately half of eligible Ontario girls vaccinated. Therefore, an evaluation of this initiative was needed to determine the factors that caused the provincial vaccination rate to reach the lowest level in Canada.

Evaluation findings revealed that 16 of the 36 health units encountered resistance from local school boards in implementing the HPV immunization program.³² Some school boards were reluctant to agree to program implementation for religious reasons. To garner school board support, health units engaged with school board authorities to refine communication materials distributed to pupils. Health units with greater resources who offered HPV vaccination in sexual health clinics throughout the year reported higher immunization rates. Program acceptability among stakeholders was also greater if health unit managers engaged with school board officials prior to program roll-out, if health promotion materials were provided to students, and educational sessions on HPV were held in schools.³⁶ Hence, HPV vaccine decision-making and subsequent uptake appeared

to vary depending on the social context of the health unit. This evaluation highlighted the necessity of studying ecologic factors related to uptake in the Canadian context.

The program in Ontario was initiated in September 2007 and continues to offer free immunization with the quadrivalent HPV vaccine (Gardasil®) to all grade 8 girls on a voluntary basis. Catch-up vaccination is offered to girls entering grade 9, provided they received at least one dose in Grade 8. Public health nurses administer the three-dose series at 0, 2, and 6 months at school clinics. Eligible girls may also receive the vaccine free of charge at their public health units or physician's office; however, the vast majority of them are vaccinated at school. Parental consent is required before this voluntary immunization occurs, however some health units allow girls who do not have parental consent to receive HPV immunization should they wish to do so.^{32,39}

2.6 Special populations at high risk for HPV-related disease

There is utility in studying the determinants of health behaviours of vulnerable subgroups of the Canadian population, bringing into sharper focus sexual health disparities and priority groups for targeted interventions.

Aboriginal people are disproportionately affected by HPV-related genital cancers and are more likely to die from a cervical cancer diagnosis in comparison with their non-Aboriginal counterparts.⁴⁰⁻⁶¹ From 1988 to 2004, the age-standardized incidence rate of cervical cancer among Aboriginal females living on Indian reserves and in villages in Quebec was more than double in comparison with the general Quebec population, and the

age-standardized mortality rate was approximately four times greater than that of the general population during this period.³ Similar disparities have been observed in the Northwest Territories (NWT). Aboriginal females report a higher prevalence of HPV infection than the general female population. Of 554 women ages 15-69 years living in Nunavik, Quebec between 2002 and 2007, 28.9% were infected with HPV.⁵³

Factors such as, cultural differences, access barriers, and lack of awareness and knowledge about the importance of Pap testing contribute to this issue.⁴⁰⁻⁶¹ There is a paucity of information on HPV immunization rates in this group and has been identified as a gap in the literature.

Similar to Aboriginal populations, Black women in the US are disproportionately affected by cervical cancer and are more likely to be diagnosed and die from this disease in comparison with non-Hispanic white women. Further, Black females with access to care are less likely than the general population to engage in vaccine preventative behaviours.^{62,32} In 2010, less than half of U.S. Black people completed the three-dose series, and in comparison with non-Hispanic white individuals, Black Americans were 33% less likely to report HPV vaccine initiation during this period.^{62,32}

Common barriers to uptake among the latter group included fear of side effects, believing that insufficient research had been conducted on the vaccine, and not having received physician recommendations for immunization. The following factors have been identified as potentially influential in increasing HPV vaccine uptake among black people in the United States: physician recommendation for HPV immunization, outreach provided to vaccine-hesitant individuals, and further education about HPV immunization and its safety profile.^{62,32}

The United States is comparable to Canada in many respects; American studies can be an important resource for 'lessons learned' and can provide directions for future analyses in this country. Similar to the U.S., social inequalities and health disparities persist in Canada. High-risk groups, including ethnic minorities and certain immigrant populations, do not fully benefit from public health programs. Cultural factors, knowledge gaps related to STI prevention strategies, and access barriers contribute to this issue. In particular, Aboriginal people are disproportionately affected by HPV disease and experience high cervical cancer mortality rates in comparison with their non-Aboriginal counterparts. Given the scarcity of literature on this topic, further research needs to be conducted on HPV vaccine uptake among racial and ethnic sub-groups in Canada.

2.7 Research Gaps and Opportunities

The literature supports the eco-social model (nesting three levels) as a relevant framework to understand vaccine uptake in Canada. In brief, the intrapersonal level describes personal factors, such as attitudes and beliefs, that impact decision-making for oneself (or other family members).¹⁷ Its main limitation is the reliance on self-reported data to collect information, thus incurring recall and social desirability biases. The

interpersonal level refers to the influence of social networks including peer groups and health care providers on health behaviours, while the community level captures the influence of social context on health outcomes. Despite the appeal of elucidating behaviour patterns through the analysis of the environment, there are limitations associated with this construct. Contextual effects are generally explained through internal psychological processes that cause individuals to be differentially susceptible to their environment and thus to take different actions.^{17,25} Not only is it difficult to measure these processes but it is nearly impossible to accurately determine the accumulated effects of the neighbourhood environments on behaviours. Nevertheless, the eco-social perspective has frequently been employed in multi-level research in the social science field and provides a valuable framework for understanding the factors that cause individuals to consume interventions.^{17,25} Thus, the HPV literature was reviewed according to eco-social model constructs to clarify the determinants that influence vaccination rates in Canada and elsewhere.

The research on the determinants of HPV vaccine uptake published to date is generally limited to non-Hispanic white people who are married, are of higher socio-economic status, and live in urban centres; thus limiting the generalizability of the findings. Many of these studies are also limited by selection bias due to low response rates. In addition, the consistent lack of reporting on the validity and/or reliability of research instruments used prevents the quantification of measurement bias. The self-reported nature of the data in some studies may result in recall bias, and the accuracy of self-reported HPV vaccine initiation information has not yet been determined. Other limitations of the studies available to date include small sample sizes, cross-sectional designs with different sampling frames, and the use of random-digit dialing methods resulting in recruitment bias toward more affluent subgroups of people. Furthermore, between-country comparisons of the determinants of HPV vaccine uptake are difficult to undertake due to incomplete data reporting on immunization practices as well as cost barriers associated with vaccine availability in some countries. Although the available evidence is generally insufficient to direct future HPV immunization program interventions in Canada, it provides a starting point for evaluating potentially modifiable determinants of HPV vaccine uptake.

Discussions on study limitations are worthwhile to better understand the current gaps in the literature and opportunities for future research. The most important limitation of the evidence on intent to vaccinate is that perceptions do not necessarily translate into vaccination behaviour. As such, several factors that influenced vaccine acceptability in the pre-licensure period were different from those associated with actual uptake of the HPV vaccine following licensure. For example, perceived vaccine efficacy and parental concerns over sexual promiscuity following immunization were significant in the pre-licensure years, but were not found to predict actual vaccine receipt.²⁶ Parental attitudes towards the HPV vaccine, however, was one of the predictors that remained significant in vaccination decision-making both before and after the vaccine was licensed for use.^{26,35} This is an important finding given that parental consent is often necessary before HPV

immunization occurs. Nonetheless, it is necessary to confirm such cross-sectional findings with cohort studies as the latter offer stronger evidence regarding potentially causal associations between determinants and actual uptake. Administrative health databases in Canada capture cohort data and are free from the selection and social desirability biases associated with most surveys, however they do not record intrapersonal characteristics, such as parental attitudes and beliefs. Proxies, however, can be used to provide information on caregiver attitudes towards the HPV vaccine in Canada. History of immunization (or lack thereof) with mandatory and/or other voluntary vaccines recorded by the Immunization Record Information System (IRIS) in Ontario can provide an indication of parental beliefs and attitudes towards vaccination.

After the HPV vaccine was available for use (post licensure), American research identified physician recommendation as the single most important determinant of HPV vaccination.^{17,30,35,37} It follows that those with limited opportunities to consult a physician fail to be informed about this therapy and hence may not fully benefit from cervical cancer prevention strategies available to the public. The U.S. health care system is complex and insurance issues pose special challenges that may not be encountered in Canada where citizens are offered universal health care. Thus, it is necessary to determine whether American findings also hold true for the Canadian context. Administrative databases in Ontario provide a rich source of health information that may be used for such purposes. The National Ambulatory Care Reporting System (NACRS), Ontario Health Insurance Plan (OHIP), and Discharge Abstract Database (DAD) capture

frequency of patient contact with the health care system; this variable may be used as a proxy for the probability of receiving physician recommendations to vaccinate. Those who report a higher frequency of medical visits may have a higher likelihood of receiving clinician recommendations to immunize.

The discourse on HPV immunization has revolved predominantly around individual-level factors. Despite the accumulation of knowledge on personal factors that may influence HPV immunization, vaccination rates have not improved and knowledge gaps regarding determinants of uptake still remain. More recent research has pointed to the importance of studying the influence of context on health behaviours. Social environments shape individuals' attitudes and actions, and people living in deprived regions have been shown to have worse health outcomes than those residing in more affluent areas.^{17,25} Material deprivation factors could partly explain the low uptake of public health interventions in certain areas. The program evaluation of the HPV program roll-out in Ontario indeed suggested the possible variation of vaccination rates across provincial health units because of contextual characteristics³², however this finding remains to be confirmed. Given that national administrative databases do not capture health unit socio-economic information, the Canadian Census can be used to extract such data. To determine whether social inequalities contribute to low uptake at the health unit level, material deprivation characteristics (representing the social context) can be measured. These include low income and education, and lack of social support, and may be used to inform future health planning efforts.

In addition to increasing intervention uptake, it is equally important to minimize health disparities and ensure that vulnerable populations have equal access to the therapies available to the general public. Population sub-groups, such as Aboriginal people, have been shown to be more vulnerable to disease and less likely to benefit from prevention efforts. Research on this topic in the HPV field is scarce and further analyses on the influence of race and ethnicity on vaccination rates are needed to provide insight into high-risk sub-groups that may experience barriers in accessing HPV immunization.

It is worth mentioning that the literature synthesized thus far has primarily focused on variables that influence HPV vaccine *uptake*. Although it is important to determine which people are benefiting from this intervention, it may be of greater public health value to investigate the correlates or specific characteristics that are linked to *non-uptake* of the vaccine. The Kingston study suggested medical history as a potentially important determinant of vaccination refusal in Canada, but small sample size precluded results from reaching statistical significance (and require confirmation). Additional analyses on the predictors of HPV vaccine non-receipt can be used to direct program roll-out efforts to specific groups that are not accessing this therapy.

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Chapter 3

METHODS

3.1 Study Objectives

The aim of the study was to provide an understanding of determinants of non-uptake of school-based HPV immunization offered to grade 8 girls in Ontario. The study objectives were:

- To identify the prevalence of non-uptake by health unit from 2007-08 to 2010-11, as well as the health unit-level factors that influenced vaccine refusal during this time; and
- 2. To identify the individual- and health unit-level determinants of non-uptake.

3.2 Study Design

A retrospective cohort of girls eligible for Ontario's school-based HPV immunization program between 2007 and 2011 was identified using administrative health databases¹⁻⁷. The outcome was HPV vaccination recorded between September 1st of the Grade 8 school year and the date of death or March 31, 2011 (study end). The Immunization Record Information System databases maintained by Ontario's health units were used to determine the vaccination status of study subjects. Individual-level characteristics of cohort members were identified through record linkage between administrative health databases at the Institute for Clinical and Evaluative Sciences (ICES) and the 2006 Canadian Census. Ecologic (health unit-level) factors that may have influenced the use of the HPV vaccine were identified through the 2006 Canadian Census. The population-

averaged effects of characteristics associated with HPV vaccination were identified using generalized estimating equations (GEE)⁸⁻¹⁰. This method takes into account the correlation introduced by the clustering within health units.

3.3 Cohort Formation

Ontario's Registered Persons Database (RPDB) was used to identify the study cohort. As school grade information is not available in the administrative databases, birth cohorts were used to identify grade 8 girls insured under OHIP, with a valid ICES key number, and eligible for the province's HPV vaccination program offered between 2007 and 2011. Given that individuals typically turn thirteen years of age by December 31st of their grade 8 year, study subjects born in 1994, 1995, 1996, and 1997 entered grade 8 in September 2007, 2008, 2009, and 2010 respectively, and became eligible for the corresponding year's vaccination program. Although this approach could have missed those who skipped or failed a grade, a re-abstraction study of the KFL&A records demonstrated that using the birth cohort definition correctly identified 96.4% of females eligible for the 2007-2009 program years.¹¹

The study index date was September 1st of the Grade 8 school year (cohort entry) and the study end was the minimum of either the date of death or March 31, 2011.

3.4 Outcome

The Immunization Record Information System (IRIS) databases maintained by Ontario's health units were merged with the cohort dataset to determine the HPV immunization

status of study subjects. A dichotomous variable was created to identify those who had been immunized with the HPV vaccine. Subjects who received at least 1 of the 3 vaccine doses were considered vaccinated, while those who did not receive any doses were classified as unvaccinated.

3.5 Data sources

The following six data sources were used: 1) Immunization Record Information System, 2) Registered Persons Database, 3) Canadian Institute for Health Information Discharge Abstract Database, 4) National Ambulatory Care Reporting System, 5) Ontario Health Insurance Plan, and the 6) Canadian census 2006. These databases contain immunization, population and demographic data, as well as health service utilization data, such as information on discharges, diagnoses, deaths, and transfers between facilities. Additional detail is provided on the data sources that were used to obtain and analyze the study cohort.

3.5.1 Immunization Record Information System

The IRIS database was developed by the Ontario MOHLTC to assist the province's 36 health units in tracking and recording immunizations of school-aged children mandated under the *Immunization of School Pupils Act (1982)*, as well as optional vaccines performed in Ontario clinics, schools, private-home day care facilities, and physician offices.⁷ Each record in IRIS contains data elements such as vaccine name, lot number and immunization date. When a student transfers to a school in a different health unit, the legal guardians are required to provide the child's immunization records to school

board authorities, who then submit the records to IRIS. As such, IRIS records are considered complete and up-to-date for individuals who move to another health unit.

This data holding is highly accurate in capturing HPV immunization information with a sensitivity of 99.8% (95% CI: 99.3 - 99.9) and specificity of 97.7% (95% CI: 96.3 - 98.7). Following transfer to ICES, 95.6% of the records in the IRIS database of the Kingston, Frontenac, Lennox and Addington (KFL&A) Health Unit were linked with Ontario's administrative health databases.¹²

For this study, IRIS databases belonging to 21 out of 36 public health units were available.

3.5.2 Registered Persons Database

The Registered Persons Database (RPDB) is maintained by the Ministry of Health and Long-Term Care and captures demographical information, such as date of birth/death, sex, and postal code for all Ontario residents covered by the Ontario Health Insurance Plan (OHIP). This population-based registry was stripped of personal identifiers at ICES and a scrambled, unique identifier was assigned to each individual.

3.5.3 Canadian Institute for Health Information Discharge Abstract Database

The Discharge Abstract Database (DAD) routinely captures demographic, clinical, and administrative information from participating facilities such as hospitals, and records are coded using the International Classification of Diseases, versions 9 and 10 (ICD-9 and

ICD-10). The submission of hospital discharge abstracts from hospitals in Ontario to CIHI is mandatory; therefore, information on acute care, chronic care, and rehabilitation is available.

Information in the DAD can be considered complete, accurate, and reliable. In 2007-08, a re-abstraction study comparing hospital medical charts with DAD records found sensitivities of 80% and 92% for significant diagnoses and interventions reported on DAD abstracts, respectively. A trend of increasing data completeness was reported from 2005-06 to 2007-08. When the ICD-10 codes in medical charts were compared with the ICD-10 codes in DAD, 87% agreement was found for significant diagnoses, suggesting high reliability of data in the DAD.¹

3.5.4 National Ambulatory Care Reporting System

The National Ambulatory Care Reporting System (NACRS) captures information on acute care institution separations, and facility- and community-based ambulatory care provided across Canada. NACRS provides information on emergency department visit dates and discharge diagnoses coded using ICD-9 and ICD-10.

When ambulatory care chart reviews were compared with the NACRS database, high agreement was reported for the 'main problem', defined as the most clinically significant reason for the patient seeking ambulatory or emergency care. Under-reporting of co-morbidities was common.⁶

3.5.5 Ontario Health Insurance Plan

Health care providers in Ontario submit claims to the Ontario Ministry of Health and Long-Term Care and are reimbursed for services provided through the Ontario Health Insurance Plan (OHIP). Each record in OHIP contains data elements such as patient identifiers, service fee codes, patient service dates, and diagnosis codes. This data holding captures both fee-for-service billings and shadow billings. Almost 5% of Ontario physicians submit shadow billings and are covered under the Alternate Funding Plan (AFP); notwithstanding that not all services performed are captured through shadow billing submissions. Health care workers that are part of Community Health Centres or Family Health Organizations operate outside the fee-for-service system and are not required to submit shadow billings, thus service data from these locations are not available.^{13,14}

3.5.6 Canadian Census

The 2006 Canadian Census was used to identify the ecologic-level variables. The Census is a self-reported survey conducted every 5 years by Statistics Canada to provide a statistical portrait of the Canadian population. The Census captures socio-demographic information such as age, sex, dwellings, marital status, etc. for different levels of geography (e.g., Census tract, sub-division, dissemination area, postal code) and is used to calculate, among other things, population estimates and plan public health care services. The Census enumerates the all citizens, landed immigrants, and non-permanent residents of Canada. By law, each household must provide the data required by the

survey. Until 2011, the Census consisted of the short- and long-forms. The long form is a more detailed version that was completed by 20% of the households. At the time of the analysis, the Census from 2006 was available to us and was therefore used in this study. An analyst at ICES derived the health units corresponding to postal codes in RPDB through record linkage with the Census.^{24,25}

3.5.7 PSTLYEAR Files

The PSTYLYEAR files are created at ICES using several data sources and contains records for all people captured through RPDB. PSTYLYEAR files are updated annually and have been available since 1991. The most accurate postal code for each person on July 1st of a given year is determined from data holdings available at ICES, such as the RPDB and CIHI-DAD, and constitutes the main data element in these files.²⁶

3.5.8 PCCF Files

ICES uses Statistics Canada Postal Code Conversion Files (PCCF) to link postal codes with identifiers for various Census subdivisions. Census subdivision measures based on 2006 Statistics Canada data are contained in this file, such as neighbourhood income quintile, as well as urban/rural status indicators. Neighbourhoods are identified as urban or rural in accordance with the Statistics Canada classification system, whereby areas with population concentrations greater than 1,000 people and a population density of at least 400 people per square kilometre, are considered urban, while areas outside these delimitations are rural. According to the Statistics Canada (2006) definition, urban populations include people living in urban cores, secondary urban cores, urban fringes of

census metropolitan areas (CMA) and census agglomerations (CA), and people living in urban areas outside CMAs and CAs.^{27,28}

3.6 Data access and record linkage

Initially, the IRIS databases were not ICES data holdings. A copy of the IRIS database of each health unit was transferred to ICES under Data Sharing Agreements to create a provincial immunization database. To preserve confidentiality and anonymity, ICES Key Numbers (IKN) were created for each record and the name of the health unit corresponding to each IKN was added.

To create IKNs, data from the RPDB were first linked with IRIS on the basis of OHIP numbers. For IRIS records with a valid OHIP number, deterministic linkage (complete match between OHIP numbers in RPDB and IRIS) was performed and IKNs were assigned to corresponding IRIS records. All personal identifiers (i.e. OHIP numbers) were then removed to preserve anonymity. For individuals with invalid or missing OHIP information in IRIS, probabilistic record linkage (e.g., pairs of data records did not contain identical entities, and 2 or more sources had to be used to identify an individual) was conducted between RPDB and IRIS on the basis of first and last name, date of birth, and sex.

All data entries in IRIS, CIHI-DAD, NACRS, OHIP, and RPDB require the use of this unique identifier, therefore complete record linkage across databases and across time was possible at the level of the individual.

3.7 Ethics

Individuals were not contacted during this study and ethics approval was received from the Queen's University Research Ethics Board.

3.8 Study period

Since most people are healthy during childhood and adolescence, history of health care utilization was examined between birth and cohort entry. Immunization with the HPV vaccine was evaluated between the study index date and study end.

3.9 Study variables

The exposures of interest for objective 1 were identified at the ecologic or health unitlevel, while exposures for objective 2 were defined at both the individual- and ecologiclevel. The outcome variable for both objectives in this study was non-uptake of the HPV vaccine, measured at the individual level.

3.10 Ecological variables

Ecologic (health unit-level) factors that may have influenced the use of the HPV vaccine were identified using the 2006 Canadian Census (Table 3-1). The percentage of people in a health unit with each characteristic was derived: lone or single parent families, rented dwellings, average income of people 15 years and older, Arabic ethnicity, West Asian ethnicity, South Asian ethnicity, East and South-East Asian ethnicity, North American Aboriginal ethnicity, Registered Indian status, females 10 to 14 years, non-family persons living alone, non-English mother tongue, non-French mother mongue, Arabic mother

tongue, Chinese mother tongue, employment (total population 15 years and over by labour force activity), visible minority status, education level (no certificate, diploma, or degree), and marital status. In addition, the employment:population ratio of people 15 years and older, and the average after tax income were also examined. Following variability and collinearity assessments using univariate analysis and correlation coefficients, respectively, eight variables were retained for further analyses (Table 3-1).

Table 3-1 Statistics Canada definitions of the variables used in the ecological analysis

Variable	Statistics Canada Definition
Average income before tax	The sum of the total income before-tax of all individuals 15 years and older who reported income (in relation to Statistics Canada's low income before tax cut-offs) for 2005 divided by the number of people with income in a health unit ^{29,30}
Lone parent	A caregiver with no spouse or common-law partner living in a dwelling with one of more children ^{$29,30$}
Household type (living alone)	Non-family person living alone in a dwelling ^{29,30}
Education level: highest certificate, diploma or degree	The highest educational qualification based on all certificated, diplomas and degrees obtained (e.g., secondary school graduation, registered apprenticeship and trades, college, university) ^{29,30}
Employment/population ratio of people 15 years and older	Ratio of the total number of people 15 years of age and over in the labour force in the week prior to May 16, 2006 to the total health unit population; respondents were classified as employed, unemployed, or not in the labour force ^{29,30}
Marital status as divorced, widowed or never married	A person's de facto conjugal status; respondents were classified as married and common-law; separated but still legally married (individuals no longer living with their spouse but not divorced); divorced (people who legally divorced and never remarried); widowed (people who lost their spouse and never remarried); never legally married (single people, and individuals whose marriage has been annulled and who have not remarried) ^{29,30}
Aboriginal ancestry	People who reported at least one Aboriginal ancestry, such as North American Indian, Métis, or Inuit ^{29,30}
Visible minority	As per the Employment Equity Act, 'persons, other than Aboriginal peoples, who are non-Caucasian in race or non-white in colour' ^{29,30}

The first six of these variables were used in previous Canadian studies to construct a commonly-used deprivation index, known as the Pampalon Index (PI). In this study, we used a similar methodology as the original study describing the PI³¹⁻³⁴ to create a *deprivation index* in order to explain contextual differences in HPV vaccine non-uptake across Ontario health units. The PI, proposed by INSQP, has been consistently used to measure social inequalities and contextual deprivation in Canada. Variations in overall scores of this composite index have been linked to geographic trends in premature mortality. The rationale for the use of a deprivation index is presented below.

3.11 Deprivation index variables

The initial index proposed by Pampalon is composed of two dimensions, one capturing social aspects of the environment and the other reflecting material conditions.³¹⁻³⁴

3.11.1 Material dimension of the original Pampalon index

The material dimension predominantly captures indicators related to education, income, and employment (Table 3-2).

Table 3-2 Summary of rationale for examining the ecologic (health unit)-level covariates in the study

Covariate	Rationale
covariate	Transmite .
Income	In American studies, low income has consistently been linked to low uptake of vaccines in general and in particular, the HPV vaccine; however, cost barriers in the U.S. preclude the generalization of American findings to the Canadian context. Interestingly, a recently published study on influenza vaccine uptake in the U.S. has shown lower vaccination rates among socially deprived groups even when immunization was provided free of charge. Results are conflicting and further research is warranted to determine the influence of income on immunization decision-making. ³⁵⁻³⁷
Education	American and Canadian studies show that high levels of education have been associated with skepticism regarding the utility of HPV immunization and therefore, with lower uptake. ³⁵⁻³⁷
Employment	There is a paucity of data on the association between employment and HPV immunization; however this variable may be viewed as a proxy for socio-economic status (SES). Although lower SES has been linked to lower HPV vaccination rates in the U.S., a B.C. study showed that parents with higher social status were more informed about the benefits and harms of HPV immunization and less likely to accept it for their daughters than caregivers with lower social status. The type of employment may be important when analyzing HPV vaccine non-uptake, however this level of detail is not available in Statistics Canada data. Since employment is closely related to SES, there is utility in including this variable in a determinants analysis. ³⁵⁻³⁷

3.11.2 Social dimension of the original Pampalon index

The social dimension of the Pampalon index reflects the state of being a single parent, single/divorced/separated, and living alone in a household (Table 3-3). It measures the level of social support, network, and social capital. By including this social dimension, aspects of the social context potentially associated with non-uptake are captured.

Table 3-3 Summary of rationale for examining the ecologic-level covariates in the study

Covariate	Rationale
Single parents	Single parents have generally been reported to have lower SES and potentially higher knowledge gaps regarding vaccinations than individuals in stable household structures. ³⁵⁻³⁷
Living alone	Living alone in a household may be a possible proxy for lower SES and thus, lower likelihood of receiving immunizations. ³⁵⁻³⁷
Single/divorced/separated	U.S. studies show that single, divorced, or separated people often experience barriers in accessing prevention strategies than those in a family composition. Canadian data on publicly-funded initiatives suggest that knowledge gaps may contribute to low prophylactic therapy use in this group. ³⁵⁻³⁷

3.11.3 Creation of the Deprivation Index for the public health unit (ecologic)-level

The material and social variables obtained from the Census were analysed independently and as an aggregated composite score derived using factor analysis. For the latter, the original two-component structure of the Pampalon deprivation index capturing social deprivation (single parent status, single/divorced, living alone) and material deprivation (education, income, employment) were examined using Principal Component Analysis (PCA) as per the original study³¹⁻³⁴. PCA is the preferred approach for developing such indexes. In contrast to the original index, we were not able to derive two separate components to independently capture material and social deprivation. In our analyses, five of the six indicators used in the original analyses by Pampalon were highly correlated and loaded onto one factor; these included average income, education status, employment/population ratio, single/divorced/separated status, and living alone. Based on the factor loadings of each of the five indicators included in our deprivation index, a score was created for each health unit, and then categorized into quartiles from least to highest deprivation. The percentage of single-parent families, the factor that in the original Pampalon index loaded as a social factor, loaded alone onto the second factor in our analysis. Hence, it was considered as an independent factor.

3.12 Individual-level variables

The exposures of interest at the individual-level included health care utilization, immunization with mandatory and optional vaccines, as well as medical history consisting of previous diagnoses. Health care utilization was described through four different measures. The medical conditions considered included those resulting in frequent contact with the health care system, and those serious enough to potentially affect the decision to vaccinate against HPV. Health services utilization was defined according to the number of hospital admissions, emergency department visits, outpatient physician visits, and total length of hospital stay. History of health services utilization was used as an indicator of health status and of the propensity to come into contact with the health care system.

3.12.1 Immunization history

To create histories of vaccination with optional and mandatory vaccines, immunization data was evaluated between birth and cohort entry. As per the Designated Vaccines

under the School Pupils Act, optional vaccines included hepatitis B and meningococcal C, while mandatory vaccines were measles, mumps, rubella, tetanus, diphtheria, and polio.⁷ Two dichotomous variables were created to identify immunization with optional and mandatory vaccines. Immunization with optional vaccines was identified if there was a record of receiving hepatitis B and meningococcal C, while immunization with mandatory vaccines consisted of complete vaccination with all the designed vaccines. History of immunization, particularly with optional vaccines, was used as a proxy for parental beliefs and attitudes towards HPV immunization.

3.12.2 Health care utilization

Health care utilization was derived using data elements from DAD, NACRS, and OHIP, and was characterized by frequency and intensity of health service use. History of health care utilization was defined according to the 1) number of hospital admissions, 2) emergency department visits, 3) outpatient physician visits, and 4) total length of hospital stay. These four measures were determined for each study subject after merging the cohort dataset with NACRS, CIHI, and OHIP. The total number of days hospitalized was determined using CIHI data, the total number of hospital and emergency room visits were identified through the CIHI and NACRS databases respectively, and the total number of outpatient physician visits was derived using OHIP data.

Health service utilization data were continuous and skewed, therefore univariate distributions were used to guide the selection of categories that capturing distinct groups of girls with varying intensity levels of health service utilization.

3.12.3 Medical history

Medical histories of study subjects were evaluated using OHIP, NACRS, and CIHI-DAD, and consisted of diagnoses with common conditions between birth and cohort entry.

To determine the data holding positions capturing the majority of diagnostic codes, a frequency count was run over all positions in CIHI and NACRS. Approximately 90%-95% of ICD-9 and ICD-10-CA diagnoses were captured by the first three positions in NACRS and the first five positions in CIHI; therefore the these positions were retained. OHIP contains a single position that captures diagnostic codes; thus a frequency count was not necessary for this data holding.

NACRS and CIHI were then merged and a frequency count of each diagnostic code was performed over all positions. This process was repeated for OHIP, and medical histories were subsequently created based on commonly identified diagnoses.

3.13 Statistical Analyses

3.13.1 Analysis of objective 1

The first step involved the creation of the *deprivation index*.

The second step involved descriptive analyses to determine whether there was variation in non-uptake by public health unit and by program roll-out year. Chi-square tests of association were performed to determine whether non-uptake varied across Ontario for each program year. Chi-square tests for trend were performed to determine whether there was a trend in the likelihood of refusal over the 4 years for each health unit.

Univariate analyses were then undertaken to explore skewness and data distributions, and the median was used to create categories for continuous and skewed variables.

Next, bivariate regressions between each exposure of interest and the outcome were performed using a liberal significance level of 0.1, and finally, a multivariate model was constructed to determine adjusted OR and 95% CI. An extension of the quasi-likelihood approach was used to analyze data that was correlated and binary. Given the relatedness of observations within the same cluster (health unit), correlated data analysis based on generalized estimating equations (GEE)³⁸ was used. A population average model was constructed to determine changes in the non-uptake of the HPV vaccine across clusters, given changes in ecologic-level covariates. The correlations between cluster data points were assumed to be equal, therefore an exchangeable correlation structure was specified.

Backward selection with a logit link was performed on the full model containing ecologic-level exposures of interest. The variable with the largest non-significant p-value

was removed in successive iterations. A liberal significance threshold of 0.1 was used for variable retention.

Confounding was assessed for variables that were dropped from the full model. A differences of 10% or more between the crude and adjusted parameter estimates, as well as statistical significance in bivariate regressions indicated confounding.

3.13.2 Analysis of objective 2

First, descriptive analyses were performed on all variables. Continuous variables that were skewed in univariate analyses were dichotomized according to the median value. To assess for multi-collinearity between individual- and ecologic-level variables, a correlation matrix was constructed.

Next, a bivariate regression model with a liberal significance threshold of 0.1 was constructed for each individual- and ecologic-level variable.

Individual- and ecologic-level variables were entered in the final model and backward selection with a 0.1 alpha level was used. The variable with the largest non-significant p-value was removed in successive iterations, and later assessed as a potential confounder.

3.14 References

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Chapter 4

Do regional social and material characteristics influence HPV vaccine decision-making? The Ontario Grade 8 HPV Vaccine Cohort Study

4.1 Preface

This chapter describes the factors associated with non-uptake of the quadrivalent HPV vaccine provided to Grade 8 girls in Ontario. Geographic and time trends in non-uptake are explored as well as the influence of contextual (health unit) characteristics on HPV vaccine refusal levels from 2007-08 to 2010-11.

The context has an important influence on vaccine decision-making, however the material and social characteristics of the context have not been explored in HPV vaccine research. To provide insight into the health unit characteristics associated with non-uptake in Ontario, a determinants analysis was undertaken.

This study is based on the first four years of the HPV vaccination program and uses data from immunization databases and the 2006 Canadian Census.

4.2 Do regional social and material characteristics influence HPV vaccination decision-making? The Ontario Grade 8 HPV Vaccine Cohort Study

ABSTRACT

Background

In 2007, the Canadian federal budget provided \$300 million over three years to the provinces and territories to implement publicly-funded HPV immunization programs. Current estimates indicate that HPV vaccine uptake varies significantly across Canada and is reported to be lowest in Ontario at 53%. The objective of this study is to identify the ecologic (health unit)-level factors that influenced the uptake of the HPV vaccine among Grade 8 girls in Ontario for the HPV immunization program roll-out between 2007-08 and 2010-11.

Methods

This study linked administrative health and immunization databases to identify a retrospective cohort of 144,047 girls eligible for Ontario's Grade 8 school-based HPV immunization program between 2007-08 and 2010-11. In this study a girl was considered vaccinated if she received at least 1 dose of the vaccine, otherwise she was considered unvaccinated. Ecologic or health unit-level factors that may have influenced HPV vaccine decision-making were derived from the 2006 Canadian Census. Given that individual health outcomes are influenced by the social context, a population-average model based on generalized estimating equations (GEE) was used to elucidate changes in the levels of refusal of the HPV vaccine given changes in ecologic-level covariates.

Results

In all, 49.3% of girls refused HPV immunization between 2007-08 and 2010-11. The prevalence of non-uptake was highest in the first program roll-out school year and declined thereafter for the majority of health units in Ontario. The lowest and highest prevalence estimates during the study period were 41.82% and 60.30%, respectively. A weak association was observed between high health unit levels of material deprivation and non-uptake of the HPV vaccine (OR=0.86, 95% CI: 0.83, 0.89).

Interpretations

Our results indicate that non-receipt of the HPV vaccine in Ontario is well below the national target. Furthermore, the influence of the context on HPV vaccine decision-making is weak, which is not surprising given the publicly-funded nature of the provincial program. To provide detailed insight into the possible association between context and non-uptake, the analysis should be repeated using smaller ecologic units, such as cities or neighbourhoods that better represent the community or area within which eligible girls live.

INTRODUCTION

World Health Organization estimates indicate that 493,243 women worldwide acquire cervical cancer each year and 273,505 die from this disease. Cervical cancer is the second most common cancer among Canadian women, particularly those between the ages of 20 and 44 years and infection with sexually transmitted human papillomavirus (HPV) is a necessary cause for the development of this malignancy.¹⁻³ Infection with low-risk HPV types 6 and 11 is associated with the development of genital warts, whereas persistent infection with high-risk types 16 and 18 is the primary cause of cervical cancer.⁴⁻⁹ An effective way to protect against infection with HPV and its sequelae is through immunization. The quadrivalent HPV vaccine (Gardasil®) has been approved for use in females and males ages 9 to 26 years, and offers protection against HPV types 16, 18, 6, and 11. The bivalent (Cervarix®) vaccine is approved for use in females between the ages of 10 and 25 years and protects against HPV types 16 and 18.⁴⁻⁹

In 2007, the Ontario Ministry of Health and Long-Term Care (MOHLTC) received \$117 million from the federal budget to fund a school-based HPV immunization program over three years; however estimates indicate that vaccine uptake is lowest in Ontario at 53%.¹⁰ Some of the factors that were reported as contributing to this low uptake included staff shortage and health unit resource strain during the initial roll-out phases, as well as logistical issues in delivering the HPV vaccine to schools across the province.¹⁰ In addition, school boards faced important challenges during the development and implementation of an efficient strategy for the provision of the HPV vaccine school-wide,

including communication gaps and delayed dissemination of HPV promotional materials from Ministry officials to school authorities. Although these factors affected only the first year of the program, uptake has remained low in Ontario,¹¹ as well as in Manitoba, Alberta, British Columbia, and the Northwest Territories¹². This underscores the need for further research on the determinants of HPV vaccine uptake.

Studies published to date have identified a number of individual-level determinants of HPV vaccine uptake including family income, education, Black race, perceived risk for HPV-related disease, and caregiver perceived benefits and harms of HPV immunization.¹³⁻¹⁶ However, few of these studies were conducted in the context of publicly-funded, school-based vaccination programs, and none examined this issue from a contextual perspective. Yet, several studies have demonstrated the importance of considering contextual factors (i.e., physical, social, and economic) when elucidating health behaviour patterns. For example, studies of the determinants of H1N1 vaccine uptake during the 2009 pandemic showed that regional socio-economic status, health service availability, and community policy (e.g., program financing requirements) were significant determinants of vaccine uptake.^{17,18} A recent study conducted in the Netherlands suggested that deprived areas with high regional percentages of antivaccination groups reported lower coverage of HPV immunization in adolescent girls.¹⁹ These findings demonstrate that the region a girl and her caregivers reside in can influence the decision to vaccinate; however, the context has rarely been considered in studies of the determinants of HPV vaccine uptake.

Given the potential importance of contextual factors such as the social and economic environment, and the negative public health and cost-effectiveness implications of low uptake of HPV immunization, it is important to explore the role of the context in the acceptance of this vaccine. This will provide better insight into the reasons for refusal of free, publicly-funded immunization aimed at cancer prevention. To this end, we conducted a population-based, retrospective cohort study of girls eligible for Ontario's Grade 8 HPV vaccination program to describe the levels of non-uptake of the HPV vaccine by health regions (i.e., health units). We also explored the association between the social and economic characteristics of the health unit within which each girl and her parents or guardians resided and non-uptake of the HPV vaccine.

METHODS

This study was approved by the Research Ethics Boards of Queen's University and Sunnybrook Health Sciences Centre.

Ontario's HPV vaccination program

Ontario's HPV immunization program was initiated in September 2007 and offers free vaccination with the quadrivalent HPV (qHPV) vaccine (Gardasil[®]) to all Grade 8 girls on a voluntary basis. Eligible girls may complete their vaccine series in Grade 9 provided they received at least one dose in Grade 8.¹⁰ Approximately 84,000 girls are eligible for the program each year. Public health nurses administer the three-dose series at 0, 2, and

6 months at school clinics. Eligible girls may also receive the vaccine free of charge at their public health units or in the physician's office, however the vast majority of them are immunized at school. Parental consent is generally required for the administration of this vaccine. All doses administered are documented in the Immunization Record Information System (IRIS) database, irrespective of the location of vaccination.¹⁰

Study design and population

A population-based, retrospective cohort eligible for Ontario's Grade 8, HPV immunization program between 2007-8 and 2010-11 was identified using Ontario's Registered Persons Database (RPDB) and the Immunization Record Information System (IRIS) databases maintained by province's health units. As a girl's grade was not available in the databases, birth cohorts were used to identify the eligible population. Individuals entering Grade 8 typically turn thirteen by December 31st of their Grade 8 year. As such, girls born in 1994, 1995, 1996 and 1997 would have been in Grade 8 in September 2007, 2008, 2009, and 2010 respectively, and hence, eligible for the corresponding year's vaccination program. Although this approach could miss those who skipped or failed a grade, a re-abstraction study of a medium-sized health unit demonstrated that the birth cohort definition correctly identified 96.4% of eligible girls.²⁰ Individuals whose immunization records were not available at the time of the analysis (i.e., data not yet transferred from their health unit for record linkage) were excluded. Cohort members were followed from September 1st of their Grade 8 year until their date of death or March 31, 2011 (study end).

Data sources and record linkage

This study used information from: (i) Ontario's Registered Persons' Database (RPDB), (ii) the Immunization Record Information System (IRIS), and (iii) the 2006 Canadian Census.

The RPDB, described in detail elsewhere²¹, is generated by Ontario's universal health insurance programs and are accessible through the Institute for Clinical Evaluative Sciences (ICES).²² This database has been used extensively for health research, and it provides individual-level information on socio-demographics and health insurance coverage for the province's residents. To preserve confidentiality and anonymity, each person is represented by a unique encrypted identifier that permits complete record linkage across databases and across time.

The IRIS database was developed by the Ontario Ministry of Health and Long-Term Care (MOHLTC) to assist the province's 36 health units in tracking and recording immunizations of school-aged children mandated under the *Immunization of School Pupils Act (1982)*.²³ The IRIS database of each health unit has expanded to capture detailed data elements on optional immunizations, such as vaccine name, lot number and vaccination date. When a student transfers to a school in a different health unit, the legal guardians are required to provide the child's immunization records to the local health unit. As such, records in IRIS are considered complete and up-to-date for students who move into the area. The IRIS database has been shown to accurately capture information

on HPV immunization with a sensitivity of 99.8% (95% CI: 99.3 - 99.9) and specificity of 97.7% (95% CI: 96.3 - 98.7).²⁰

A copy of the IRIS database of each health unit was transferred to ICES under individual Data Sharing Agreements to create a provincial immunization database that can be record linked to the province's administrative health databases. We added the name of the health unit to each entry in IRIS prior to the data transfer to assist us with identifying the health unit where each person had been vaccinated.

For information on population characteristics, we used data from the Canadian Census, a mandatory self-reported survey conducted every 5 years by Statistics Canada to provide a statistical portrait of the Canadian population. The Census captures socio-demographic information for different levels of geography (e.g., Census tract, sub-division, dissemination area, postal code) and is used to calculate population estimates and plan health care services. The Census enumerates all citizens, landed immigrants, and non-permanent residents.²⁴⁻²⁵ The postal codes available through the Census enabled us to identify the health units to which eligible girls belonged.

HPV vaccination status

In this study, a cohort member's HPV vaccination status was the outcome of interest and was determined through record linkage between RPDB and IRIS. A girl was classified as

'vaccinated' if she received at least 1 of the 3 recommended doses of the HPV vaccine during follow-up, otherwise she was considered 'unvaccinated'.

Characteristics of the health units

The contextual level of interest for this study was the health unit within which a cohort member resided at the time of their first dose of the HPV vaccine. We explored the economic and social characteristics of health units in relation to non-uptake of the HPV vaccine using information extracted from the 2006 Canadian Census (Appendix B).

For each health unit characteristic of interest, we obtained the percentage of residents in that health unit with the characteristic of interest or the average value for each region's residents; these factors were initially continuous. For example, some social characteristics that were considered included the percentage of single-parent families, the percentage of residents who are separated, divorced or widowed, and the percentage of persons 15 years and older living alone. Some material characteristics that were considered included the percentage income before tax of people aged 15 years and older, and the employment/population ratio of people aged 15 years and older. We used information from the 2006 Canadian Census because this represented the most recent census information available at the time of our analysis, as well as a time period prior to cohort entry (i.e., preceding the decision to vaccinate). In addition, we included

contextual factors such as percentage of visible minorities and Aboriginal populations, since these may be important predictors of HPV vaccine non-uptake.

A *deprivation index* was created for our contextual level (i.e., health unit) using principal component analysis (see statistical analysis section), and it was derived in a similar way as the original Pampalon index of deprivation.²⁶⁻²⁹ The primary advantage of such an index for our study was the ability to assess the influence of a number of important contextual factors with one variable (i.e., data sparing technique) given the limited number of health units contributing to the analysis.²⁶⁻²⁹

STATISTICAL ANALYSIS

Descriptive analysis

To describe the patterns of HPV vaccine non-uptake, we derived the percentage of girls who refused HPV immunization for the first four program years between 2007-08 and 2010-11. Non-uptake was then stratified by health unit and by program year, and chi-square tests were used to determine whether vaccination refusal varied significantly by geography and over time.

Creation of the deprivation index

The original two-component structure of the Pampalon deprivation index includes a dimension capturing social deprivation (the state of being a single parent, being single/divorced, and living alone) and one reflecting material deprivation (education,

income, employment). Each dimension is composed of three indicators (i.e., characteristics of the health units in our study) that we analyzed using principal component analysis. A summary measure based on the six characteristics was created; PCA is the preferred approach for developing such indexes.²⁶⁻²⁹ In contrast to the original index²⁶⁻²⁹, we were not able to derive two separate components to independently capture material and social deprivation. In our analyses, five of the six Pampalon indicators were highly correlated and loaded onto one factor (Appendix B); these included average income, education status, employment/population ratio, single/divorced/separated status, and living alone. These contextual factors were subsequently used to construct a single component to describe the health units. Based on the factor loadings of each of the five indicators included in our deprivation index, a score was created for each health unit, and then categorized into quartiles from least to highest deprivation. The percentage of single-parent families, the factor that in the original Pampalon index loaded as a social factor, loaded alone onto the second factor in our analysis. Hence, it was considered as an independent factor.

The distribution of the health unit characteristics not included in the deprivation index (i.e., Aboriginal status, visible minority status, single parents) were examined for skewness, and the median was subsequently used to create dichotomous cut-points (i.e., above or below the median value).

Bivariate and multivariate analyses

To assess whether the characteristics of the health unit within which a girl and her parents or guardians reside might have influenced the decision to refuse the HPV vaccine, the value of the corresponding health unit's characteristic was attributed to the girl (the unit of analysis). To estimate the population-averaged effects of these health unit-level characteristics on HPV vaccine non-uptake (unvaccinated *vs.* vaccinated), while accounting for the correlation introduced by the clustering within health units, we used generalized estimating equations (GEE) with a logit link and an exchangeable correlation structure. First, each health unit characteristic was considered separately and modeled against the outcome in bivariate models. Next, a correlation matrix with the variables that comprised the index was built and collinearity was assessed. Finally, a multivariate model was constructed containing the quartiles of the deprivation index and the three independent characteristics not contained in the index. In the final analysis, a backward approach was used to select variables and identify independent determinants of vaccine non-uptake using an a priori selected significance threshold of 0.1. Model fit was assessed using the QIC goodness of fit statistic for GEE proposed by Pan.³⁰

RESULTS

Based on birth year, we identified 144,047 girls eligible for Ontario's free HPV vaccination program between 2007-08 and 2010-11 whose immunization records were available at the time of the analysis. At cohort entry, girls were between 12.7 and 13.7 years of age (mean 13.2 years). Overall, 49.3% (n=71,048) of girls refused HPV

immunization between 2007-08 and 2010-11. During this time period, non-uptake varied from a low of 41.8% (95% CI: 40.2%-43.5%) to a high of 60.3% (95% CI: 59.4%-61.2%) (Figure 4.1). In 8 out of 21 health units, over half of the girls did not receive the HPV vaccine.

Figure 4-1 Overall prevalence of HPV vaccine non-uptake across participating Health Units during the first four years of the vaccination program



Overall, there was a statistically significant difference in non-uptake across health units for each of the first four years of the HPV vaccination program (Table 4-1). Furthermore, non-uptake varied significantly across program years for 13 out of 21 health units. The largest absolute difference in non-uptake between the first and fourth program year was 16.4% for Health Unit #16 - a decline from 55.4% to 39.0%, indicating that significantly more girls were vaccinated over time. The majority of health units experienced a downward trend in non-uptake over time, with vaccination refusal being highest in the first year of the program for 16 out of 21 health units.

Health Unit	Non-uptake (%) 2007/08	Non-uptake (%) 2008/09	Non-uptake (%) 2009/10	Non-uptake (%) 2010/11	P-value [†]
1	60.4	57.1	61.3	62.5	0.0076
2	54.6	59.4	62.2	59.5	< 0.0001
3	58.1	50.8	56.7	58.1	0.4700
4	57.9	51.2	57.2	53.3	0.3606
5	58.9	51.9	54.7	53.7	0.2199
6	51.2	56.7	NA	NA	0.0153
7	52.5	52.1	53.0	55.9	0.2683
8	54.7	55.7	47.2	51.4	0.0042
9	55.1	48.0	51.7	43.8	0.0021
10	56.3	41.9	47.2	51.5	0.0784
11	53.9	45.7	48.5	47.8	0.0010
12	50.2	47.3	50.1	44.2	0.0842
13	54.6	42.6	44.7	49.0	< 0.0001
14	51.9	43.8	41.3	49.6	0.1526
15	46.1	45.5	46.2	48.8	0.1863
16	55.4	42.5	46.3	39.0	0.0009
17	49.0	46.1	44.0	42.1	0.0048
18	48.0	39.8	45.1	38.4	0.0015
19	44.2	38.7	42.0	46.1	0.2105
20	47.4	40.1	41.1	38.6	< 0.0001
21	48.6	40.5	38.8	38.6	< 0.0001
P-value [‡]	< 0.0001	< 0.0001	< 0.0001	< 0.0001	

 Table 4-1 Patterns of HPV vaccine non-uptake according to participating Health

 Units and program year

[†] From chi-square trend test for the association between non-uptake and program year for each health unit.

[‡] From chi-square trend test for the association between non-uptake and heath unit for each program year.

A higher percentage of residents in a health unit either identifying as Aboriginal, or having no high school diploma/certificate/degree (low level of education), or reporting living alone was associated with a statistically significantly higher odds of non-uptake in

comparison with lower percentages of each of these health unit characteristics (OR=1.06; 95% CI 1.04-1.09, OR=1.09; 95% CI 1.07-1.12, OR=1.1; 95% CI 1.07-1.11, respectively) (Figure 4-2). However, these associations were weak. Further, the absolute difference in the prevalence of non-uptake below and above the median value for each factor was small (1.6% for Aboriginal people; 0.9% for single parents; 2.6% for people of visible minority status). The difference between the first and fourth quartile of the deprivation index was 3.4%. In contrast, a lower percentage of residents identifying as being a member of a visible minority group or being in the highest quartile of deprivation was associated with a significantly lower odds of non-uptake (OR= 0.90; 95% CI 0.88-0.92) and OR=0.87; 95% CI 0.84-0.91, respectively). Health unit average income above the Ontario median did not influence the decision to refuse HPV vaccination (OR=1.0; 95% CI 0.98-1.02).

Figure 4-2 Prevalence of HPV vaccine non-uptake according to contextual characteristics of participating health units



Health unit characteristics

1. Aboriginals high: above the median value of 3% for the percentage of residents identifying as Aboriginal.

2. Single parents high: above the median value of 15% for the percentage of residents living in singleparent families.

3. Visible minorities high: above the median value of 13% for the percentage of residents identifying as visible minorities.

4. Education high: above the median value of 21% for the percentage of residents identifying as having no high school degree, certificate, or diploma.

5. Income high: above the median value of \$36,937.

6. Living alone high: above the median value of 8% for the percentage of residents identifying as living alone.

7. Employment high: above the median value of 66.5% for the percentage of residents in the labour force. 8. Single status high: above the median value of 16% for the percentage of residents who are single, divorced, or widowed.

9. Q1: quartile 1 of the area deprivation index.

10. Q2: quartile 2 of the area deprivation index.

11. Q3: quartile 3 of the area deprivation index.

12. Q4: quartile 4 of the area deprivation index (highest level of deprivation).

When a multivariate model was constructed using the quartiles of the deprivation index and the three independent characteristics not contained in the index, a strong doseresponse trend was evident for the odds ratios of the index quartiles. The adjusted odds ratios were unexpectedly high, thus further descriptive analyses and collinearity assessments were undertaken. Cross-tabulations between Aboriginal status and deprivation index quartiles indicated the presence of cells with frequency counts equal to zero. Similar findings were observed for visible minority status and single parents.

To assess for multi-collinearity, Spearman's rank correlation and simple logistic procedures were performed whereby covariates were regressed against one another. Backward and forward selection procedures were also undertaken to determine the effect of eliminating or adding a variable on covariates already present in the model. The elimination of Aboriginal status and single parents greatly reduced the adjusted odds ratios, indicating that the initial model may have been over-adjusted and multicollinearity potentially present. Therefore, a model with the deprivation index and single parents was built, followed by a model including visible minorities, Aboriginal status, and single parents, but excluding the area deprivation index. Both models showed greater stability than in the initial regression when the index quartiles and the three independent variables were included.

Table 4-2 shows the results for the first multivariate model that included single parents and the area deprivation index. The odds of refusing the HPV vaccine was 5% lower when the percentage of single-parent families was higher than the median value of 15% (OR=0.95; 95% CI 0.93, 0.97). Lower levels of material deprivation did not appear to be statistically significantly associated with non-uptake for quartiles two and three; however, the highest quartile reflecting the highest level of area deprivation was associated with 14% lower odds of non-uptake (OR=0.86; 95% CI 0.83, 0.89).

Table 4-2 Crude and adjusted odds ratios of non-uptake of the HPV vaccine for the social and material characteristics (including the area deprivation index) of health units in Ontario

Characteristic	Non-uptake (%)	Crude OR (95% CI)	Adjusted [†] OR (95% CI)
Percentage of single-parent families Low (reference) High*	49.6 48.7	1.00 0.97 (0.95, 0.99)	1.00 0.95 (0.93, 0.97)
Deprivation index Quartile 1- low (reference) Quartile 2 Quartile 3 Quartile 4- high deprivation	49.8 48.9 49.2 46.4	1.00 0.96 (0.94, 0.99) 0.98 (0.95, 1.01) 0.87 (0.84, 0.91)	1.00 0.97 (0.94, 1.00) 0.98 (0.95, 1.01) 0.86 (0.83, 0.89)

[†] Adjusted for all other factors listed in the table.

* Above the median value of 15% for the percentage of residents living in single-parent families.

Table 4-3 shows the results for the second multivariate model that included Aboriginal people, single parents, and visible minorities. High percentage of Aboriginal people and high percentage of single parents did not appear to influence non-uptake (OR=1.03; 95% CI 1.00, 1.06, and OR=0.98; 95% CI 0.95, 1.00, respectively), however the odds of non-uptake was 8% lower when the percentage of visible minorities was higher than the median value of 13% (OR=0.92; 95% CI 0.90, 0.94).

Table 4-3 Crude and adjusted odds ratios of non-uptake of the HPV vaccine for the social and material characteristics (excluding the area deprivation index) of health units in Ontario

Characteristic	Non-uptake (%)	Crude OR (95% CI)	Adjusted [†] OR (95% CI)
Percentage of Aboriginals Low (reference) High [‡]	48.7 50.3	1.00 1.06 (1.04, 1.09)	1.00 1.03 (1.00, 1.06)
Percentage of single-parent families Low (reference) High*	49.6 48.7	1.00 0.97 (0.95, 0.99)	1.00 0.98 (0.95, 1.00)
Percentage of visible minorities Low (reference) High ^I	50.6 48.0	1.00 0.90 (0.88, 0.92)	1.00 0.92 (0.90, 0.94)

[†] Adjusted for all other factors listed in the table.

[‡] Above the median value of 3% for the percentage of residents identifying as Aboriginals.

* Above the median value of 15% for the percentage of residents living in single-parent families.

¹ Above the median value of 13% for the percentage of residents identifying as visible minorities.

DISCUSSION

Our study found that between 2007-08 and 2010-11, 49.3% of the girls did not initiate HPV vaccination during this period, with fewer girls refusing immunization over time. The prevalence of non-uptake varied significantly over the four program years for the majority of health units, with the highest vaccination refusal levels reported during the first year. By 2010-11, most health units documented non-initiation levels between 41.82% (95% CI 40.19, 43.46) and 60.30% (95% CI 59.45, 61.15), but not one was able to reach immunization refusal of 20% and all of them exceeded this target. This suggests that the national target of 20% refusal (or similarly, 80% initiation) is very difficult to reach. Health unit characteristics did not exert a strong influence on HPV vaccine

decision-making with the exception of area deprivation. Although certain health unit factors were statistically significantly associated with vaccination refusal in the adjusted models, the absolute difference in the prevalence of non-uptake above and below the median value was small for all variables (ex. in table 4.2, the difference for single parents was 0.9%). Although the second and third quartiles of the area deprivation index did not appear to be associated with vaccination status, the fourth quartile reflecting high area deprivation was statistically significantly associated with vaccine acceptability.

Several factors have been put forth to explain the overall low acceptance in Canada. The introduction of HPV immunization generated considerable debate, with many parents questioning the harms and benefits of this initiative, as well as the role of special interest groups in vaccine marketing. Widespread public debate regarding the effectiveness of vaccination and its efficacy in preventing HPV-related cancers likely led to decreased support by health care practitioners and increased public skepticism. In the U.S., concern about government interference with parental autonomy emerged when manufacturers began lobbying for HPV vaccination as a requirement for school attendance. Consequences of these promotional efforts persisted for several years in the U.S. and likely influenced parents in Canada making vaccination decisions for their school-aged children. Safety concerns and misunderstanding about the optimal timing of vaccination may have further contributed to the overall lack of support.

Studies on this issue focused predominantly on personal characteristics related to noninitiation, and often neglected the influence that community factors may have on vaccine acceptance. A qualitative survey of Ontario health unit managers conducted in 2009 suggested that during the first year of the program, health units experienced resistance from school and local public health authorities during the initial implementation, as well as staff shortage, and considerable public health resource strain. Despite increased promotion and public awareness regarding HPV, coverage increased only modestly during the subsequent years. Therefore, other unexplained factors were driving the low immunization levels, however no systematic studies of the determinants contributing to the low uptake in Canada had been undertaken.

Our study contributes to a growing body of research on determinants of HPV immunization, and fills a gap in the literature on predictors of HPV vaccination specific to the Canadian context. In contrast to American studies, we observed limited contextual influence on non-uptake, which may be attributed to the publicly-funded nature of the program in Canada. Despite this, our findings showed that high material deprivation was weakly associated with lower prevalence of refusal of the HPV vaccine. A B.C. study reported that parents with a higher level of education were more informed about HPV immunization benefits and harms, but were ultimately less likely to accept the vaccine for their daughters.¹⁴ If material deprivation is considered a proxy for socio-economic status and overall awareness or knowledge, then our results are somewhat consistent with those reported by the B.C. study authors. Given that material deprivation at the health unit

level does not translate into SES associations at the individual level, caution should be used when interpreting findings. The contextual characteristics were intended as a substitute for measures of individuals, however the ecologic units in this study were large geographical areas, and misclassification may have resulted when health unit characteristics were attributed to individuals. To ensure that a high degree of homogeneity in the social and material conditions is attributed to each person, future studies should use smaller spatial units that best represent the proximal community or area within eligible girls reside (ex. city or neighbourhood).

Of interest, the odds of non-uptake was only 3% higher for areas with a high regional percentage of Aboriginal people (the prevalence of non-uptake for areas with a high regional percentage of Aboriginal people was similar to areas with low proportions of Indigenous groups). This is surprising given results from published literature on this issue. Previous studies have shown that cultural and access barriers³³⁻⁴⁴ contribute to the low uptake of Pap screening and high rates of HPV infection and mortality in this population. Focus group surveys have suggested that immunization designed to protect against STI-related diseases may be associated with stigma in these groups, and that Aboriginal women may feel uncomfortable discussing sexual issues with health care workers who are not Indigenous, potentially making prophylactic intervention a potential challenge in this population.³³⁻⁴⁴

Published literature has consistently shown that the frequency of health service utilization is low among individuals of Indigenous origin and may be caused by access barriers. Aboriginal people in Canada are significantly more likely to live at least 400km from a hospital compared to non-Aboriginal people, and the odds of visiting a physician in the past year is half as likely (OR=0.47, 95% CI: 0.35-0.64) if an individual lives 400+ Km from a hospital compared to someone who lives within 50 Km of a hospital.⁴⁵ If a dose of HPV immunization is missed during scheduled school visits, there may be challenges associated with obtaining the required doses. Research on HPV immunization among Aboriginal females is scarce and often based on small quantitative studies or qualitative focus group findings that are often not generalizable to the general Indigenous population. Further epidemiological research is needed on this issue, and smaller ecologic units should be used to avoid the possible misclassification caused by the attribution of health unit characteristics to individuals.

The majority of the studies on HPV vaccination are conducted in the U.S. where lower vaccination coverage has consistently been reported for vulnerable population subgroups, such as Hispanic and Black women. African Americans are less likely to have documented immunization than non-Hispanic white women, and in 2010, only a third of Black women initiated the three-dose regimen.³² In the U.S., access barriers are common among disadvantaged groups; thus, it is inappropriate to extrapolate the findings to the Canadian context where universal health care is available for all citizens and public health infrastructure is well established. In contrast to American studies, our findings showed that areas with a higher percentage of visible minorities appeared to be less likely to refuse HPV immunization (although the absolute difference in non-uptake between areas with high and low percentages of visible minorities was small). Again, findings from the U.S. cannot be compared to results from our study since the determinants reported in American research are often tied to financial and organizational barriers, and are largely associated with a difficult-to-navigate, fragmented health care system. Since visible minorities in Canada have the same access to the HPV vaccine as the general population, it is not surprising that coverage levels are mostly unaffected by the population composition and ethnic distribution.

Our study has strengths but also several limitations. Although similar deprivation indices as ours have been used in other Canadian etiological analyses, aggregate data cannot be used to infer associations at the level of the individual. The supplementary analysis of personal characteristics related to deprivation would have added a second dimension to our study, however we did not have access to such data. Future studies should assess the effect of context using smaller geographical areas.

Selection bias was minimized with the use of population-based administrative health databases, however important determinants were not captured by these sources. For example, the perceptions and beliefs of Vaccine Preventable Disease (VPD) managers that coordinated and implemented the HPV vaccination program during the study period

would have provided a better understanding of the reasons for the low coverage over the years. Future research should employ a qualitative design to elucidate the challenges and barriers experienced by health units when implementing the program, as well as best practices in achieving higher coverage.

CONCLUSION

Our study shows that HPV vaccine non-initiation levels varied significantly across health units over the four years of the program roll-out. This study provided important insights into community factors related to the high refusal of HPV immunization in Ontario. Results show that the context appears to have a weak influence on non-uptake, however analyses should be repeated using smaller spatial resolutions.

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Chapter 5

Individual and contextual determinants of non-uptake of the HPV vaccine; the Ontario Grade 8 HPV Vaccine Cohort Study

5.1 Preface

This chapter describes the determinants associated with non-uptake of the HPV vaccine in Ontario between 2007-08 and 2010-11. It focuses on factors that influenced non-uptake at two levels: the individual and the context (health unit).

Published literature has predominantly focused on personal characteristics associated with the initiation of the three-dose regimen, and has neglected to assess the potentially important influence of the context. The previous chapter showed that regional deprivation may be a determinant of non-uptake. In this study, individual-level variables will be examined while considering the influence of health unit characteristics on HPV vaccine decision-making.

This study is based on the first four years of the HPV vaccination program and uses data from administrative health and immunization databases.

5.2 Individual and contextual determinants of non-uptake of the HPV vaccine; the Ontario Grade 8 HPV Vaccine Cohort Study

ABSTRACT

Background

In 2007, the Ontario Ministry of Health and Long-Term care received 113 million dollars from the federal budget to implement a publicly-funded HPV immunization program; however, HPV vaccine coverage in Ontario continues to remain well below the national target. Studies of the factors influencing vaccine acceptability have focused predominantly on personal characteristics in the context of privately-funded health care systems where access barriers are common. Nevertheless, there is evidence to suggest that characteristics of the community within which individuals reside can have an important influence on personal decision-making, however this has been overlooked in HPV immunization studies.

Objectives

This study identified individual-level factors that influenced HPV vaccine non-uptake among Grade 8 girls in Ontario while also considering the effects of health unit-level characteristics.

Methods

The study linked administrative health and immunization databases to identify a retrospective cohort of 144,047 girls eligible for Ontario's Grade 8 publicly funded, school-based HPV immunization program between 2007 and 2011. The socio-

demographic characteristics, vaccination histories, health services utilization and medical histories of cohort members were ascertained using administrative health databases, while the social and economic characteristics of each health unit were derived from the 2006 Canadian Census. Girls were classified as vaccinated if they received at least 1 dose of the HPV vaccine, otherwise they were classified as unvaccinated. Generalized estimating equations (GEE) with a logit link were used to estimate the population-average effects of individual-level and health unit-level characteristics on vaccine non-uptake.

Results

Between 2007 and 2011, approximately half (49.3%) of the eligible girls in Ontario refused HPV immunization. Non-uptake was strongly associated with a history of autism (OR=1.60; 95% CI 1.34, 1.90) or Down's syndrome (OR=1.37; 95% CI 1.16, 1.63), refusal of mandatory or optional vaccines (OR=2.23; 95% CI 2.07, 2.40, and OR=3.96; 95% CI 3.87, 4.05, respectively), and fewer physician visits (OR=1.45; 95% CI 1.35, 1.55). Although regional deprivation did not appear to influence vaccine decision-making, health units with the highest level of regional deprivation were associated with lower odds of vaccination refusal compared to more privileged health units (OR=0.82; 95% CI 0.79, 0.86).

Interpretations

Our study provides new insights into opportunities to improve the uptake of the HPV vaccine that have not yet been considered in previous studies. These include, targeted education and awareness programs for caregivers of adolescents with intellectual and

developmental disabilities, and offering the vaccine through publicly-funded, schoolbased clinics.
INTRODUCTION

The quadrivalent HPV (qHPV) vaccine, designed to protect against HPV types 6,11, 16, and 18, was approved for use in Canada in July 2006. In 2007, the Canadian government allocated \$300 million to the provinces and territories, on a per capita basis, to fund the first three years of a national, school-based, HPV vaccination program.^{1,2} Despite widespread promotion of the vaccine, half of the provinces and territories have not been able to achieve the targeted coverage of 80%, with Ontario documenting one of the lowest levels of acceptance at 53%.³

The reasons for the low acceptance of the HPV vaccine offered through a publiclyfunded school-based program that essentially removes financial and organizational barriers are largely unknown.⁴⁻⁶ It has been suggested that the short turnaround time between the funding announcement and the scheduled implementation of Ontario's HPV immunization program, combined with resistance from local school boards in offering STI immunization to young children, contributed, at least in part, to the low acceptance of the HPV vaccine.⁴ However, coverage has remained low through the first four years of the program,⁵ and only one of 72 school boards refused to participate⁴. A recent study conducted in a small region of Ontario reported that medical history, vaccination history, and frequency of health services utilization appeared to have an important influence on HPV vaccine acceptability.⁷ However, the study's sample size was too small to draw conclusions with certainty. Decision-making with respect to health behaviours has been shown to be influenced by a myriad of factors at the individual level and to a lesser extent, at the community or regional level.⁸⁻¹¹ Published studies of the determinants of HPV vaccine acceptance have predominantly focused on individual-level characteristics and have disregarded the potentially important influence that an individual's environment can have on health behaviours, including HPV vaccination.

We undertook a population-based, retrospective cohort study of grade 8 girls eligible for Ontario's HPV vaccination program to identify the individual-level determinants of refusal of the HPV vaccine, while accounting for the social and material characteristics of the health units within which these girls reside.

METHODS

This study was approved by the Research Ethics Board of Queen's University and Sunnybrook Health Sciences Centre.

Ontario's HPV vaccination program

Ontario's HPV immunization program was initiated in September 2007 and offers free vaccination with the quadrivalent HPV (qHPV) vaccine (Gardasil[®]) to all Grade 8 girls on a voluntary basis, and parental consent is generally required.(need a reference here from the MOHLTC website) Public health nurses administer the three-dose series at 0, 2, and 6 months at school clinics. Eligible girls may complete the series in Grade 9

provided they received at least one dose in Grade 8. Although eligible girls may receive the vaccine at their public health unit or in a physician's office, the vast majority are immunized at school. All doses of the HPV vaccine, regardless of the location of vaccination, are documented in the Immunization Record Information System (IRIS) database. Approximately 84,000 girls are eligible for this program each year.⁴

Study design and population

We identified a retrospective cohort of girls eligible for Ontario's Grade 8 school-based HPV immunization program between 2007 and 2011 using the province's administrative health records. As a girl's grade was not available in these data holdings, birth cohorts were used to identify the eligible population. As girls entering Grade 8 typically turn thirteen by December 31st of their Grade 8 year, those born in 1994, 1995, 1996 and 1997 would have been in Grade 8 in September 2007, 2008, 2009, and 2010 respectively, and would have been eligible for the corresponding year's vaccination program. Although this approach could miss girls who skip or fail a grade, a re-abstraction study of a medium-sized health unit demonstrated that the birth cohort definition correctly identified 96.4% of eligible girls.⁴ Girls whose immunization records were not available at the time of the analysis (i.e., data not yet transferred from their health unit for record linkage) were excluded from the cohort. Cohort members were followed from September 1st of their Grade 8 year until their date of death or March 31, 2011 (study end).

Data sources and record linkage

Four administrative health databases were used for this study: (1) the Registered Persons' Database (RPDB) to identify the birth cohorts and obtain information on the sociodemographic characteristics of cohort members, (2) the Discharge Abstract Database (CIHI-DAD) for dates of hospital admissions and discharge diagnoses coded using the International Classification of Diseases, Ninth and Tenth Revision (ICD-9 and ICD-10), (3) the National Ambulatory Care Reporting System (NACRS) for information on emergency department visit dates and diagnoses coded using ICD-9 and ICD-10, and (4) the Ontario Health Insurance Plan (OHIP) for information on fee-for-service claims submitted by physicians including service dates and diagnoses captured using a threedigit version of the ICD-9. These databases are continuously updated with data from the province's universal health insurance programs and can be accessed through the Institute for Clinical Evaluative Sciences' (ICES) satellite unit located at Queen's University. Described elsewhere in detail¹³⁻¹⁸, these databases have been used extensively in health research. Each Ontario resident covered by the OHIP plan is represented by a unique encrypted identifier that enables complete record linkage at the level of the individual across databases and time.

To obtain cohort members' immunization histories, we used the Immunization Record Information System (IRIS) database that was developed by the Ministry of Health and Long-Term Care (MOHLTC) to assist the province's 36 health units in tracking and recording immunizations of school-aged children mandated under the *Immunization of* *School Pupils Act (1982)*; this database is also used to document as the receipt of optional vaccines. The IRIS database contains records on vaccine name and lot number, as well as vaccination date. This database has been shown to accurately capture information on HPV vaccination with a sensitivity of 99.8% (95% CI: 99.3 - 99.9) and specificity of 97.7% (95% CI: 96.3 - 98.7).¹²

We also used data from the 2006 Canadian Census to describe the social and material characteristics of the health unit in which a girl and her parents or guardian resided. The Canada Census is a mandatory, self-reported survey conducted every five years by Statistics Canada to enumerate the citizens of this country and to provide a socio-demographic portrait of the Canadian population. The Census captures socio-demographic information for different levels of geography, such as the health unit.¹⁹

HPV vaccination status

In this study, the HPV vaccination status of eligible girls was the outcome of interest, and was identified by record linking cohort members with the IRIS database. A girl was classified as 'vaccinated' if she received at least one of the three recommended doses of the HPV vaccine, otherwise she was considered 'unvaccinated'.

Individual-level characteristics

We determined the socio-demographic characteristics, vaccination history, medical and health care utilization history of each cohort member using the administrative health and immunization databases previously described. The RPDB was used to obtain information on date of birth, sex, neighbourhood income quintile, and urbanicity at cohort entry. Neighbourhood income was obtained through record linkage of a girl's postal code with the 2006 Canadian Census, and categorized into provincial quintiles. Postal codes were also used to determine whether people lived in rural or urban areas. In accordance with the Statistics Canada classification system, areas with population concentrations greater than 1,000 people and a population density of at least 400 people per square kilometre, were considered urban, while areas outside these delimitations were classified as rural.¹⁹

Vaccination history was derived from the IRIS database and included immunizations received from birth to cohort entry. The optional vaccines that were considered included hepatitis B and meningococcal C since these are offered in grade 7, and mandatory vaccines included the measles, mumps, rubella (MMR) vaccine, and the diphtheria, polio, and tetanus immunizations. Vaccination history, particularly with optional vaccines, was used as a proxy for parental beliefs and attitudes towards immunizations in general.

The medical and health services utilization histories of cohort members were assessed between birth and cohort entry using the physician services (OHIP), emergency department visits (NACRS) and hospitalizations (CIHI-DAD) databases. The medical conditions considered included those resulting in frequent contact with the health care system, and those serious enough to potentially affect the decision to vaccinate against HPV (e.g., autoimmune disorders, cancer, congenital anomalies, heart disease, neurological diseases). Health services utilization included the number of outpatient physician visits, emergency department visits, hospital admissions, and in-patient length of stay prior to cohort entry. History of health services utilization was used as an indicator of health status and of the propensity to use the health care system.

Characteristics of the health units

We also extracted data from the 2006 Canadian Census on the social and material characteristics of the health units within which cohort members resided at cohort entry (Appendix B). Since health units are responsible for the administration and delivery of the HPV immunization program in Ontario, the health unit was chosen as the community (ecologic) level of interest for this study. For each health unit, we derived the percentage of residents with the social and material characteristic of interest (e.g., percentage of single-parent families, the percentage of residents who are separated, divorced or widowed, the percentage of persons with no high school diploma or with a low level of education). We used information from the 2006 Census as this represented the most recent data available at the time of our analysis, as well as a time period preceding cohort entry (i.e., prior to the decision to vaccinate). Further, visible minority groups and Aboriginal people have been identified as facing unique challenges or barriers in obtaining the HPV vaccine²⁰⁻²⁶, however, we did not include these characteristics in the analysis. In the ecological model of the first manuscript, these variables were highly correlated with the deprivation index and may not be independent predictors of nonuptake.

An index of *area deprivation* encompassing both social and material characteristics of individual health units was developed to reduce the large number of highly correlated indicators of social and material deprivation; a data reduction technique was used given the limited number of health units contributing to the analysis (n=21). This index of *area deprivation* was modelled after the Pampalon index of social and material deprivation,²⁷ and was derived using principal component analysis²⁸. This approach reduced the dimensionality of the health unit-level characteristics available from the census data.⁵ We modelled the same six social and material factors as those included in the Pampalon index (Appendix B) but only five of them loaded as a component/dimension. Based on the factor loadings of each of the five indicators included in our *area deprivation* index, a score was created for each health unit and categorized into quartiles from lowest to highest deprivation. The percentage of single-parent families, the factor that in the original Pampalon index loaded as a social factor, loaded alone onto the second factor in our analysis. Single parents was not considered in this study as it was shown to have minimal influence on vaccine decision-making in the first manuscript.

STATISTICAL ANALYSIS

We used generalized estimating equations (GEE) to identify the individual-level determinants of HPV vaccine refusal (i.e., non-uptake) while accounting for the characteristics of the health unit in which eligible girls and their parents or guardians resided. The GEE model accounted for the correlation introduced by the clustering of

individuals within health units while estimating the population average effect of the determinants of interest (i.e., exposures) on the outcome (i.e., non-uptake). Since the outcome is binary (vaccinated *vs.* unvaccinated) and the correlation between subjects in health units is assumed to be equal, we used GEE with a logit link and an exchangeable correlation structure. In these models, the characteristics of the health unit were attributed to the girl (unit of analysis).

Health service utilization data were continuous and skewed, and therefore were categorized in a way that captured distinct groups with lower and higher intensity of utilization. Backward selection was performed on a GEE model that included both individual- and health unit -level variables using a significance threshold of 0.1 for variable retention.

RESULTS

Based on birth year, we identified 144,047 girls eligible for Ontario's school-based vaccination program between 2007-08 and 2010-11, with a mean age of 13.2 years at cohort entry (range 12.7 and 13.7 years). Overall, 49.3% (n=71,048) refused HPV immunization, and non-uptake varied from a low of 41.8% (95% CI: 40.2-43.5) to a high of 60.3% (95% CI: 59.4-61.2) during the study period for the health units represented in this study.

The prevalence of non-uptake of the HPV vaccine was similar across neighbourhood income quintiles and urban/rural status indicating no gradient in vaccine refusal by neighbourhood affluence or place of residence (Table 5-1). With the exception of frequency of contact with a general practitioner and a history of autism and Down's Syndrome, the prevalence of non-uptake was also similar across various frequencies of health services utilization and according to a girl's medical history. Non-uptake was highest among girls who had also refused immunization with mandatory and/or optional vaccines (78.8% and 69.4%, respectively), and among girls with the lowest frequency of contact with a general practitioner (55.3%). The level of social and material deprivation was weakly associated with vaccination decision-making, although lower odds of non-uptake was observed for the fourth quartile of the area deprivation index.

The individual-level characteristics that were strongly associated with vaccine nonuptake included immunization history, frequency of visits to a general practitioner, and medical history (Table 5-2). Refusal of HPV immunization was common among those who opted out of optional vaccines and mandatory vaccines in the past (OR=3.96; 95% CI 3.87, 4.05, and OR=2.23; 95% CI 2.07, 2.40, respectively), and was also common among girls with the fewest contacts with their general practitioner compared to those with the highest number of contacts (OR=1.45; 95% CI 1.35, 1.55). A history of autism was a strong predictor of non-uptake (OR=1.60; 95% CI 1.34, 1.90), as was a history of Down's syndrome (OR=1.37; 95% CI 1.16, 1.63). The social and material deprivation characteristics of the health units within which a girl and her parents or guardians resided were weak determinants of HPV vaccination status. The highest level of deprivation (quartile four of the index) was associated with lower odds of non-uptake compared to areas with the lowest level of deprivation (OR=0.82; 95% CI 0.79, 0.86). Despite this, the absolute difference in non-uptake between the lowest and highest quartiles was only 3.4%.

Table 5	-1 Prevalei	nce of non-uptal	se o	of the H	PV	vacci	ine accoi	rding	g to i	ndividua	l- and
health	unit-level	characteristics	of	Grade	8	girls	eligible	for	the	Ontario	HPV
vaccina	ation progr	am									

Baseline characteristics[†]	Number with characteristic	HPV vaccine non- uptake (%)
Individual-level characteristics		
Socio-demographics		
Neighbourhood income quintile 1 st (Lowest income) 2 nd 3 rd (Reference) 4 th 5 th (Highest income) Missing	21,357 25,689 30,823 32,495 30,803 2,880	51.6 47.3 46.2 48.3 49.7 92.1
Place of residence		
Urban (reference) Rural	122,746 21,301	49.6 47.9
Vaccination history		
Refusal of mandatory vaccines [‡] No (reference) Yes Refusal of optional vaccines*	139,887 4,160 83,600	48.5 78.8 34.8
Yes	60,447	69.4
Health services utilization		
Frequency of hospitalizations [§] Low (<=1) (reference) Medium (2-4) High (>=4)	110,167 29,350 4,530	48.3 49.5 52.6
Length of inpatient hospital stay $\$$		
Low (<=2) (reference) Medium (3-11) High (>=11)	103,292 38,359 2,396	49.8 48.1 47.4
Frequency of emergency department visits $\$$		

Low (0) (reference) Medium (1-4) Medium-high (5-12) High (>=13)	48,413 69,796 21,229 4,609	50.7 48.9 47.9 47.3
Frequency of outpatient p visits [§]	hysician	-7.5
Low (<=42) Medium (43-116) Medium-high (117-206) High (>=207) (reference)	36,861 74,797 26,794 5,595	55.3 47.9 46.1 44.4
Medical history		
Congenital anomalies No (reference) Yes	139,324 4,723	49.3 50.2
Viral diseases No (reference) Yes	48,977 95,070	52.4 47.8
Heart disease No (reference) Yes	117,427 26,620	49.5 48.5
Obesity No (reference) Yes	137,783 6,264	49.5 45.0
Autism No (reference) Yes	143,448 599	49.3 64.3
Mental disorders No (reference) Yes	99,459 44,588	49.2 49.5
Neurological diseases No (reference) Yes	131,075 12,972	49.3 49.7
Down's syndrome No (reference) Yes	143,408 639	49.3 60.6
Musculoskeletal disorders No (reference)	95,377 109	50.2

Yes	48,670	47.5
Lung disease		
No (reference)	80,797	50.4
Yes	63,250	48.0
Endocrine disease		
No (reference)	138,578	49.3
Yes	5,469	49.0
Benign neoplasm		
No (reference)	130,398	49.5
Yes	13,649	47.7
Cancer		
No (reference)	141,556	49.3
Yes	2,491	49.3
Malnutrition		
No (reference)	137,489	49.4
Yes	6,558	47.2
Immune system disorders		
No (reference)	43,173	52.5
Yes	100,874	48.0
Health unit-level characteristics		
Index of area deprivation (quartiles)		
1 st (lowest level of deprivation) (ref.)	93.093	49.8
2^{nd}	21.249	48.9
$\overline{3}^{rd}$	18,482	49.2
4 th (highest level of deprivation)	11,223	46.4

[†] Ascertained prior to the start of eligibility for the Ontario HPV vaccination program (cohort entry).

[‡] Mandatory vaccines assessed included measles, mumps, rubella, tetanus, diphtheria, polio.

* Optional vaccines assessed included hepatitis B, meningococcal C.

[§] Ascertained anytime prior to the start of eligibility for the Ontario HPV vaccination program (cohort entry). Categories based on the frequency distribution of each factor.

[¶] Ascertained anytime prior to the start of eligibility for the Ontario HPV vaccination program (cohort entry).

Characteristic	Crude	Adjusted †
Individual-level characteristics		
Neighbourhood income quintile 1 st (lowest income) 2 nd 3 rd (reference) 4 th 5 th (highest income) Missing	1.24 (1.20, 1.29) 1.04 (1.01, 1.08) 1.00 1.09 (1.05, 1.12) 1.15 (1.11, 1.18) 13.53 (11.80, 15.52)	1.13 (1.09, 1.17) 1.01 (0.98, 1.05) 1.00 1.12 (1.08, 1.15) 1.21 (1.17, 1.25) 7.18 (6.30, 8.20)
Health services utilization		
Frequency of emergency department visits [§] Low (0) (reference) Medium (1-4) Medium-high (5-12) High (>=13)	1.00 0.93 (0.91, 0.95) 0.89 (0.87, 0.92) 0.87 (0.82, 0.93)	1.00 1.03 (1.01, 1.06) 1.02 (0.98, 1.06) 0.99 (0.93, 1.06)
Frequency of hospitalizations [§] Low (<=1) (reference) Medium (2-4) High (>=4)	1.00 0.95 (0.93, 0.98) 1.13 (1.07, 1.20)	1.00 0.94 (0.91, 0.97) 0.96 (0.90, 1.03)
Frequency of outpatient physician visits [§]		
Low (<=42) Medium (43-116) Medium-high (117-206) High (>=207) (reference)	1.55 (1.46, 1.64) 1.15 (1.09, 1.22) 1.07 (1.01, 1.14) 1.00	1.45 (1.35, 1.55) 1.24 (1.17, 1.32) 1.12 (1.05, 1.19) 1.00
Immunization history		
Refusal of mandatory vaccines No (reference) Yes	1.00 3.95 (3.66, 4.26)	1.00 2.23 (2.07, 2.40)
Refusal of optional vaccines No (reference) Yes	1.00 4.25 (4.16, 4.35)	1.00 3.96 (3.87, 4.05)
Medical history [¶]		

Table 5-2 Determinants of non-uptake of HPV immunization: crude and adjusted odds ratios for individual- and health unit-level characteristics

Congenital anomalies

No (reference) Yes	1.00 1.04 (0.98, 1.10)	1.00 1.03 (0.97, 1.10)
Viral diseases No (reference) Yes	1.00 0.83 (0.81, 0.85)	1.00 0.96 (0.94, 0.99)
Heart disease No (reference) Yes	1.00 0.96 (0.93, 0.98)	1.00 1.03 (1.00, 1.06)
Obesity Low (reference) High [‡]	1.00 0.83 (0.79, 0.88)	1.00 0.87 (0.83, 0.92)
Autism No (reference) Yes	1.00 1.85 (1.57, 2.19)	1.00 1.60 (1.34, 1.90)
Mental disorders No (reference) Yes	1.00 1.01 (0.99, 1.04)	1.00 1.04 (1.01, 1.07)
Neurological diseases No (reference) Yes	1.00 1.01 (0.98, 1.05)	1.00 1.06 (1.02, 1.10)
Down's syndrome No (reference) Yes	1.00 1.58 (1.35, 1.85)	1.00 1.37 (1.16, 1.63)
Health unit-level characteristics		
Index of area deprivation (quartiles) 1 st (lowest level of deprivation) (reference) 2 nd 3 rd 4 th (highest level of deprivation)	1.00 0.97 (0.94, 0.99) 0.98 (0.95, 1.01) 0.87 (0.84, 0.91)	1.00 1.02 (0.99, 1.06) 1.01 (0.97, 1.05) 0.82 (0.79, 0.86)

[†] Ascertained prior to the start of eligibility for the Ontario HPV vaccination program (cohort entry); adjusted for all other factors listed in the table

[‡] Mandatory vaccines assessed included measles, mumps, rubella, tetanus, diphtheria, polio.

* Optional vaccines assessed included hepatitis B, meningococcal C.

[§] Ascertained anytime prior to the start of eligibility for the Ontario HPV vaccination program (cohort entry). Categories based on the frequency distribution of each factor.

[¶] Ascertained anytime prior to the start of eligibility for the Ontario HPV vaccination program (cohort entry).

DISCUSSION

Our findings indicate that between 2007-08 and 2010-11, 49.3% of adolescent girls refused HPV vaccination. Non-initiation of the HPV vaccine was influenced by prior diagnoses of autism or Down's syndrome, and infrequent contact with a physician. Other factors found to be weakly associated with non-uptake included the social and material characteristics of the health unit; namely, the level of area deprivation. We did not find disparities commonly reported in the literature^{20,21} such as higher vaccination levels for girls living in urban regions in comparison with rural areas. In fact, there appeared to be greater acceptance of the HPV vaccine for girls residing in health units with higher levels of social and material deprivation.

The low overall coverage of this free vaccine could reflect missed opportunities to administer it in the medical setting. Parents have been shown to be reluctant to consent to the vaccination of young children ages 11-13 years and oftentimes prefer delaying immunization until children are older.^{6,20,21} Studies have consistently indicated that an important determinant of caregiver consent for the HPV vaccine is receiving a physician recommendation.^{6,20,21} However, it appears that physicians may share similar beliefs as parents, and some may not perceive their patients to be at risk for HPV infections.^{6,20,21} Physician reluctance to administer immunization and to discuss sexuality-related concerns with younger girls may be problematic given that almost a third of females are sexually active by grade 9.²⁹

The strong association between a diagnosis of Down's syndrome and a diagnosis of autism and refusal of the HPV vaccine suggests the possible presence of vaccination-related concerns among parents of children affected by these diseases. Despite the favourable safety findings of premarketing trials of the HPV vaccine,³⁰⁻³² post-marketing reports of serious adverse events following HPV immunization may have instigated concern among caregivers regarding the safety of this vaccine. However, we did not observe a strong association between non-uptake and other medical conditions. This may suggest the existence of alternative explanations for the low uptake of the HPV vaccine in this population.

The increasing number of persons with intellectual and developmental disabilities living in the community rather than in institutions, has increased public awareness regarding the sexual and reproductive health of this population.³³⁻³⁴ In addition, there is growing recognition of the need for the development of specialized education programs and health services to meet the needs of this population.³³⁻³⁴ Although intellectual disability (ID) requires specialized support in relation to sexually transmitted infection (STI) prevention and sexual abuse, research has shown that adolescents with intellectual impairments lack information in such areas.³³⁻³⁴ Children with special needs are increasingly being mainstreamed into regular school programs. This, in combination by public policy developers, and parental hesitancy in discussing sexual matters with their ID offspring contribute to the dearth of information provided to this group.³³⁻³⁴ Adolescents with

special needs have knowledge gaps regarding sexual health, notwithstanding that they report similar age of onset and rates of sexual activity as their typically developing peers.³³⁻³⁴ The absence of STI information developed for and communicated to these children by educators and parents reinforces misconceptions about people with disabilities.³³⁻³⁴ As such, caregivers may perceive that HPV immunization is not necessary for this vulnerable population. Alternatively, the low uptake by this population may be explained by access barriers for those living in group or foster homes, or a shifting of medical priorities given the competing demands of looking after an adolescent with an intellectual and developmental disability. The low uptake could also reflect the residual negative impact of the autism and MMR vaccine scare that has since been refuted.³⁵ Future research should focus on identifying the factors contributing to the low uptake of HPV vaccination among children who have autism or Down's syndrome, and potentially target outreach efforts to this group.

Given the publicly-funded school-based nature of the Canadian HPV vaccine program, it is not surprising that refusal of immunization is our study was minimally influenced by the level of health unit deprivation.

In contrast with studies conducted in the United States, our results further suggest that girls living in a region with a high level of social and material deprivation may be more likely to receive the HPV vaccine than those living in areas with a low level of deprivation. Our findings highlight the importance of offering the HPV vaccine through publicly-funded school-based programs that remove many of the barriers to access.

Refusal of HPV vaccination was also very low among those who received optional and mandatory vaccinations in the past, such as hepatitis B and MMR. This finding is consistent with that of previous research on flu vaccination.³⁶ Moreover, analyses conducted in the Netherlands showed that girls who received the MMR vaccine in the past were over six times more likely to accept HPV immunization in comparison with girls who did not report MMR vaccination.³⁷

Our study has a number of limitations that need to be considered. First, the factors available for analysis were restricted to those captured by administrative health databases and the Canadian Census; thus, residual confounding may have been introduced if important determinants, such as psychosocial characteristics, were not included in the analysis. In addition, we do not know whether the level of health unit deprivation that was identified as a possible determinant of vaccine acceptance would have remained in the final model if we had had the corresponding information at the level of the individual. As such, area deprivation may be a proxy for the status of individuals rather than an independent measure of the environment within which girls and their parents or guardians reside. Furthermore, misclassification may have been introduced through the use of large ecologic units (i.e. health unit), as these may not accurately represent the proximal community within which the girls and their caregivers reside. Therefore, future studies should address this issue by using smaller spatial resolutions such as the city or neighbourhood. Second, the diagnostic codes used to establish medical histories have not yet been validated, particularly for an adolescent population; nevertheless, these databases have been extensively used in medical and epidemiologic research including to create disease cohorts.¹³⁻¹⁸ Third, we made inferences about individuals from aggregate data, notwithstanding that people may be differentially affected by characteristics of their environment. Consequently, additional studies of the effects of the living environment on HPV vaccine non-uptake that also includes this information at the level of the individual are now indicated. A similar argument can be made for the use of neighbourhood income as a proxy for household income. However, we expect to see minimal differences, if any, on uptake if individual-level income data is used in the context of a publicly-funded program where financial barriers have, for the most part, been removed. Finally, our results may not be generalizable to other age groups or jurisdictions.

Our study provides new and important insights with regards to where to focus future efforts to improve HPV vaccine uptake that have not yet been considered in previous studies. Caregivers of adolescents with autism or Down's syndrome deserve special attention given that this young population sub-group is associated with low vaccine acceptability but is at disproportionately higher risk for STIs and cervical cancer. Consideration should be given to offering the HPV vaccine through publicly-funded, school-based immunization programs as an effective means of addressing the social and economic inequities reported by others. In addition, given the important influence that physicians have on caregiver attitudes and behaviours, they should seek every opportunity to discuss HPV-related concerns, the benefits and the risks of the HPV vaccine with those who can benefit from HPV immunization.

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Chapter 6

GENERAL DISCUSSION

6.1 Introduction

Guidelines by the Society of Obstetricians and Gynaecologists of Canada recommend administering the HPV vaccine to 11-13 year old girls to provide protection against HPVrelated cancers and genital warts. Evidence from 5-year clinical trials showed that HPV immunization is safe and effective in cohorts consisting primarily of healthy adolescent females.¹⁻¹⁰ Each year, the Ontario Ministry of Health and Long-Term Care invests approximately \$39M to fund a free vaccination program offered to grade 8 girls through school clinics.¹¹ Despite this, uptake in Ontario remains well below the national target of 80% set by the National Advisory Committee on Immunization (NACI). Concerted efforts have been made to increase acceptability for this vaccine, however available data do not indicate improvements in HPV vaccine coverage in Canadian provinces.¹² Furthermore, HPV immunization levels in Canada (53%-70% in most provinces)¹² pale in comparison to other western countries, such as England and Australia where approximately 80% of 11-12 year old girls have initiated the 3 dose regimen.^{13,14} Without further efforts to identify the unique challenges associated with the high levels of refusal of the HPV vaccine in the Canadian context, uptake will continue to remain well below the national target.¹⁵ To provide detailed insight into the determinants associated with refusal of school-based HPV immunization, we sought to characterize individualand health-unit-level characteristics among grade 8 girls from 2007-08 to 2010-11.

6.2 Main findings

The first objective was to identify the prevalence of non-uptake by public health unit and by program roll-out year, as well as the health unit-level factors that influenced nonuptake of the HPV vaccine in Ontario over four years. This was the first Canadian study to describe the possible influence of contextual characteristics at the level of the public health unit on vaccine acceptability. The highest odds of vaccination refusal appeared to be during the first year of the program for the majority of Ontario health units, however a downward trend in non-uptake was observed thereafter. There were significant differences in non-uptake across the province (41.8% - 60.3%) during this time, suggesting that health-unit characteristics may partly explain differences in vaccination refusal. Indeed, high health unit percentage of Aboriginal people was associated with non-uptake, while high deprivation levels and high regional percentages of visible minorities were associated with high vaccine acceptability.

The second objective was to identify the individual- and ecologic-level determinants of non-uptake of HPV immunization. It provided novel insights into the influence of medical history and intensity of health care utilization on vaccination refusal, while taking into consideration the effect that the context can have on personal decisionmaking. Results showed that low health care utilization, refusal of mandatory and other optional vaccines, as well as previous diagnoses with development disorders such as autism or Down's syndrome were strongly associated with non-uptake. The odds of refusing immunization increased for those reporting less contact with the medical establishment. In other words, higher health service use, particularly GP consultations, was associated with greater vaccine acceptability.

In this thesis, proxies were used to measure beliefs and attitudes in relation to HPV vaccination. Individuals who opted out of mandatory or optional immunizations in the past were significantly more likely to refuse the HPV vaccine in Grade 8. Interestingly, health-unit level characteristics remained important determinants and were independently associated with non-uptake even after adjusting for individual-level characteristics. Similar to the first manuscript, higher levels of contextual deprivation and higher regional percentages of visible minorities were associated with lower odds of therapy refusal, while greater regional percentages of Aboriginal people resulted in lower uptake.

6.3 Results in the context of evidence

Community characteristics can influence health behaviours independently of individuallevel factors, such as age, socio-economic position, and gender. Several studies suggest residential context as a key determinant of health behaviours, whereby environmental constraints or opportunities to engage in particular actions are created through social processes such as social norms, psychosocial stress, and media advertising. In addition, political and administrative policies and regulations can impact decision-making, such as school-entry vaccination requirements.¹⁶⁻²⁰ Some health behaviours are more sensitive to environmental contexts above and beyond the influence of personal characteristics. This has been elucidated through studies on flu vaccination, whereby lower vaccination rates have consistently been reported for poorer communities in the United States.²¹ This is in contrast to the results from both thesis manuscripts that suggested high levels of regional deprivation were associated with lower odds of non-uptake of the HPV vaccine. It is possible that people living in more deprived areas may not go through the same decision-making processes as their more affluent counterparts, and HPV-related promotional activity may have had more success in poorer regions. The literature shows that individuals of lower socio-economic status (SES) rely on different sources of medical information than higher SES groups.²² A cross-sectional study of caregivers living in British Columbia during 2008-09 showed that highly educated groups reported sophisticated data collection and information processing and were more likely to have access to the Internet as well as other forms of media than those who reported lower educational attainment. Access to online sources of information may also translate into opportunities to peruse Web-sites with contradictory information. Highly educated parents reported distrust of the medical community and perceived that they were able to process clinical data in the absence of assistance from health care practitioners.²² This unique group had concerns regarding vaccine safety, believed they did not have sufficient information or time to make an informed decision, and perceived that they were better equipped to make immunization decisions for their children than the GP. It is possible that they may prefer delaying the vaccination of their daughters until later ages, particularly as they would have the means to purchase it. Therefore, if regional deprivation is a proxy for individual-level socio-economic status, it follows that caregivers living in deprived areas may be more likely to rely on mainstream information delivered by special interest groups or industry-sponsored campaigns than caregivers living in more affluent health units.

Although financial and healthcare barriers are essentially removed in a publicly-funded context, results showed that Aboriginal ethnicity remained an independent determinant of non-uptake in a model that included health-unit-level variables (although the absolute difference in non-uptake between areas with high and low regional proportions of Aboriginal people was very small). Several studies indicate that Aboriginal people in Canada are at a higher risk of developing and dying from HPV-related disease than other groups. Aboriginal people are also less likely to undergo routine Pap screening in comparison with non-Aboriginal people. Factors such as, cultural differences, access barriers, and lack of awareness and knowledge about the importance of HPV prevention strategies contribute to this issue.²³⁻²⁶ Distance from large population centres is also important in predicting health service use among Indigenous groups: 49.7% of Inuit, 6.8% of Métis, 9.2% of First Nations, and 1.3% of non-Aboriginal people live at least 400 Km from a hospital, and the odds of visiting a physician in the past year is 0.47 (95% CI: 0.35-0.64) if an individual lives more than 400 Km from the hospital compared to someone who lives within 50 Km of a hospital.²⁶ After controlling for distance to health care facility and region of residence, Inuit people are still significantly less likely to have visited a physician in the previous year in comparison with non-Aboriginal individuals. Further research is needed to elucidate the reasons for the low uptake in this group, and to determine if targeted interventions are necessary to increase HPV-related knowledge, acceptance, or accessibility.

In our study, previous diagnoses of autism and Down's syndrome were important predictors of HPV vaccine refusal. Since parents are the key decision makers in vaccination behaviour, there is evidence to suggest that caregivers with physically and mentally disabled children perceive STI therapies as unnecessary for their offspring. Recent published studies indicate that caregivers of young people with intellectual disability (ID) may have negative attitudes or unrealistic beliefs in relation to their children's sexuality.²⁷ In comparison with parents of young people who are healthy, caregivers of children with ID are often unaware or perceive their child to be disinterested in sexual behaviour, and further believe that discussing sexual matters with their child may lead to inappropriate actions. In addition, mothers of children with ID may prefer to discuss sexual health issues at a later age in adolescence and attach less importance to educating their offspring about sexually transmitted infections. Even caregivers who are more accepting of the sexuality of offspring with developmental disorders, parental awareness is oftentimes not translated into action. Although mothers perceive daughters with ID to be at higher risk for sexual abuse than typically developing children, they are more cautious when discussing sexuality with this group.²⁷⁻³⁰ This issue needs to be addressed. Research has shown that, compared to healthier individuals, girls with long-term health problems or physical disabilities are almost twice as likely to experience sexual violence, and are at high risk for acquiring STIs including HPV. If caregivers believe grade 8 children with autism or Down's syndrome are not yet ready to learn about sexual health, it is not surprising that HPV vaccination coverage is lower in this group. As children with physical or mental problems are increasingly mainstreamed, it is important that school health workers and administrators are aware of the vulnerabilities of these children, and that HPV promotional materials are adapted to the needs of this group.

Caregivers with ID children may perceive negative attitudes from others regarding their child's developmental disability, and may believe that other parents with healthy children do not understand the unique challenges associated with caring for individuals with Down's syndrome or autism.²⁷⁻³⁰ This is why the former group of parents often reports fewer social networks than caregivers with typically developing adolescents. This presents an optimal opportunity for health care professionals to discuss such issues in the medical setting and to address the sexuality-related concerns of parents who have children living with disabilities.

Given that parental consent is generally required for HPV immunization, caregiver beliefs, attitudes, and behaviours need to be taken into consideration when designing routine vaccination programs. Despite the relatively low level of knowledge that American caregivers appear to have regarding HPV and cervical cancer, many responded favourably when the program was initiated. Surveys showed that parents who were supportive of vaccinations and perceived HPV immunization to be safe were also more likely to consent to its administration.³¹⁻³³ Indeed, the second manuscript suggested that girls who reported history of optional vaccination against hepatitis B and meningococcal C were significantly more likely to receive the school-based HPV vaccine. Insights into personal beliefs towards the HPV vaccine offer potentially modifiable targets for interventions.

Cross-sectional surveys of caregivers living in Alabama³⁴ and North Carolina³² revealed that the single most important factor associated with HPV vaccination consent was receiving a physician recommendation. This underscores the impact that primary care physicians have on parental vaccination decision-making and in addressing concerns about benefits and harms related to immunization in healthy as well as disabled children.

6.4 Strengths and Limitations

6.4.1 Selection bias

This thesis has many strengths including the use of population-based administrative databases. Although selection bias may be a threat to the validity of cohort study findings, the use of population-based databases ensured that the target population was available for analysis. The birth cohort definition may exclude a small percentage of eligible participants, particularly those held back or advanced in school. However, this definition has recently been validated in a re-abstraction study using Kingston, Frontenac, Lennox and Addington Public Health (KFL&A) data and has been found to correctly identify 96.4% of eligible grade 8 girls.³⁵ There was no association between being missed by the birth cohort definition and vaccination status.

Loss to follow-up may have occurred if individuals migrated to regions not captured by the 21 out of 36 IRIS databases (however this effect is expected to have had a negligible impact on the results).

6.4.2 Validation of the IRIS database

Data on HPV vaccination in the IRIS data holding can be considered accurate. A recent re-abstraction study of the KFLA IRIS database showed that HPV vaccination status is captured with a sensitivity of 99.8% (95% CI: 99.3-99.9) and a specificity of 97.7% (95% CI: 96.3-98.9), and vaccination date is estimated to be 98.6% accurate. ³⁵ Under the mandate of the Immunization of School Pupils Act (1982), health units are legally bound to track and record immunizations; therefore, it is expected that other health units in Ontario record vaccination information into IRIS with a similarly high validity and accuracy.

6.4.3 Misclassification

People who obtained care outside of Ontario or at private facilities prior to cohort entry may have incomplete clinical information in provincial data holdings, thereby introducing misclassification. Hence, the effect of the intensity of health care utilization on HPV vaccine non-uptake may be under-estimated for girls with incomplete medical information. This type of non-differential misclassification is expected to occur to the same extent in groups who did/ did not receive the HPV vaccine. Non-differential missclassification may bias the odds ratios towards the null. In addition, many of the diagnostic codes that were used to establish medical histories have not yet been validated, thus adding another possible source of misclassification bias. The code could represent a misdiagnosis or miscoding, however it is expected that such errors would occur equally in HPV vaccinated and non-vaccinated groups, regardless of the clinical profile or personal characteristics of study subjects. Therefore, any misclassification would be non-differential, biasing the odds ratios towards the null and underestimating the strengths of the associations.

6.4.4 Residual confounding

The variables available for analysis were restricted to those captured by the administrative databases. Residual confounding may have been introduced if important determinants, such as psychosocial variables (e.g., awareness and attitudes towards HPV), were not included. Nevertheless, our study captured prior immunization history that can be regarded as a proxy for parental acceptance of vaccinations.

6.4.5 Ecological fallacy

Ecological fallacy may have been introduced in this thesis in two ways. In the GEE analysis, each study subject was assigned the characteristics of the health unit that she resided in, and all exposures of interest were modeled against an outcome that was measured at the level of the individual. Associations observed at the ecological or public health unit level cannot be translated to the individual-level. Aggregate group data was

used to draw similar inferences when using neighbourhood income as a proxy for household income.

6.5 Future research

To better assess the impact of the environment on non-uptake, future studies should collect population data at a smaller level of analysis, such as the dissemination area. Multi-level modelling may seem an attractive option with the use of smaller clusters, particularly as there would be greater within-area homogeneity and larger between-area heterogeneity. However, one should consider the difficulty in applying such models in the absence of information on psychological processes needed to explain the web of causality between the context, personal attributes and the motivation to engage in healthpreventative behaviours.

The assessment of contextual effects can provide detailed insight into immunization determinants, however several challenges are associated with this approach. The difficulty in measuring the accumulated effects of neighbourhood environments on behaviour, and in elucidating behaviours through psychosocial theoretical frameworks make the study of contextual effects challenging. Also the inability to accurately determine important social and physical aspects, such as social control and social capital limit the analysis and understanding of the context on individual behaviour.
6.6 Implications of the results and conclusions

First, compared to parents with healthy children, caregivers with offspring diagnosed with ID may have different beliefs and attitudes towards the sexuality of their children. Since people living with disabilities are at high risk for sexual abuse and HPV, it is important that parents are informed when making immunization decisions for others. Future studies should assess the HPV-related knowledge, awareness, and attitudes of caregivers with ID children, with stratification by education status. Highly educated parents are a unique group with potentially different decision-making processes than other segments of the population. They may have different beliefs regarding the sexuality of children with disabilities than other parents. Since they are highly influential in society and often assume leadership roles²², it is important that they are well-informed about the benefits and harms of the HPV vaccine.

Second, considering the important influence of GPs in parental decision-making, communication between the family physician and the patient related to sexual health needs to be encouraged. The risks and benefits associated with vaccination, and the appropriate age of dose initiation need to be clearly communicated. Primary care clinicians also act as advisors to policymakers and healthcare institutions, therefore additional training and communication tools may need to be provided to this group to facilitate effective discussions.^{36,37}

Third, to address public skepticism and mistrust in newly-established initiatives, such as this, support from policy developers and healthcare professionals are needed, as well as effective partnerships between the health system and the media, and the delivery of accurate information by health workers to communities.^{36,37} Comprehensive communication strategies are needed with messages specifically tailored to address the unique information needs and concerns of special groups.^{36,37}

Finally, it is worthwhile to conduct additional HPV vaccine safety analyses, particularly on population-representative samples of people with different health profiles. This will provide the evidence base needed to continue making vaccination recommendations for the general population, as well as for vulnerable, less healthy sub-groups of females.

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Diagnosis	OHIP Code	ICD-9 Code	ICD-10-CA Code
Previous Diagnoses			
Viral conditions	070, 033, 052, 053, 054, 057, 075, 078, 079	570, 573, 050- 059	B15-B19, B00- B09
Cancer	140-209, 180	140-209, 235- 239, C53	C00-C97, D37- D48, C53
In-situ carcinoma and benign lesions	210-239	210-234	D00-D36
Disorders of the endocrine system	243, 244, 245, 250 259	243, 244, 245, 259 250	E01.8, E02, E03, E06, E10-E14, E20-E35
Malnutrition Obesity	260-269.9 278	260-269.9 278	E40-E46 E66
Autism Down's syndrome	299 758	299 758	F84.0, F84.1
Congenital anomalies	741-746	741-746	Q00-Q07, Q10- Q18, Q20-Q28
Mental disorders	290 – 299, 300-319	290-299, 300- 319	F00-F99
Neurological disorders	320-359	320-359	G00-G09, G20- G26, G35-G37, G40, G51.0, G70, G71.0
Cardiovascular diseases	390-442, 785	390-442, 785	R00-R01, I00- I02, I05-I09, I10- I15, I20-I25, I26- I28, I30-I52, I60- I69, R00-R01
Immune-mediated disorders	477, 691, 708	477, 691, 708	J30, L20-L30
Respiratory diseases	010-011, 486, 769	010-018, 480- 486, 769	A15-A19, J12- J18, J80, P22
Diseases of the musculoskeletal system	737, 739, 781	737, 739, 781	M95-M99, T14.4, M20-M25

Appendix A ICD 9, ICD 10-CA, and OHIP Diagnostic Codes

Appen	dix	B
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Health unit characteristic	Statistics Canada Census definition	Social or material factor	Included in the original Pampalon index?	Included in the area deprivation index?
(Low) education level	Proportion of people aged 15 years and older with no high school diploma, certificate or degree	Material	Yes	Yes
Employment /population ratio	Ratio of individuals 15 years of age and older who are employed to the total population 15 years of age and older	Material	Yes	Yes
Average income	Average personal (before tax) income of individuals 15 years of age and older	Material	Yes	Yes
Living alone	Proportion of individuals 15 years of age and older living alone	Social	Yes	Yes
Separated /divorced /widowed	Proportion of individuals 15 years of age and older who are separated, divorced or widowed	Social	Yes	Yes
Single parents	Proportion of lone-parent families	Social	Yes	No