The Impact of Human Papillomavirus Vaccination on Adolescent Health Outcomes: An Application of the Regression Discontinuity Design

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ABSTRACT

In 2006, Canada was among 49 countries to approve Gardasil®, a quadrivalent human papillomavirus (HPV) vaccine designed to protect against types of HPV that cause 70% of cervical cancers and more than 90% of anogenital warts. Soon after, the Canadian government launched a publicly funded, school-based HPV vaccination program aimed at immunizing young girls. Despite considerable hype about Canada's HPV vaccination program, it also faced a great deal of controversy. For example, concerns were raised about the effectiveness of the vaccine, particularly in the young age group targeted for vaccination, as well as about the possibility that vaccination would lead to increased risky sexual behaviour. As a result, levels of HPV vaccine use in some jurisdictions were far below expected, reaching nationwide lows of 50-53% in Ontario, Alberta, and Manitoba. Although HPV vaccine use has improved to a certain degree, concerns over HPV vaccination persist, as there continues to be limited information on the real-world effects of this vaccine and no information on the population-level impact of vaccination programs on the burden of disease. Moreover, the few observational studies that have studied the effects of the vaccine have done so by directly comparing vaccinated and unvaccinated girls, an approach that is vulnerable to irremediable confounding bias. The overall aim of my thesis work was to assess causal effects of HPV vaccination on adolescent health outcomes in Ontario, Canada. To this end, I used provincial administrative health and immunization databases to carry out a population-based, retrospective cohort study of 260,493 girls.

The first objective of this thesis was to assess whether a quasi-experimental approach, known as the regression discontinuity design (RDD), would be appropriate for assessing the causal effects of Ontario's Grade 8 HPV vaccination program. This was done by assessing the assumptions of the RDD. The findings suggested that although the assumptions were generally satisfied in this study context, an unexpected effect of birth timing had the potential to confound the results. Therefore, modifications to the standard RDD analyses were required. This manuscript is presented as an introduction to the RDD for health researchers and provides a tutorial on how to assess the four fundamental assumptions of the RDD for a given study question.

The second objective of this thesis was to use the RDD to evaluate the impact of the HPV vaccine and of Ontario's Grade 8 HPV vaccination program on cervical dysplasia and anogenital

warts. Statistically significant reductions in dysplasia attributable to both vaccination (risk ratio [RR] 0.56, 95% confidence interval [CI] 0.36 to 0.87) and program eligibility (RR=0.79; 95% CI 0.66 to 0.94) were observed. Although not statistically significant, results also suggested clinically meaningful reductions in anogenital warts at both the vaccine level (RR=0.57 to 95% CI 0.20 to 1.58) and the program level (RR=0.81, 95% CI 0.52 to 1.25). These findings provide strong evidence of the early health benefits of publicly funded HPV vaccination in Canada.

The third and final objective of this thesis was to assess the potential indirect effect of HPV vaccination on clinical indicators of sexual behaviour (i.e., pregnancy and non-HPV-related sexually transmitted infections). The results of this study provided no indication of an increase in risk of the composite endpoint attributable to the vaccine (RR=0.96, 95% CI 0.81 to 1.14) or the vaccination program (RR=0.99, 95% CI 0.93 to 1.06). Findings were similar when each endpoint was assessed separately. The results of this study suggest concerns over increased risky sexual behaviour following HPV vaccination are unwarranted and should not be a barrier to vaccination.

This thesis contributes to advancing public health policy in Canada by providing the first evidence of the health effects of Canada's publicly funded HPV vaccination program. The results of these studies can be used to assist HPV vaccine educational efforts across the country and should be used to guide future HPV vaccine program research. This thesis also contributes to the advancement of epidemiologic methodology by applying the regression discontinuity design, which is relatively new to epidemiology, to assess the causal effects of this intervention. Additional research is needed to monitor and strengthen Canada's HPV vaccination program, as well as to further develop the flexibility of the RDD for epidemiologic questions.

RÉSUMÉ

En 2006, à l'instar de 28 autres pays, le Canada approuvait l'utilisation de Gardasil®, un vaccin quadrivalent contre le virus du papillome humain (VPH) protégeant contre les types de VPH causant 70% des cancers cervicaux et plus de 90% des verrues ano-génitales. Rapidement, le gouvernement canadien a lancé un programme de vaccination dans les écoles financé par l'État afin d'immuniser les jeune filles. Celui-ci a été accueilli avec enthousiasme, bien qu'il ait également généré une importante controverse. Par exemple, l'efficacité du vaccin a été mise en doute, en particulier en raison du jeune âge visé par le programme. De plus, certains ont émis l'hypothèse que la vaccination pourrait résulter en une augmentation des comportements sexuels à risque. Ainsi, les niveaux d'administration du vaccin ont été bien en deçà des attentes dans certaines juridictions, atteignant aussi peu que 50-53% de la population visée en Ontario, en Alberta et au Manitoba. Bien que les niveaux d'utilisation aient augmentés quelques peu, ces préoccupations persistent. En effet, l'information au sujet des effets réels du programme de vaccination demeure limitée et il n'y a toujours pas de données sur l'impact de ce type de programme sur le fardeau des maladies au niveau populationnel. Les quelques études observationnelles ayant étudié les effets du vaccin ont comparé directement les filles vaccinées ou non, bien que cette approche soit vulnérable à un biais de confusion irrémédiable. L'objectif global de ma thèse consistait donc à évaluer les effets causals de la vaccination contre le VPH sur la santé des adolescentes en Ontario. Pour ce faire, j'ai mis sur pied une cohorte rétrospective populationnelle en utilisant des bases de données administratives et de vaccination.

Le premier objectif de cette thèse était de déterminer si l'approche quasi-expérimentale de régression discontinue serait adéquate pour évaluer l'effet causal du programme ontarien de vaccination contre le VPH en 8^{e} année. Pour ce faire, nous avons évalué les hypothèses inhérentes à l'approche de régression discontinue. Les résultats obtenus suggèrent que bien que ces hypothèses soient généralement satisfaites dans le contexte de notre étude, un effet inattendu du moment de la naissance a été découvert pouvant résulter en un biais de confusion. Des modifications à l'approche standard de régression discontinue ont donc été nécessaires. Cet article est présenté à titre d'introduction à l'approche de régression discontinue pour les chercheurs en santé. Il s'agit d'un tutoriel pour évaluer les quatre hypothèses de l'approche de régression discontinue pour une question donnée.

Le second objectif de cette thèse consistait à appliquer l'approche de régression discontinue afin d'évaluer l'impact du vaccin et du programme de vaccination en 8e année de l'Ontario sur la dysplasie cervicale et les verrues ano-génitales. Une réduction statistiquement significative au niveau des dysplasies a pu être attribuée autant à la vaccination (rapport de risque [RR] 0.56, intervalle de confiance à 95% [IC] 0.36 à 0.87) qu'à l'éligibilité au programme (RR=0.79, IC 95% 0.66 à 0.94). Quoi que non significatifs statiquement, les résultats obtenus suggèrent aussi une réduction au niveau des verrues ano-génitales avec la vaccination (RR=0.57, IC 95% 0.20 à 1.58) et avec l'éligibilité au programme (RR=0.81, IC 95% 0.52 à 1.25). Ces résultats démontrent les bénéfices en santé du programme de vaccination financé par l'État au Canada.

Le troisième et dernier objectif de cette thèse était d'évaluer les effets indirects potentiels de la vaccination contre le VPH sur certains indicateurs du comportement sexuel tels que les grossesses et les infections transmises sexuellement autre que le VPH. Les résultats obtenus avec un indicateur composé n'apportent aucune évidence d'une augmentation du risque attribué à la vaccination (RR=0.96, IC 95% 0.81 à 1.14) ou au programme (RR=0.99, IC 95% 0.93 à 1.06). Des résultats semblables ont été obtenus lorsque chaque indicateur était utilisé séparément. Ceci suggère que les inquiétudes par rapport à une augmentation des comportements sexuels à risque suite à la vaccination contre le VPH ne sont pas fondées et ne devraient pas prévenir la vaccination.

Cette thèse contribue à l'avancement des politiques de santé publique du Canada puisqu'il s'agit de la première évaluation des effets sur la santé du programme publique canadien de vaccination contre le VPH. Les résultats des trois études présentées pourront contribuer aux efforts d'éducation au sujet du vaccin contre le VPH à travers le pays. Elles devraient également être utilisées afin de guider les recherches futures sur le programme de vaccination contre le VPH. Cette thèse contribue à l'avancement des méthodes épidémiologiques par l'application de l'approche de régression discontinue pour évaluer les effets causals de cette intervention, une approche relativement nouvelle en épidémiologie. D'autres études sont nécessaires pour continuer la surveillance et l'amélioration du programme canadien de vaccination contre le VPH et pour développer l'approche de régression discontinue pour la rendre flexible à des questions épidémiologiques variées.

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CONTRIBUTION OF AUTHORS

Manuscript 1: Smith LM, Kaufman JS, Lévesque LE, Strumpf EC. Strategies for Evaluating the Fundamental Assumptions of the Regression Discontinuity Design: A Case Study Using a Human Papillomavirus Vaccination Program. [To be submitted to the *Annals of Epidemiology.*]

Manuscript 2: Smith LM, Strumpf EC, Kaufman JS, Lofters A, Schwandt M, Lévesque LE. The Impact of Human Papillomavirus (HPV) Vaccination on Cervical Dysplasia and Anogenital Warts Among Adolescent Girls: The Ontario Grade 8 HPV Vaccine Cohort Study. [Currently under revisions for re-submission to *Pediatrics.*]

Manuscript 3: Smith LM, Kaufman JS, Strumpf EC, Lévesque LE. The Effect of Human Papillomavirus (HPV) Vaccination on Clinical Indicators of Sexual Behaviour Among Adolescent Females: The Ontario Grade 8 HPV Vaccine Cohort Study. [*Canadian Medical Association Journal,* in press.]

This thesis presents the results of research that I initiated and executed under the guidance of my co-authors. I wrote the thesis protocol, which I later helped expand into an operating grant that was funded by the Canadian Institutes for Health Research. I also assisted in securing access to the data required for this thesis. This involved acquiring permission to use the Immunization Records Information Systems (IRIS) data of 34 Ontario health units and transferring the data to the Institute of Clinical Evaluative Sciences (ICES), as well as acquiring permission to use other ICES data holdings. Given the restricted access students have to data at ICES, I wrote the code used to cut the raw data for my study cohort, but this process was executed by Guoyuan Liu, a biostatistician working with Dr. Linda Lévesque. Guoyuan and Dr. Lévesque also did some data cleaning of the IRIS data, as these data are also used for studies outside the context of this thesis. Otherwise, I conducted all data management and statistical analyses required for the execution of the three manuscripts included in this thesis. I also wrote the three thesis manuscripts, which were critically reviewed by all co-authors. Throughout the

execution of this thesis, Dr. Jay Kaufman, Dr. Erin Strumpf, and Dr. Linda Lévesque provided me with methodological, clinical, and substantive support.

Dr. Jay Kaufman (PhD) is a Professor in the Department of Epidemiology, Biostatistics, and Occupational Health at McGill University; he also holds a Canada Research Chair in Health Disparities. As my thesis co-supervisor, Dr. Kaufman played a major role in the conception, design, analysis, and interpretation of these thesis studies and critically reviewed all three manuscripts. Dr. Kaufman provided invaluable methodological support to all three manuscripts.

Dr. Erin Strumpf (PhD) holds a joint appointment in the Departments of Epidemiology, Biostatistics, and Occupational Health and Economics at McGill University. As my thesis co-supervisor, Dr. Strumpf played a major role in the conception, design, analysis, and interpretation of these thesis studies and critically reviewed all three manuscripts. Dr. Strumpf provided crucial guidance in my understanding and execution of the primary methodological approach used in this thesis (i.e., the regression discontinuity design).

Dr. Linda Lévesque (BScPhm, PhD) is an Associate Professor in the Department of Public Health Sciences at Queen's University and is the Principal Investigator of the Ontario Grade 8 HPV Vaccine Cohort Study. Dr. Lévesque played the principal role in acquiring the study data and obtaining funding for these studies. As a thesis committee member, Dr. Lévesque also played a major role in the conception, design, analysis, and interpretation of the studies, and critically reviewed all three manuscripts.

Dr. Aisha Lofters (MD, PhD) is an Assistant Professor and Clinician-Scientist in the Department of Family and Community Medicine at the University of Toronto, as well as a family physician at St. Michael's Hospital in Toronto, who has done extensive research in the area of cervical cancer screening. Dr. Lofters provided her expertise to the design of Manuscript 2. She also critically reviewed the manuscript.

Dr. Michael Schwandt (MD, MPH) is a family physician whose practice focuses on the diagnosis and treatment of sexually transmitted infections among adolescents. Dr. Schwandt provided clinical expertise for the design of Manuscript 2. He also critically reviewed the manuscript.

All authors were involved in acquiring funding for the three thesis manuscripts.

STATEMENT OF ORIGINALITY

The work presented in this thesis constitutes original scholarship that contributes to advancing knowledge about the effects of HPV vaccination and also contributes to advancing epidemiologic methodology. Specifically, in Manuscript 1, I provide one of the first introductions to the regression discontinuity design in the epidemiologic literature, and Manuscripts 2 and 3 present one of the first applications of this design in the field. Manuscripts 2 and 3 are the first studies to assess the health effects Canada's publicly funded, school-based HPV vaccination program. Manuscript 2 provides one of the first observational studies of the real-world effects of HPV vaccination on cervical dysplasia and anogenital warts to date, and Manuscript 3 provides the second (and largest) study of the effects of HPV vaccination on clinical indicators of sexual behaviour. The application of the regression discontinuity design in Manuscripts 2 and 3 represents a significant methodological advancement over previous studies on these topics. These manuscripts also provide the first assessment of the intention-to-treat effects of HPV vaccination outside of clinical trials, thereby contributing to the understanding of the population- or program-level effects of the vaccine.

While I received guidance from my committee members and co-authors on the substantive, methodological, and statistical aspects of this thesis, I declare that the conception, execution, and drafting of the work in this thesis are my own.

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ACRONYMS AND ABBREVIATIONS

Acronym/Abbreviation	Definition
AGW	anogenital warts
ARD	absolute risk difference
ASCUS	atypical squamous cells of undetermined significance
CI	confidence interval
CIHI	Canadian Institute for Health Information
CIHR	Canadian Institutes of Health Research
DAD	Discharge Abstract Database
DTP	diphtheria-tetanus-pertussis
Gr.	Grade
HPV	human papillomavirus
HSILs	high-grade squamous intraepithelial lesions
ICD-9	International Classification of Diseases – version 9
ICD-10	International Classification of Diseases – version 10
ICES	Institute for Clinical Evaluative Sciences
IKN	ICES Key Number
IRIS	Immunization Recording Information System
ITT	intention-to-treat
LPHA	local public health agency
LSILs	low-grade squamous intraepithelial lesions
MMR	measles, mumps, rubella
MOHLTC	Ministry of Health and Long-Term Care
NACRS	National Ambulatory Care Reporting System
OHIP	Ontario Health Insurance Plan
Pap	Papanicolaou
QHPV	quadrivalent human papillomavirus
RCT	randomized control trial
RR	relative risk *or* risk ratio
RD	risk difference
RDD	regression discontinuity design
RPDB	Registered Persons Database
STI	sexually transmitted infection

CHAPTER 1: GENERAL INTRODUCTION

1.1 Introduction

The human papillomavirus (HPV) is the most common sexually transmitted infection in the world, affecting 50-75% of all sexually active individuals.[1-3] While the vast majority of infections self-resolve without clinical sequelae,[4] others can lead to important health consequences, including cervical cancer and anogenital warts (AGW).[5,6]

In 2006, Canada was among 49 countries to approve Gardasil®, a three-dose vaccine designed to protect against four types of the human papillomavirus (HPV) that cause 70% of cases of cervical cancer and more than 90% of cases of anogenital warts.[7-9] Soon after, the Canadian government announced they were allocating $300 million to provinces and territories to fund the first three years of a national HPV immunization program for young girls.[10] While these programs were highly anticipated by some individuals, they were also met with a great deal of controversy surrounding, in large part, the unanswered questions about the real-world effects of the HPV vaccine.[11-16] Of particular concern was the limited information on the effectiveness of the vaccine, especially in the young age group targeted for vaccination, as well as the potential indirect effect of HPV vaccination on risky sexual behaviour. As a result, levels of HPV vaccine acceptance were much lower than anticipated in some jurisdictions, reaching nationwide lows of 50% in Alberta and Manitoba, 53% in Ontario, and 58% in Saskatchewan.[17]

Despite the fact that almost seven years have passed since provincial/territorial HPV vaccination programs were implemented, there continues to be very little information on the real-world effects of this vaccine and no information on the population-level impact of vaccination programs on the burden of disease. Moreover, previous epidemiologic studies of the effects of the vaccine have utilized methods of analysis that are notoriously vulnerable to confounding bias, suggesting improved methodology in this area is required. Given the importance of understanding the causal effects of HPV vaccination for optimizing the health benefits and cost-effectiveness of Canada's publicly funded HPV vaccination program, there is a clear need for large, population-based studies of the HPV vaccine and of HPV vaccination programs.

1.2 Research Objectives

The overall aim of my doctoral research was to assess the causal effects of publicly funded, school-based HPV vaccination in Ontario. The three specific objectives of this thesis were as follows:

1. To assess whether the regression discontinuity design is an appropriate approach to assessing the impact of HPV vaccination on health outcomes.
2. To evaluate the effectiveness of the HPV vaccine and Ontario's Grade 8 HPV vaccination program on reducing cervical dysplasia and anogenital warts among adolescent girls.
3. To determine the effect of publicly funded, school-based HPV vaccination on clinical indicators of sexual behaviour among girls in Ontario.

1.3 Organization of Thesis

This seven-chapter, manuscript-based thesis is organized around three core chapters (Chapters 4-6). Each of these chapters contains a research manuscript that addresses one the three research objectives. In particular, Chapter 4 (which contains Manuscript 1) assesses whether the assumptions of the RDD are met in this study context; Chapter 5 (which contains Manuscript 2) uses the RDD to investigate whether HPV vaccination in Ontario has led to reductions in cervical dysplasia and anogenital warts; and Chapter 6 (which contains Manuscript 3) evaluates the effects of HPV vaccination in Ontario on clinical indicators of sexual behaviour among adolescent girls. Each of these chapters begins with a preface to the manuscript. Chapters 5 and 6 also provide additional results and discussion not contained in the manuscript. To support these core chapters, Chapter 2 provides a detailed background on the research objectives, and Chapter 3 provides an overview of the methodology used to execute the studies, as well as additional details on data collection and analysis not contained in the manuscripts. Finally, Chapter 7 contains an overall summary of the findings in Manuscripts 1-3, a discussion of the methodological, public health, and clinical implications of this thesis work, and provides directions for future research. Appendices not cited in the manuscripts are provided directly after Chapter 7. All works cited in this thesis, including in Manuscripts 1-3, are listed in the References List at the end of this document.

CHAPTER 2: LITERATURE REVIEW

2.1 The Burden of HPV

The human papillomavirus (HPV) is the most commonly diagnosed sexually transmitted infection (STI) in the world.[1] In fact, it is believed that 50-75% of all sexually active individuals will be infected with anogenital HPV at some point during their life.[2,3] Although the vast majority of these infections are transient and self-resolve within one to two years,[4,18] others persist and lead to clinical sequelae. A number of conditions are associated with anogenital HPV infections, but arguably the most common is anogenital warts (AGW) and the most devastating is cervical cancer.

Globally, anogenital warts affect approximately 1% of all sexually active adults aged 15-49.[19] In Canada, this burden primary affects young women, as evidenced by population-based studies from both British Columbia and Manitoba, which indicate that age- and sex-stratified incidence of anogenital warts peaks among women aged 20-24 years at approximately 4-5 cases per 1000 population.[20,21] Although anogenital warts rarely lead to serious health consequences, they are highly infectious[22] and their presence can lead to significant psychological, physical, emotional, social, and sexual problems for those affected.[19,23-25] Since the psychological distress of having anogenital warts if often greater than the morbidity of the disease, quick and successful treatment is necessary. However, treatment of anogenital warts tends to be painful, lengthy, and costly.[26] Furthermore, an estimated 25-67% of cases of AGW reappear within three month of initial clearance.[22]

HPV is also a necessary, although not sufficient, cause of cervical cancer,[5] which is the second most common cancer and the fifth leading cause of cancer mortality among women worldwide.[27] This burden primarily affects developing nations, where cervical cancer screening via Papanicolaou (Pap) tests is not yet commonplace. In contrast, given the effectiveness of early detection and subsequent treatment of pre-malignant and malignant cervical lesions,[28,29] countries like Canada have seen major declines in the incidence and mortality of cervical cancer following widespread, regular use of Pap tests. Despite efforts to promote the importance of cervical cancer screening and to make Pap tests accessible to the female population, Pap tests remain under-utilized,[30] particularly by populations most vulnerable to HPV infections, such as

those of low income.[31] Consequently, every year in Canada approximately 1,300 women are diagnosed with cervical cancer and 380 women die from the disease.[29]

Of the more than 40 genotypically distinct types of HPV that infect the anogenital tract,[1,32] it is believed that HPV types 6 and 11 cause more than 90% of anogenital warts[9] and that HPV types 16 and 18 cause 70% of cervical cancers.[8] HPV 16 and 18 have also been associated with cancers of the anus, vagina, penis, vulva, and oropharynx.[33] Apart from the incredible burden these conditions have on the individual and their loved ones, they also come at a great cost to Canada's publicly funded healthcare system. In fact, it is estimated that HPV types 6, 11, 16, and 18 cost the Canadian healthcare system more than $33 million annually in direct healthcare costs alone.[34]

2.2 HPV Vaccines

In 2006, Health Canada approved Gardasil® (Merck, Whitehouse Station, New Jersey), a quadrivalent HPV (qHPV) vaccine designed to protect against HPV types 6, 11, 16, and 18.[7,35] At that time, the vaccine was indicated as a three-dose series for prophylactic use against HPV infections in females aged 9 to 26 years.[36] Since then, the vaccine has been authorized for use in females up to 45 years of age, as well as for males aged 9 to 26 years.[37] As the vaccine is not indicated for the treatment of an existing HPV infection, it is considered most effective when administered before the onset of sexual activity. Accordingly, the National Advisory Committee on Immunizations currently recommends that the vaccine be given to girls between the ages of 9 and 13 years, when the likelihood of previous infection is still low.[37]

A bivalent HPV vaccine (Cervarix®, GlaxoSmithKline, Philadelphia, Pennsylvania), designed to protect against HPV types 16 and 18, is also available. However, this vaccine was not approved for use in Canada until February of 2012,[38] and it does not fall under Canada's publicly funded healthcare program. Therefore, the quadrivalent HPV vaccine is the focus of this thesis.

2.3 Canada's HPV Immunization Program

In March of 2007, the Canadian government announced they were allocating $300 million to provinces and territories on a per-capita basis to launch the first three years of a national HPV

vaccination program aimed at immunizing young girls.[10] Since this money was allocated to provinces and territories on a per-capita basis, the Ontario government received $117 million to design and implement its program.[39]

Ontario's Grade 8 HPV Vaccination Program began in September of 2007. Since then, the program has offered all three recommended doses of the quadrivalent HPV vaccine free-of-charge to all Grade 8 girls in the province.[40,41] The program is delivered through the province's 36 local public health agencies (LPHAs), primarily through school-based immunization clinics. As such, most vaccine doses are administered by public health nurses in September/October, November/December, and March/April of each school year to correspond with the recommended 0-, 2-, 6-month dosing schedule of the vaccine. However, eligible girls also have the option of receiving doses at their physician's office or LPHA. Since the qHPV vaccine is not mandatory in Ontario, participation is the program is completely voluntary. When the program first began, girls had until the end of their Grade 8 school year to initiate the vaccination series and until the end of their Grade 9 year to complete it. In September of 2012, Ontario began offering a "catch-up" program in which girls in Grades 9-12 who had not received or completed their vaccination series in Grade 8 had the option of doing so until the end of their Grade 12 year. Girls who were not eligible for the program (e.g., passed through Grade 8 before the 2007 implementation date) were only able to obtain the qHPV vaccination series from their physician or at their LPHA at a cost of approximately $150 per dose. Similar provincial and territorial programs are available across Canada, though they differ on the basis of such factors as implementations date, target age group, and catch-up strategies.[10]

2.4 HPV Vaccine Controversy

Marketed as one of the first cancer-preventing vaccines, the HPV vaccine has received a great deal of attention from the media, as well as from public health, scientific, and medical communities and the general public.[42,43] In fact, the vaccine received expedited approval in a number of countries and was the subject of intensive marketing, lobbying, and public health campaigns around the world.[43] Despite great hype about the HPV vaccine, it also faced a great deal of controversy in Canada[44] and beyond.[11-16] In large part, this controversy was due to unanswered questions about the real-world effects of the HPV vaccine, especially in the young age group targeted for vaccination. Two areas of major public concern focused on the

effectiveness of the vaccine in this population and the potential indirect negative effects of vaccination on sexual behaviour.[45] Because of these and other unanswered questions, there were major concerns that expensive, large-scale HPV vaccination programs were implemented too quickly, and that additional research was needed to further support the purported effects.[13,44,46]

2.5 Effectiveness of HPV Vaccination

Evidence on Cervical Dysplasia

Although the primary purpose of the HPV vaccine is to reduce the burden of cervical cancer, given the long latency between HPV infection and cervical cancer (1-20 years),[47] surrogate endpoints of pre-cervical cancerous lesions, broadly referred to as cervical dysplasia, were used in randomized controlled trials (RCTs). Indeed, RCTs of the HPV vaccine have shown it to be highly efficacious in preventing HPV vaccine type-specific pre-cancerous cervical lesions in per-protocol populations.[48,49] For example, the largest RCT showed vaccine efficacy in this scenario to be 96% (95% CI 86% to 100%).[50] While such high levels of efficacy are generally those reported in the media and by healthcare officials, the same trial reported that vaccine efficacy dropped to 44% (95% CI 26% to 58%) in the intention-to-treat population, and then to 17% (95% CI 1 to 31) when outcomes were included regardless of causal HPV type (i.e., not restricted to dysplasia caused only by HPV 16 and 18). These findings are not surprising given the vaccine only protects against types of HPV that cause 70% of cervical cancers and does not treat existing infections. Nevertheless, these findings suggest the effects of the vaccine in real-world settings vary depending on the baseline incidence of HPV types 16 and 18 and the risk profile of girls vaccinated. As such, monitoring the effects of the vaccine outside of clinical trials is crucial to understanding the value of the vaccine in the real world.

To date, few studies have assessed the real-world effectiveness of the HPV vaccine on cervical dysplasia – two from Australia[51,52], one from Denmark,[53] and one from Manitoba.[54] All studies compared the risk of cervical dysplasia between vaccinated and unvaccinated girls using Cox proportional hazards regression[51,53,54] or multinomial logistic regression[52] and reported hazard ratios or odds ratios ranging from approximately 0.40 to 0.79. While the studies from Australia and Denmark are promising, their generalizability to the Canadian population is questionable. The only Canadian study was based on 3,541 females aged 15 years and older who received the quadrivalent HPV vaccine between September 2006 and April 2010 in Manitoba

through private health insurance.[54] Vaccinated females were age-matched to up to three unvaccinated females (n=9,594). Cox proportional hazards regression models estimated vaccine efficacy in this population was 35% (95% CI -19% to 65%) for high-grade squamous intraepithelial lesions (HSILs), 21% (-10% to 43%) for low-grade SILs, and -1% (-44% to 29%) for atypical squamous cells of undetermined significance (ASCUS). Evidently, this study leaves much room for uncertainty as all confidence intervals are wide and include the null. Furthermore, this study is based on vaccines received through private means and therefore provides no information on Canada's national publicly funded HPV vaccination program.

Evidence on Anogenital Warts

Trial results were perhaps more clear-cut for AGW than for cervical dysplasia, showing near perfect efficacy (~99%) and high effectiveness (>80%) in preventing the endpoint of interest.[48,55,56] Although detection of AGW is the earliest possible disease outcome to measure when evaluating the effectiveness of HPV vaccination, there are surprisingly few epidemiologic studies on this topic. All of the ecologic studies on trends in anogenital warts following introduction of the HPV vaccine, most of which have come out of Australia,[57-61] have suggested reductions in incidence rates. However, given the ecologic nature of these studies, it is impossible to discern whether the declines are attributable to HPV vaccination or to other factors. Only one individual-level study has been published on this topic. In particular, Leval et al.[62] used time-to-event analyses to estimate incidence rate ratios of AGW in an open cohort of females aged 10 to 44 years. Authors reported that vaccine effectiveness was highest among girls vaccinated before 14 years of age (93%, 95% CI 73% – 98%) and was also high among women who received all three doses and initiated the series before age 20 (76%, 95% CI 73% to 79%).

Limitations of Existing Evidence

Although RCTs are often believed to provide the goal standard of evidence, the generalizability of trial results to the general population and routine practice is limited given the highly selected nature of study participants and strictly controlled trial conditions.[63] For example, the generalizability of RCTs results to the young age groups targeted by publicly funded initiatives has been questioned,[44] as the average age of participants in clinical trials was 20 and less than 5% were under the age of 15.[64] As described above, there are some observational

studies of the effectiveness of the HPV vaccine in the real world; however, all of these studies directly compared vaccinated and unvaccinated girls. As discussed in "Methodological Challenges in Vaccine Research" (below), this approach to analysis is susceptible to important confounding bias. As such, alternative methods of analysis are needed. Another major limitation of the existing evidence base is there continues to be no information on the population-level effectiveness of HPV vaccination programs on the burden of cervical dysplasia and anogenital warts. This effect is impossible to derive from vaccine effectiveness alone as it depends on a number of additional factors, including vaccine coverage (i.e., the proportion of the population that receives the vaccine), the HPV risk profile of girls who self-select into the program, and the prevalence of HPV types not targeted by the vaccine. Determining the population-level impact of HPV vaccination is fundamental to understanding the true health and economic benefits of these vaccine programs.

2.6 HPV Vaccination and Sexual Disinhibition

Opposition to HPV vaccination programs has also been associated with the concern that HPV vaccination might lead to sexual disinhibition [15,45,65-67] – that is, that HPV vaccination may give girls a false sense of protection against *all* STIs that may lead them to, for example, initiate sexual behaviour at an earlier age or refrain from using condoms during intercourse. The potential for changes in sexual health behaviours has also been debated with respect to school-based sexual education and condom programs, but there is little evidence to suggest these interventions actually result in riskier behaviour.[68] Moreover, this effect relies on the notion that girls practice safer sexual practices because of fear of HPV, with little consideration for the risk of non HPV-related STIs (e.g., genital herpes, chlamydia) or the potential for unwanted pregnancy, which does not appear to be the case.[45,65,67]

To date, one study has reported on the association between HPV vaccination and clinical indicators of risky sexual behaviour. In particular, Bednarczyk et al.[69] followed 11-12 year old girls for up to three years and compared sexual behaviour-related outcomes (i.e., contraceptive counseling, pregnancy, or STI testing or diagnosis) between vaccinated and unvaccinated girls. The authors reported an incidence risk difference of 1.6 per 100 person-years (95% CI -0.03 to 3.24) and an adjusted rate ratio of 1.29 (95% CI 0.92 to 1.80) and concluded there was not a significantly elevated risk of the composite endpoint attributable to the HPV vaccine. Since its

publication in October 2012, this article has been frequently cited as evidence of a lack of association between HPV vaccination and increased risky sexual behaviours; however, the small sample size (N=1,398) and corresponding wide confidence intervals left room for considerable uncertainty, especially since the point estimates were suggestive of a potential increased risk. Moreover, because this study directly compared vaccinated and unvaccinated individuals, the results may have been confounded by health behaviours affecting both the probability of the outcome and the decision to vaccinate. The few additional studies of HPV vaccination and sexual disinhibition have focused on perceptions of increased risk following vaccination, rather than actual risk,[70,71] or have relied on self-reports of sexual behaviour,[72,73] which are notoriously vulnerable to the recall bias, response bias, and social desirability bias[74,75]. Furthermore, all were based on small samples, ranging from 193 to 1,243 females.

Better understanding the relationship between HPV vaccination and sexual disinhibition is important since fear of increased risky sexual behaviour is considered a major reason why some parents have decided not to have their daughters vaccinated,[76] which may help explain suboptimal HPV vaccine coverage in jurisdictions like Ontario.[10,77] Moreover, sexual disinhibition has important consequences because it leads to increased risk of sexually transmitted infections and teen pregnancy, both of which would undoubtedly undermine the potential individual and public health benefits of HPV vaccination.

2.7 Methodological Challenges in Vaccine Research

Observational studies of vaccine effects are vulnerable to confounding bias, in large part because individuals who opt for vaccination tend to have a much different health profile than those who do not.[78-81] As a result, traditional methods of analysis that directly compare vaccinated and unvaccinated populations are susceptible to irremediable bias. This methodological challenge has been well known in the vaccine safety literature for a number of years.[78,79] As a result, alternative methods that address this source of bias, like the self-controlled case-series (a self-matched, case only approach), have become increasingly common.[82-84]

Unfortunately, novel methodological approaches are not often applied to studies of vaccine effectiveness, as evidenced by the fact that all previous epidemiologic studies of the HPV vaccine have estimated effects by comparing vaccinated and unvaccinated populations and adjusting for potential confounders.[51-54,62,69] While model-based adjustment methods are

appropriate in situations when important confounders are known and measured, evidence consistently suggests that health beliefs and behaviours are strongly associated with both the decision to receive the HPV vaccine,[76,85-87] as well as with HPV, HPV-related infections,[18,88-91] and adolescent sexual behaviour.[52,53,54,55] As the specific health beliefs implicated are not only difficult to identify, but also to quantify, the estimates of HPV vaccine effectiveness reported to date are suspect. There is a number of causal approaches that should be considered to deal with concerns over confounding bias (e.g., instrumental variables, marginal structural models, propensity scores[92]), but the unique features of the regression discontinuity design (RDD) may make it most appropriate for studying the causal effects of HPV vaccination in Ontario.

2.8 The Regression Discontinuity Design

The RDD is a quasi-experimental approach developed specifically to address concerns over confounding bias in the assessment of new policies and interventions.[93,94] The defining feature of the RDD is the method by which exposure is assigned. Specifically, the RDD is used in situations when assignment to a policy or intervention (e.g., HPV vaccination) is made based on the value of an underlying observable continuous factor (e.g., Grade 8 year), referred to as the "forcing variable", being on one side of a pre-specified cut-off (e.g., program implementation date). As a result, the probability of being exposed to the policy or intervention changes discontinuously (i.e., abruptly jumps or drops) at the cut-off as a function of the forcing variable. The forcing variable may also be associated with the outcome of interest, but this association is assumed to be smooth; therefore, any discontinuity in the conditional distribution of the outcome as a function of the forcing variable at the cut-off is interpreted as the causal effect of the intervention.

The advantage of the RDD over more traditional designs rests on the notion that the assignment cut-off is determined externally, usually by administrative decisions, creating a quasi-experimental situation in which the exact location of the cut-off is random with respect to the characteristics of the individuals around the cut-off. Therefore, the cut-off is akin to a randomization tool, arbitrarily assigning individuals close to the cut-off to the exposed or control group. Importantly, studies show that randomized experiments and the RDD produce similar estimates in regions near the cut-off.[95]

Given the parallels between RCTs and the RDD, the latter is used as a powerful alternative in situations when RCTs are unethical or otherwise unfeasible.[96] Although the design is currently relatively absent from the epidemiology literature, it has been used extensively in economics, where it has been applied to important health questions. For example, the RDD has been used to assess the impact of new screening guidelines for breast, colorectal, and prostate cancers, where age was the forcing variable and recommended age of screening was the cut-off.[97] It has also been used to evaluate the effects of expanded Medicaid coverage starting at birth on subsequent mortality, where birth date was the forcing variable and program implementation date was the cut-off.[98] Given the special features of the RDD and its demonstrated value in evaluating important health questions while minimizing confounding bias, its potential application in future epidemiologic studies merits further investigation.

CHAPTER 3: OVERVIEW OF DATA AND ANALYSES

3.1 Study Data

Ontario's Population-Based Health Databases

Data for this study were obtained from the population-based databases generated by Ontario's universal health insurance programs. Five of the six databases used were readily available though the Institute for Clinical Evaluative Sciences (ICES) in Toronto (ICES-Central). In particular, I used: (1) the Registered Persons Database (RPDB), Ontario's population registry of insured persons, for information on insurance coverage and socio-demographics, (2) the Ontario Health Insurance Plan (OHIP) database for dates, diagnoses, and procedures corresponding to all fee-for-service claims by physicians, (3) the Discharge Abstract Database (DAD) for dates, diagnoses, and procedures corresponding to all hospitalizations, (4) the Same-Day Surgery (SDS) database for dates and procedures corresponding to same-day surgeries, and (5) the National Ambulatory Care Reporting System (NACRS) for dates, diagnoses, and procedures corresponding to all emergency department visits (Appendix A).

Since ICES's goal is to facilitate unbiased health research, concentrated efforts are continuously made to assess and improve the quality of the health data they house.[99-103] For example, while most of the information in the RPDB is accurate, because some information is out-of-date, ICES created the Best Yearly Postal Code file that updates the RPDB with information from other data sources. A number of validation studies have also been performed. Moreover, a range of strategies are used to help overcome some of the limitations of the databases. For example, one limitation of the OHIP database is that diagnostic codes can refer to major disease categories rather than specific diagnoses. To address this issue, procedure and fee codes are used in addition to diagnostic codes, as was recently done successfully for the capture of cervical cancer screening.[104] Despite some limitations, Ontario's health databases provide a wealth of otherwise unavailable health information. As such, these databases are used extensively for health research, including in post-marketing evaluations of drugs and vaccines.[105-108]

The Immunization Records Information System (IRIS)

The sixth data source was the Immunization Records Information System (IRIS), which was used to obtain information on vaccinations, including qHPV vaccinations. IRIS was developed in 1993 by the Ministry of Health and Long-Term Care (MOHLTC) to enable each of Ontario's 36 Local Public Health Agencies (LPHAs) to track and record the vaccination status of all school-aged children in their jurisdiction.[109] IRIS was originally intended to maintain accurate, up-to-date information on the six diseases for which immunization is mandated under the *Immunization of School Pupils Act (1982)* and the *Day Nurseries Act (1990)* – i.e., measles, mumps, rubella, diphtheria, tetanus, and polio. However, it is also used to capture information on optional vaccines, particularly those that are publicly funded. As such, it contains information on the date of administration of all qHPV vaccine doses provided through Ontario's publicly funded program, as well as self-reports of doses obtained outside of the program (e.g., prior to the girl's Grade 8 year). Since the LPHA-based IRIS databases are not centralized, when a student transfers to a school in a different health unit, his or her vaccination history must be recorded into that IRIS database so the new health unit can fulfil its mandate to monitor the immunization status of the incoming student. This information is most often obtained by the receiving LPHA from the transferring LPHA, but may also be obtained by self-reports from the child's guardians, who are legally required under the *Immunization of School Pupils Amendment Act (1984)* to report any vaccinations their child has received.

In 2009, Dr. Linda Levesque's (thesis committee member) research team initiated the process of centralizing the province's 36 IRIS databases at ICES so the IRIS data could be record linked with other population-based databases housed at ICES. Under the *Health Protection and Promotion Act*, the Medical Officer of Health (MOH) of each LPHA is the health information custodian of the IRIS data. Therefore, the first step of the centralization process involved soliciting the MOH of each LPHA to participate in this study. Next, the MOH negotiated and signed a data sharing agreement (DSA) with ICES to permit the transfer and record linkage of the IRIS data. After the DSA was executed, at least one member of Dr. Lévesque's research team travelled to the LPHA to transfer a complete copy of their IRIS data to ICES-Central via a secured and monitored high encryption portal, where it was received by one of ICES's two Data Covenantors. Before data were accessible for research purposes, the Data Covenantor removed all personal identifying information and replaced this information with a unique encrypted

personal identifying number, referred to as the ICES Key Number (see "Record Linkage" below). By January 22, 2014, the IRIS database of 34 LPHAs, representing approximately 78% of the Ontario population, had been transferred to ICES and were available for use in this thesis (Figure 3.1). The data sharing agreements for the two remaining health units had not yet been negotiated by the time the analyses of this thesis were undertaken.

Figure 3.1 Geographic representation of participating health units*

*The black regions represent health units whose immunization records were not available for use in this thesis.

Since IRIS data had never before been used for research purposes, we assessed the validity of the HPV vaccine data by re-abstracting the paper records ("gold standard") of a medium-sized LPHA (Kingston, Frontenac, Lennox, and Addington Public Health) and comparing them to the electronic IRIS records.[110] Our results indicated that the sensitivity and specificity of girls' HPV vaccination status was 99.8% (95% confidence interval [CI] 99.3-99.9) and 97.7% (95% CI 96.3-98.7), respectively. We also found that 98.6% of vaccination dates were accurate to the day. The high validity of these data can be explained, at least in part, by the standardized IRIS recording procedures that have developed as a result of the requirements in the *Immunization of School Pupils Act, 1982,*[111] and the fact that these records represent the documentation of a delegated

medical act for Registered Nurses working for LPHAs. Consequently, we expect the high validity of these data to be generalizable to other IRIS databases.

Record Linkage

At ICES, every individual who has ever been issued an Ontario Health Insurance Plan (OHIP) number is represented by a unique encrypted personal identifier called an ICES key number (IKN). Because IRIS is a new ICES data holding, upon the transfer of an IRIS dataset to ICES, a designated ICES staff member used the OHIP number in IRIS (when available) to identify the IKN corresponding to each IRIS record through deterministic record linkage. This process occurred three times for this study – for the first 22 IRIS databases transferred, for the following 10 databases transferred, and for the last 2 databases transferred. A perfect match between OHIP number in IRIS and IKN was found for 82.6% of records in the first record linkage (Nicholas Gnidziejko, ICES Health Data Administrator, personal communication, June 14, 2012), 80.7% in the second (Charlotte Ma, ICES Health Data Administrator, personal communication, October 29, 2013), and 83.0% in the third (Charlotte Ma, personal communication, July 7, 2014). Because IKNs are present in all individual-level data holdings at ICES, they enabled complete, anonymized individual-level record linkage across all six databases used in this study.

Data Access

Access to the administrative health databases housed at ICES was secured through Dr. Lévesque's appointment as an Adjunct Scientist at ICES. As previously described, access to individual IRIS databases was secured through data sharing agreements between ICES and the MOH of participating LPHAs. These agreements stipulate that only Dr. Lévesque and individuals she authorizes have access to the data.

All analyses were executed at the ICES satellite at Queen's University in Kingston, Ontario (ICES-Queen's); however, all data were stored at ICES-Central in a password-protected file and were accessed from ICES-Queen's by virtue of a dedicated, secure, high encryption portal that is regularly monitored by designated ICES staff. Both ICES sites have a number of security and privacy safeguards to ensure data security and confidentiality. The practices and procedures in

place to protect these data are reviewed by the Information and Privacy Commissioner of Ontario every three years.

Database Diagnostics and Cleaning

The quality of data received from each source was thoroughly assessed. Two issues of particular importance were (1) consolidation of qHPV vaccination records from IRIS databases across health units and (2) handling of missing data.

Consolidation of qHPV vaccination data. Because IRIS databases of individual health units were not centralized, when a student moved to a new health unit, his or her complete vaccination history had to be inputted into the IRIS databases of the receiving LPHA. As previously mentioned, this information was generally obtained by the receiving LPHA from the transferring LPHA, but may also have been provided by a legal guardian. As such, duplicate vaccination records were present for students who moved health units at some point during their schooling. Of particular importance to this thesis was duplication of HPV vaccination records, as this could artificially increase the number of doses counted for that girl, thereby potentially misclassifying her exposure status. In instances of perfect duplication of HPV records, the duplicate records of the receiving health unit were deleted. More problematic, however, were instances when dates between IRIS databases were not perfectly matched (e.g., different day, month, year), as these could represent inaccurate re-recording or a new dose administered by the receiving health unit. In such cases, additional information in the girl's records (such as the "source" variable, which indicates whether the information was from health unit staff, a parental report, physician reports, etc.) and the pattern of HPV vaccine dates were used to identify the correct vaccination date. This process was performed independently by Dr. Lévesque and the biostatistician working with her, and discrepancies were resolved through discussion. Records were flagged if the correct date remained uncertain so they could be used in sensitivity analyses.

In the entire IRIS dataset (i.e., not restricted to the thesis cohort), 196,533 girls had at least one qHPV vaccine record; 6,370 (3.2%) of these girls moved health units following cohort entry. While the vast majority of duplicate entries were perfect matches on date, the records of 128 (0.07%) girls needed to be verified manually due to date discrepancies. When the data were restricted to the thesis cohort, the dates of a small number of HPV vaccination records (18 of 226,920) had been flagged as potentially problematic. Among all cohort members, I identified an

additional 76 records as having potentially erroneous dates because they occurred with within 10 days of another dose; these were also flagged. This type of error could have arisen within a health unit when, for example, two individuals inadvertently inputted the same record and one did so incorrectly. Both forms of potentially problematic records (n=94) were excluded from the primary exposure definition, but were included in a sensitivity analysis.

Missing data. Following cohort identification, I obtained all records available for cohort members in the OHIP, DAD, NACRS, and SDS databases – 46,225,857 records from OHIP, 1,208,946 from NACRS, 346,014 from DAD, and 123,817 from SDS. All records contained an admission date, but a small proportion of records were missing a discharge date in the NACRS (8.9%), DAD (0.0003%), and SDS (0.05%) databases. OHIP data does not contain a field for discharge date since these records represent a physician consultation or procedure rather than an episode of care. To impute missing discharge dates in NACRS, DAD, and SDS database, the mean, median, and mode length of stay was determined for records in that database with non-missing discharge dates. As expected given the acute care nature of emergency department services and same-day surgeries, the mean, median, and mode length of stay in the NACRS and SDS databases were all equal to 0. Therefore, missing discharge dates were assigned the same date as the admission date. Only 1 record in DAD was missing a discharge date. Since the mean, median, and mode length of stay for records for non-missing records was 3.57 (standard deviation 6.9), 2, and 2, respectively, the missing discharge date was set to two days following the admission date. At least one diagnostic code was present in all OHIP, DAD, and SDS databases; this field was missing in 55 NACRS records, all of which were dated February 2012. Given the extremely low proportion of records affected by this and the fact that these records likely truly represent an episode of care, they were maintained in the database as doing so would not negatively affect outcome or covariate ascertainment.

Information on socio-demographics was obtained using an ICES macro that linked the cohort members' postal code to the Statistics Canada Postal Code Conversion File. This file supplemented data in the RPDB with information on neighbourhood income quintile and rural/urban residency. Most fields in this database did not contain missing data; however, neighbourhood income quintile was missing for 2,457 (0.94%) cohort members and urban/rural residency was missing for 1,746 (0.7%). In instances when urban/rural residency was missing, income quintile was always missing, but there were 711 instances where income quintile was

missing but urban/rural residency was not. The majority (n=401) of these cases represented girls who lived in rural areas. Since neighbourhood income quintile and urban/rural residency were primarily used in this study to describe the study cohort, missing values were not imputed. When neighbourhood income quintile was included as a covariate in sensitivity analyses, both a complete case analysis was performed, as well as an analysis in which an additional income category was created to indicate the information was missing.

3.2 Study Population and Cohort Formation

This was a population-based cohort study of all girls in Grade 8 in Ontario during the 2005/06 to 2008/09 school years. This includes two years of girls who were eligible for publicly funded qHPV vaccination (i.e., in Grade 8 in 2007/08 and 2008/09) and two years of girls who were not eligible (i.e., in Grade 8 in 2005/06 and 2006/07). Although school grade is not available in the data, because the vast majority of girls enter Grade 8 in their thirteenth year of life, birth year was used to estimate school grade. Specifically, we used the RPDB to identify all females born in 1992, 1993, 1994, and 1995 and, through record linkage with IRIS, restricted these birth cohorts to girls whose immunization records were available at the time of this study and who were residing in Ontario on September 1 of 2005, 2006, 2007, and 2008, respectively.

Cohort entry was defined as September 1 of the girl's Grade 8 school year. Cohort exit was defined as the minimum of date of death or March 31 of Grade 12 (*end of follow-up*). As such, cohort members were followed for a maximum of 4.6 years between the ages of 12-13 and 16-17 years, thereby controlling for confounding by age at the design stage (Table 3.1).

Table 3.1 Follow-up by birth cohort (grade, age)

	Birth Cohort	School Year							
		2005/06	2006/07	2007/08	2008/09	2009/10	2010/11	2011/12	2012/13
Ineligible	1992	Gr. 8, 12-13	Gr. 9, 13-14	Gr. 10, 14-15	Gr. 11, 15-16	Gr. 12, 16-17			
	1993		Gr. 8, 12-13	Gr. 9, 13-14	Gr. 10, 14-15	Gr. 11, 15-16	Gr. 12, 16-17		
Eligible	1994			Gr. 8, 12-13	Gr. 9, 13-14	Gr. 10, 14-15	Gr. 11, 15-16	Gr. 12, 16-17	
	1995				Gr. 8, 12-13	Gr. 9, 13-14	Gr. 10, 14-15	Gr. 11, 15-16	Gr. 12, 16-17

Gr. = Grade

3.3 Measurement

Baseline Characteristics

To describe the study cohort, a number of baseline characteristics were identified relating to socio-demographics, vaccination history, frequency of healthcare use, and medical history (Appendix B). Although we were limited to information available in administrative databases, these data were used to identify certain proxies for certain health beliefs and behaviours.

The RPDB was used to obtain information on socio-demographic at cohort entry, including age, birth quarter, neighbourhood income quintile, and urban/rural residency. Birth quarter was a categorical variable that indicated the time of year during which a girl was born – January 1 to March 31, April 1 to June 30, July 1 to September 31, or October 1 to December 31. Neighbourhood income quintile was defined according to methods developed at Statistics Canada and was assigned by linking a girl's postal code at cohort entry with data from the 2006 Canadian Census. A girl's postal code was also used to determine whether she resided in an urban area (defined as a community size of at least 10,000 persons) or a rural area (less than 10,000 persons).

The IRIS database was used to ascertain vaccination history – that is, if a cohort member received at least one dose of the measles, mumps, and rubella (MMR), diphtheria, tetanus, and pertussis (DTP), and hepatitis B vaccine anytime before cohort entry. A category was also created to indicate whether the girl had received at all three vaccines before cohort entry. MMR and DTP were chosen because measles, mumps, rubella, diphtheria, and tetanus are all "designated diseases" under the *Immunization of School Pupils Act (1990)*[111], which mandates that all school children be immunized against these diseases unless their guardian has completed a statement of medical exemption or a statement of conscious or religious belief. As such, refusal of these vaccines generally represents strong anti-vaccine attitudes. Immunization against hepatitis B, on the other hand, is not required, but hepatitis B vaccination is offered free to all children in Grade 7 through a school-based program. Therefore, uptake of the hepatitis B vaccine may be interpreted as general vaccine acceptance.

The NACRS, DAD, SDS, and OHIP databases were used to determine healthcare use. Healthcare use was defined based on the frequency of emergency department visits, hospitalizations, same-day surgeries, and outpatient physician visits in the two years before cohort entry. Each type of use was categorized based on the frequency distribution of the data.

Among girls with at least one hospitalization, the mean inpatient length of stay was determined based on the number of days spent hospitalized. Frequency of healthcare use was a proxy for the general health status of cohort members, as well as for a tendency to make use of available health services.

The DAD, NACRS, SDS, and OHIP databases were also used to identify whether a cohort member has been previously diagnosed with an important medical condition (Appendix C). In particular, we identified the presence of cancer, mental illness, or sexual-health related outcomes in the two years before cohort entry, as well as Down's syndrome, congenital anomalies, and intellectual disabilities between birth and cohort entry.

Exposure Variables

To determine the effect of Ontario's Grade 8 HPV vaccine *program* on the outcomes of interest, exposure was based solely on program eligibility; therefore all girls in Grade 8 before September 2007 were classified as "ineligible" and all those in Grade 8 following program implementation were classified as "eligible". To estimate the effect of the quadrivalent HPV vaccine on the outcomes, exposure was defined based on HPV vaccine receipt. HPV vaccine exposure status was obtained during the girl's Grade 8 and 9 academic years since the program allows girls until August 31 of their Grade 9 year to complete their vaccine series. Girls who received all three doses of the vaccine during that time were classified as "vaccinated" and girls who received 0-2 doses were "unvaccinated". Receipt of all three doses was chosen to define vaccine exposure because the vaccine is indicated as a three-dose series. Secondarily since recent evidence suggests that two doses are sufficient to confer immunity[112], exposure was defined based on receipt of two doses in Grades 8 to 9. Also, since doses are meant to be received within one year, we assessed vaccine impact based on receipt of three doses in Grade 8. The impact of our choice of exposure definition and exposure ascertainment period were further assessed in sensitivity analyses.

Outcome Variables

In this thesis, there were three outcomes of interest – cervical dysplasia, anogenital warts, and indicators of sexual behaviour. All outcomes were identified using the DAD, NACRS, OHIP, and SDS databases.

To assess the effectiveness of the vaccine and the vaccination program, our outcomes of interest were cervical dysplasia and anogenital warts. Cervical dysplasia was chosen instead of cervical cancer given the long latency period between HPV infection and cervical cancer (10-30 years) and the young age group of our study population. For this same reason, cervical dysplasia was also the endpoint of interest in the randomized controlled trials of the HPV vaccine.[48,49] Unfortunately, the diagnostic and treatment codes for cervical dysplasia have not been validated in these databases. To address this limitation, we created three definitions of cervical dysplasia in consultation with substantive experts in the field to reflect varying degrees of potential misclassification. In particular, a "broad" category of dysplasia was created to capture the greatest number of outcomes, but it came with the risk of the greatest number of false positives. Accordingly, we expected this definition to have the highest sensitivity but the lowest specificity. We also created "possible" and "probable" categories to reflect increasing levels of outcome specificity, recognizing that these may have decreasing levels of sensitivity. Similarly, since anogenital warts has not been validated in the databases, we consulted with substantive experts to create "broad", "possible", and "probable" categories of this outcome to reflect increasing levels of specificity and decreasing levels of sensitivity. These categories were determined based on a diagnosis or treatment for anogenital warts. The details of the coding algorithms used to ascertain outcomes of cervical dysplasia and anogenital warts are provided in Manuscript 2 (Appendices 5-B and 5-C).

To assess the potential indirect effect of HPV vaccination on sexual behaviour, we identified clinical indicators of sexual behaviour. Specifically, the outcome of interest was composite endpoint of pregnancy and non-HPV-related STIs. Although these are not direct measures of sexual behaviour, as such measures are unavailable in administrative health databases, they are direct *consequences* of risky sexual behaviour. Pregnancy was defined based on a diagnostic or treatment code relating to pregnancy, miscarriage, therapeutic abortion, or delivery. An STI was defined based on a diagnosis or treatment for syphilis, gonococcal infections, or "other" venereal diseases (e.g., herpes, chlamydia, trichomoniasis). The codes used to identify these outcomes are detailed in Manuscript 3 (Appendix 6-B).

3.4 Analysis

The primary methodological approach used in this thesis was the regression discontinuity design (RDD), which is explained in detail in Chapters 4, 5, and 6. In brief, the RDD is a quasi-experimental approach used to assess the causal impact of interventions in situations when assignment to the intervention is determined, at least in part, by the value of an observed continuous covariate (referred to as the forcing variable) being on a particular side of a pre-specified cut-off. In the case of Ontario's Grade 8 HPV vaccination program, the intervention is HPV vaccination and girls are assigned to this intervention based on whether they are in Grade 8 before or after the September 2007 program implementation date. Since, school grade was determined based on birth date, birth date forms the basis of the forcing variable and girls born December 31, 1993 *vs.* January 1, 1994 define each side of the eligibility cutoff. For analysis purposes, birth date was collapsed into three-month intervals (referred to as birth year quarters), and each birth year quarter was assigned a value of -8 to 7 based on its proximity to the cut-off. For example, all girls born October 1, 1993 to December 31, 1993 were assigned a value of -1 and those born January 1, 1994 to March 31, 1994 were assigned a value of 0. The following sections are provided to supplement information on the analyses carried in Chapters 5 and 6.

Estimation of Absolute Risk Differences

In its traditional form, the RDD is used in situations where there is a continuous forcing variable and a continuous outcome variable.[94] Accordingly, linear regression-based analyses are employed and absolute risk differences are estimated. In this thesis, there is a continuous forcing variable, but the outcomes of interest are dichotomous. Although it is a widely held belief that linear regression-based analyses are only valid for outcomes that are normally distributed, studies have shown this to be incorrect. For example, Lumley et al.'s simulated data analyses demonstrated that in large samples, such as those common to public health datasets, linear regression is valid for any distribution, including the binomial distribution.[113] Similarly, Hellevik argues against the belief that linear regression should not be used for dichotomous outcome variables, and demonstrates that, although the homoscedasticity assumption may be violated in these cases, this is of little practical importance.[114] Given the population-based nature of this thesis and the correspondingly high sample size of the thesis cohort, linear regression-based analyses were employed in this context.

Estimation of absolute risk differences was carried out using a Stata program (represented by "–rd–"), which implements the regression discontinuity design by estimating linear regression on both sides of the cut-off.[115] To estimate the program impact, this approach involved only one stage (referred to here as "one-stage local linear regression"). To estimate vaccine impact, a second stage was needed ("two-stage local linear regression"). The following paragraphs and equations will describe how one- and two-stage local linear regressions were carried out in this thesis. Additional details on implementation of local linear regression in the RDD setting can be found in other published works.[94,116]

To estimate the impact of the program on our outcomes, program eligibility was the exposure of interest. Therefore, linear regression was used to estimate the association between program eligibility and the outcome. Since the –rd– program estimates regression equations on each side of the cut-off, the following was estimated on the left side (*l*) of the cut-off:

$$Y_i = \alpha_{yl} + \beta_{1yl}(X_{il} - c) + \varepsilon_{il}$$

Eq. 1

An analogous model was estimated on the right side (*r*) of the cut-off:

$$Y_i = \alpha_{yr} + \beta_{1yr}(X_{ir} - c) + \varepsilon_{ir}$$

Eq. 2

In these equations, Y is the outcome for individual i, X is the numeric value of the forcing variable, c is the cut-off, and ε is the error term. Since the cut-off is -1 on the left side (corresponding to the forcing variable for births dates of October to December 1993) and 0 on the right side (corresponding to the forcing variable for birth dates of January to March 1994), the magnitude of discontinuity at the cut-off is estimated as:

$$\tau_y = \alpha_{yr} - \alpha_{yl}$$

Eq. 3

The result of equation 3 is interpreted as the program impact on the outcome.

To estimate vaccine impact, a second stage is added to the analysis to take into account the fact that exposure (i.e., HPV vaccination) changed probabilistically rather than deterministically at the cut-off. Therefore, while one stage involves determining the magnitude of discontinuity in the outcome regressions (as described above in equations 1-3). The other stage involves determining the magnitude of discontinuity in the treatment regressions (as described below in equations 4-6). This is done using linear regression for HPV vaccine exposure, fitting a regression function on each side of the cut-off.

On the left side (*l*):

$$W_i = \alpha_{wl} + \beta_{1wl}(X_{il} - c) + \varepsilon_{il}$$

Eq. 4

On the right side (*r*):

$$W_i = \alpha_{wr} + \beta_{1wr}(X_{ir} - c) + \varepsilon_{ir}$$

Eq. 5

In these equations, W is the dichotomous variable for actual vaccine receipt (vaccinated *vs.* unvaccinated) in individual i, X is the value of the forcing variable, c is the cut-off, and ε is the error term. The magnitude of discontinuity is estimated as:

$$\tau_w = \alpha_{wr} - \alpha_{wl}$$

Eq. 6

The effect of HPV vaccination on the outcome of interest is estimated as the ratio of the two discontinuities – i.e., that estimated in equation 3 and that estimated in equation 6:

$$\tau = \frac{\alpha_{yr} - \alpha_{yl}}{\alpha_{wr} - \alpha_{wl}} = \frac{\tau_y}{\tau_w}$$

Eq. 7

Additional investigations confirmed that, as suggested by Imbens and Lemieux,[94] under the same conditions, the –rd– program yielded the same results as the following linear regression equation, which can therefore, in practice, replace equations 1 and 2 (Appendix D):

$$Y_i = \beta_{Y0} + \beta_{Y1}(X_{1i}) + \beta_{Y2}(X_{2i}) + \beta_{Y3}(X_{1i})*\beta_{Y4}(X_{2i}) + \varepsilon_i$$

Eq. 8

where X_1 is the dichotomous variable indicating program eligibility and X_2 is the forcing variable. In this case, β_1 yields the effect of the program.

Similarly, the following equation can replace equations 4 and 5:

$$W_i = \beta_{W0} + \beta_{W1}(X_{1i}) + \beta_{W2}(X_{2i}) + \beta_{W3}(X_{1i})*\beta_{W4}(X_{2i}) + \varepsilon_i$$

Eq. 9

Vaccine impact is then estimated by the ratio of these two effects:

$$\tau = \beta_{Y1} / \beta_{W1}$$

Eq. 10

While technically Stata's –rd– program employed equations 1-7, confirming that equations 8-10 yielded the same results was important for determining how to estimate the relative effects of the program and the vaccine.

Estimation of Relative Risks

As mentioned above, traditionally, the regression discontinuity design is used to estimate absolute risk differences. Since absolute estimates are considered more appropriate than relative estimates for public health and clinical decision-making,[117] they were undoubtedly valuable to the objectives of this thesis. However, since absolute measures of effect are a function of the underlying baseline incidences of disease, their external validity is limited. Relative measures of effect, on the other hand, are generally more comparable across studies and populations;[118,119] therefore, they were also of interest. Indeed, given the complementary information provided by

absolute and relative measures, the statement on strengthening the reporting of observational studies in epidemiology (STROBE Statement) recommends reporting both whenever possible.[118]

Maximum likelihood methods are theoretically suitable for the RDD context,[120,121] yet few studies have estimated relative measures of effect using this design,[120,122,123] and to my knowledge none have been applied in the context of a fuzzy/two-stage design. Given the well-established connection between instrumental variables and the fuzzy RDD,[94,124] the instrumental variable literature offered insight into how to address the second part of this question.[125,126] Accordingly, a two-stage sequential log-binomial regression approach was used in which the first stage predicted treatment as a function of the forcing variable and covariates (Eq. 11), and the second stage predicted the outcome based on the values predicted in the first stage (Eq. 12).[126] For this analysis, standard errors were calculated using bootstrapping, a non-parametric approach used to evaluate the distribution of a statistic based on random re-sampling.[127]

The following two equations were used to estimate the relative impact of the vaccine at the cut-off:

$$Log(W_i) = \beta_0 + \beta_1(X_{1i}) + \beta_2(X_{2i}) + \beta_1(X_{1i})*\beta_2(X_{2i}) + \varepsilon_i \quad \text{Eq. 11}$$

$$Log(Y_i) = \beta_0 + \beta_1(W^1{}_i) + \beta_2(X_{2i}) + \beta_1(W^1{}_i)*\beta_2(X_{2i}) + \varepsilon_i \quad \text{Eq. 12}$$

Where W is the dichotomous variable for vaccine receipt (vaccinated *vs.* unvaccinated) in individual i, X_1 is the dichotomous assignment variable (eligible *vs.* ineligible), X_2 is the value of the forcing variable, ε is the error term, Y is the outcome, and W^1 is the predicted probability of treatment from Eq. 11. Exponentiating β_1 in Eq. 12 yields an estimate of the effect of vaccination.

To estimate the relative impact of the program, a one-stage approach was used that was analogous to the one-stage approach used to estimate risk differences (Eqs. 1-3 or Eq. 8).

$$Log(Y_i) = \beta_0 + \beta_1(X_{1i}) + \beta_2(X_{2i}) + \beta_1(X_{1i})*\beta_2(X_{2i}) + \varepsilon_i$$

Eq. 13

Exponentiating β_1 (the coefficient for program eligibility) yields an estimate of the program impact at the cut-off.

Additional Analytic Considerations

Additional important elements of the RDD include selection of the bandwidth, the kernel, and potential covariates. Bandwidth selection is employed to reduce the sample to observations closest to the cut-point that are considered most exchangeable. The method recommended for determining the optimal bandwidth was proposed by Imbens and Kalyanaram[128] and is the default option in the –rd– Stata program. Similarly, to weigh observations closest to the cut-off most heavily, a triangular kernel is typically selected over a rectangular kernel; this is also the default option in Stata. Finally, the quasi-experimental nature of the RDD generally implies that no covariates are included in the model.

The relative age effect observed in the descriptive analyses (Chapter 4) suggested these standard choices would not be suitable to this thesis context. In particular, the analyses revealed that girls born earliest in the calendar year generally had a much higher risk of sexual behaviour-related events compared with girls born later in the year. Moreover, this risk generally decreased across birth quarter, meaning girls born January to March were at the highest risk, followed by those born April to June, July to September, and October to December. As a result, observations closest to the cut-off on the ineligible and eligible sides (October-December 1993 *vs.* January-March 1994), which are supposed to be the most exchangeable, represented girls with low and high baseline risks of sexual health-related outcomes, respectively. These results also suggested that girls of the same birth quarter across birth years would be more comparable than girls directly on either side of the cut-off. Accordingly, in all primary analyses, the bandwidth was specified to include all girls in 1992-1995 birth cohorts, rather than allowing the sample to be restricted to girls closest to the cut-off. Moreover, a rectangular kernel was used instead of a triangular kernel, and population weights were applied such that girls in the 1993 and 1994 birth cohorts were weighted twice as heavily as girls in the 1992 and 1995 birth cohorts. These population weights were used to maintain the notion that observations closest to the cut-off are

more exchangeable than observations farther from the cut-off. Finally, birth quarter was included as a covariate in the model. The robustness of the results to all the aforementioned decisions was examined in sensitivity analyses.

Although the addition of covariates is not typical of a standard RDD analysis, covariates are increasingly used to expand the RDD and accommodate a broader range of situations.[129] In our analyses, birth quarter was added as dummy variable in the regression models, requiring that the basic equations described above be modified. To illustrate, Eq. 8 was modified as follows:

$$Y_i = \beta_0 + \beta_1(X_{1i}) + \beta_2(X_{2i}) + \beta_3(X_{1i})*\beta_4(X_{2i}) + \beta_5(X_{3i}) + \beta_6(X_{4i}) + \beta_7(X_{4i}) + \varepsilon_i$$

Eq. 14

where Y represents the outcome for individual i, X_1 is the dichotomous variable reflecting eligibility status, X_2 is the value of the forcing variable, and X_3, X_4, and X_5 are dummy variables for birth quarter – January-March, April-June, and October-December, respectively; July-September was the reference category. Dummy variables for birth quarter were included when estimating both the probability of HPV vaccination (e.g., Eq 9) as well as the risk of the outcome (e.g., Eq 8).

Additional Verifications

Sensitivity Analyses. A number of additional analyses were undertaken to test the robustness of our results to the various assumptions made with respect to the exposure and outcome definitions and time windows, the categorization of the forcing variable, covariate adjustment, population weights, kernel selection, and bandwidth. For example, in light of recent evidence suggesting two doses of the qHPV vaccine may be sufficient to confer benefit,[130,131] the primary vaccine impact analyses were repeated using an exposure definition of at least two doses. Also, since all three doses of the HPV vaccine are meant to be received in Grade 8, the exposure and outcome ascertainment windows were modified such that qHPV vaccine exposure was ascertained between September 1 and August 31 of Grade 8 and outcomes were ascertained between September 1 of Grade 9 and March 31 of Grade 12. Sensitivity analyses were also conducted that controlled for additional baseline covariates, such as neighbourhood income

quintile, hepatitis B vaccination, and a recent sexual health-related outcome (e.g., diagnosis of a sexually transmitted infection, cervical cancer screening, pregnancy).

Birth year as a proxy for school grade. As mentioned in "Study Population and Cohort Formation", using birth year to estimate Grade 8 year was expected to introduce a small degree of error. To examine this error in the study population, I used an alternative method of identifying Grade 8 year. In particular, I used date of hepatitis B vaccination as a proxy for Grade 7 year and defined Grade 8 year as the school year following receipt of this vaccine. Hepatitis B vaccination was considered a better tool to estimate cohort entry date than birth year because of its proximity to Grade 8. It was not used as the primary method of determining cohort entry date because not all cohort members opt to receive the hepatitis B vaccine.

To apply this method, IRIS was used to identify cohort members who received at least one dose of the hepatitis B vaccine in the 730 days before or 365 days after their cohort entry date. If the vaccine was received in the 365 days before cohort entry, the girl's cohort entry date was considered correctly classified and "on schedule". Receipt of the vaccine during the 366-730 days before cohort entry or within the 365 days following cohort entry indicated the girl's cohort entry date has been misclassified and was "ahead" or "behind" the estimated school grade, respectively.

205,186 (79%) cohort members received at least one dose of the hepatitis B vaccine in the 730 days before or 365 days after cohort entry; the cohort entry date of the remaining cohort members could not be assessed. Among girls who received the vaccine during the specified time frame, 4.4% of cohort members had been held back a school grade (or had delayed school entry) and 1.1% had been advanced a school grade (or had started school early). These findings suggest that the cohort entry date was correctly classified for 94.5% of cohort members and was misclassified for 5.5%. This misclassification was similar across birth year such that 94.5%, 94.4%, 94.5%, and 94.8% of girls were correctly classified in the 1992, 1993, 1994, and 1995 birth cohorts, respectively. However, the degree of misclassification was associated with birth timing, where girls born earliest in the calendar year (January-March) were the most likely to have been advanced a school grade and girls born latest in the calendar year (October-December) were the most likely to have been held back (Appendix E).

Since birth year was used to define exposure and outcome ascertainment windows in addition to cohort entry date, it was particularly important to assess the robustness of the results

to this form of misclassification. Therefore, the primary analyses were repeated on a cohort comprised only of the 193,981 girls for whom year of cohort entry was classified as "on-schedule". These girls represent 94.5% of cohort members for whom cohort entry date could be verified (n=205,186) and 74.5% of the entire cohort (N=260,493).

Analytic Approach. Given the modifications made to the standard RDD analysis, theoretically, a number of different analytic strategies could have been chosen to execute these analyses. Therefore, I examined the robustness of the results to other analytic approaches. As previously mentioned, the primary analyses employed Stata's –rd– program to estimate risk differences, and I also identified linear regression equations that yielded the same estimates. Analogous models to estimate relative risks using log binomial regression analyses were also created. Also, in an effort to evaluate the validity of applying the log binomial strategy, a sensitivity analysis was performed in which the absolute effects were derived from the relative risks[132,133] using Stata's –margins– command. These marginal effects were compared with those obtained from the linear regression-based models. Also, given the analogies between the two-stage/fuzzy RDD and instrumental variables, I compared the vaccine impact analyses from the –rd– program, which are based on Wald estimators, with two-stage least squares regression.

CHAPTER 4: TESTING THE ASSUMPTIONS OF THE REGRESSION DISCONTINUITY DESIGN

4.1 Preface to Manuscript 1

As described in Chapter 3, studies of the real-world effectiveness of the HPV vaccine to date have been based on comparisons between vaccinated and unvaccinated populations, and are therefore vulnerable to confounding bias. As such, alternative methods of analysis that allow for causal inference are required. To this end, I initially considered several potential methodological approaches for my questions on the effects of HPV vaccination. Ultimately, the regression discontinuity design (RDD) appeared to be the most suitable. Subsequently, I did extensive reading in the econometrics literature to better understand the RDD, during which time it became apparent that testing the assumptions of the RDD would be a crucial step to determining whether the RDD was in fact an appropriate approach to use in this study context. My literature searches also revealed there was virtually no information in the epidemiologic literature on this design, and the practical papers that were available from other fields were generally written in a very technical manner. To address this gap in the epidemiologic and RDD literature, the following manuscript (Manuscript 1) is presented as an introduction to the RDD for health researchers and a tutorial on how to assess the assumptions of the RDD for a given study question. My question on the effects of HPV vaccination on cervical dysplasia is used as the applied example.

Manuscript 1 will be submitted to the *Annals of Epidemiology*.

4.2 Manuscript 1 – Strategies for Evaluating the Fundamental Assumptions of the Regression Discontinuity Design: A Case Study Using a Human Papillomavirus Vaccination Program

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ABSTRACT

The regression discontinuity design (RDD) is a quasi-experimental approach used to avoid confounding bias in the assessment of new policies and interventions. It is applied specifically in situations when assignment to the policy/intervention is determined by the value of an underlying observed continuous covariate (e.g., birth date, income, age) being on one side of a pre-specified cut-off. As such, individuals with values closest to the cut-off are essentially randomly assigned to the policy/intervention. Despite its popularity in fields like economics, the RDD remains relatively unknown in epidemiology, where its application may be of equal value. In this paper, we provide an introduction to the RDD for health researchers, describe the four fundamental assumptions of the design, and offer strategies that can be used to assess whether these assumptions are met in a given study setting. For illustrative purposes, we implement these strategies to assess whether the RDD is appropriate to use for a study of the impact of HPV vaccination on cervical dysplasia. These findings highlight the importance of assessing the assumptions of the RDD prior to executing the analyses and, more broadly, point to the need for thorough descriptive analyses before the execution of any study.

Introduction

Health researchers are often faced with the task of evaluating the effects of a new healthcare program or medical intervention that has been implemented as a result of a change in public policy or practice guidelines. Since these changes occur outside the strictly controlled settings of randomized controlled trials, a major challenge in their evaluation is confounding bias. A recent example of such a policy change was the implementation of population-based human papillomavirus (HPV) vaccination programs, which are aimed at reducing the burden of cervical cancer in the population.[42] To date, observational studies have assessed the effectiveness of HPV vaccination by comparing vaccinated and unvaccinated females.[51-54] Unfortunately, studies comparing vaccinated and unvaccinated groups are notoriously vulnerable to confounding bias since health beliefs and behaviours associated with the decision to receive a vaccine are virtually impossible to identify and quantify and may also be associated with the outcomes of interest.[78-81] In such cases, alternative methods of analysis should be implemented.

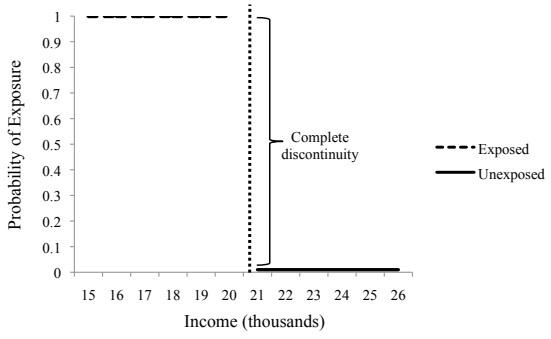
The regression discontinuity design (RDD) is a quasi-experimental approach that was developed specifically to avoid confounding bias in the assessment of new policies and interventions.[93] This design first appeared in the psychology and education literature and has been used extensively in the field of economics,[122] but it remains relatively unknown in epidemiology, where its application may be of equal value. Given the parallels between the randomized control trial (RCT) and the RDD, the latter is used as a powerful alternative in situations when RCTs are unethical or otherwise unfeasible.[96] For example, in health economics the design has been used to assess the impact of new screening guidelines for breast, colorectal, and prostate cancers,[97] as well as to evaluate the effects of expanded Medicaid coverage on mortality.[98] Clearly, the RDD has the potential to be an important tool that other health researchers use to evaluate the causal effects of policies and interventions as well. As with any methodology, however, a thorough investigation of the data and an evaluation of whether or not the design is appropriate for the study question at hand is a necessary preliminary step.

In this paper, we provide an introduction to the regression discontinuity design, describe the four fundamental assumptions of the design, and offer strategies that can be used to assess whether these assumptions are met for a given study. For illustrative purposes, we implement these strategies to assess whether the RDD is appropriate to use for our study on the impact of HPV vaccination on cervical dysplasia.

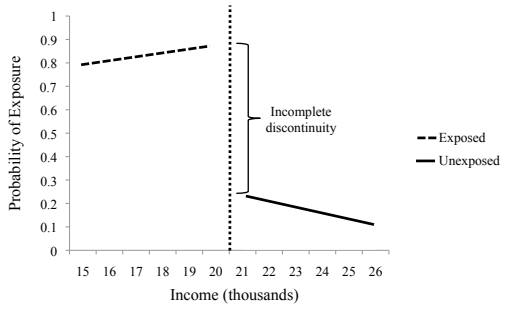
Overview of the RDD

The defining feature of the RDD is the method by which exposure is assigned. Specifically, the RDD is used in situations when assignment to a policy/intervention (e.g., free drug coverage) is made based on the value of an underlying observable continuous factor (e.g., income), referred to as the "forcing variable", being on one side of a pre-specified cut-off (e.g., $20,000). As a result, the probability of being exposed to the policy/intervention changes discontinuously (i.e., abruptly jumps or drops) at the cut-off as a function of the forcing variable. Exposure may be completely or partially determined by the assignment rule; the design simply requires that the likelihood of actually being exposed to the policy/intervention change discontinuously between groups at the assignment cut-off. Correspondingly, there are two settings for the RDD – the sharp RDD and the fuzzy RDD. In the sharp RDD, exposure to the intervention is completely determined by the forcing variable, meaning all individuals on one side of the cut-off are considered exposed (exposed group) and all individuals on the other side are not (control group); therefore, the probability of exposure changes from 0 to 1 at the cut-off (Figure 4.1-A). On the other hand, the fuzzy RDD allows for incomplete discontinuity in the probability of exposure at the cut-off (Figure 4.1-B). The fuzzy setting can arise when incentives for participation change dramatically with the introduction of the policy/intervention, but are not powerful enough to shift all individuals assigned to the policy/intervention from unexposed to exposed. This situation is analogous to non-compliance in an RCT. The RDD analysis, which is traditionally based on linear regression models, is then used to determine whether there is a corresponding discontinuous change in the probability of the outcome (e.g., perceived health status at 6 months) at that same cut-off. The magnitude of this discontinuity is used to estimate the causal effect of the policy change or intervention (Figure 4.1-C).

A.



B.



C.

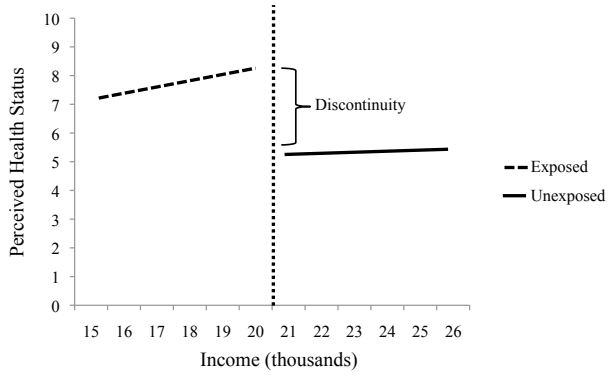


Figure 4.1 Hypothetical RDD setting

A. Exposure discontinuity - Sharp RDD; B. Exposure discontinuity - Fuzzy RDD; C. Outcome discontinuity

The strength of the RDD rests on the notion that the assignment cut-off is determined externally, usually by administrative decisions, creating a quasi-experimental situation in which the exact location of the cut-off is random with respect to the characteristics of the individuals around the cut-off. Therefore, the cut-off is akin to a randomization tool, arbitrarily assigning individuals close to the cut-off to the exposed or control group. Importantly, studies show that randomized experiments and the RDD produce similar estimates in regions near the cut-off.[95] Additional resources on the RDD are available in other published works.[93,94,120-122]

Case Study

Ontario's Grade 8 HPV Vaccination Program is a publicly funded, school-based program that was implemented in September 2007.[40] It offers all three doses of the quadrivalent HPV vaccine free to all Grade 8 girls in the province. Since the HPV vaccine is not mandatory in Ontario, receipt of the vaccine through Ontario's program is optional. Moreover, ineligible girls (e.g., girls who were in Grade 8 before 2007) were able to receive the vaccine through their family physician at a cost of approximately $450 for the three-dose series.

To assess whether the RDD was appropriate for assessing the causal impact of Ontario's program on cervical dysplasia, we used data from the Ontario Grade 8 HPV Vaccine Cohort Study (e.g., sections 3.1 and 3.2 of this thesis). In brief, we used Ontario's population-based administrative health and immunization databases for information on socio-demographics, vaccination history, hospitalizations, emergency department visits, same-day surgeries, and

physician services. Using these data, we identified a population-based cohort of all girls in Grade 8 in Ontario in the two years before (2005/06-2006/07) and after (2007/08-2008/09) the September 2007 implementation date (N=260,493). Since school grade was not available in the data, Grade 8 year was determined based on birth year since >95% of students are 13 years old by December 31 of their Grade 8 school year.[134] Additional details on the data and cohort can be found elsewhere (e.g., sections 3.1 and 3.2 of this thesis).

Defining Variables for RDD

Baseline Characteristics

We identified a number of baseline characteristics relating to socio-demographics, vaccination history, frequency of healthcare use, and medical history to describe the study cohort. In terms of socio-demographics, we determined age, birth quarter (categorized based on the time of year during which a girl was born), neighbourhood income quintile, and urban/rural residency. We also obtained information on previous receipt of the measles, mumps, and rubella (MMR), diphtheria, tetanus, and pertussis (DTP), and hepatitis B vaccines. Healthcare use was defined based on the frequency of emergency department (ED) visits, hospitalizations, same-day surgeries, and outpatient physician visits in the two years before Grade 8. Each type of use was categorized based on the frequency distribution of the data. Among girls with at least one hospitalization, the mean inpatient length of stay was also determined. Finally, we identified whether a cohort member had been previously diagnosed with cancer, a mental illness, an intellectual disability, a congenital anomaly, or Down syndrome, as well as whether she had a diagnosis or procedure related to sexual behaviour (e.g., diagnosis of a sexually transmitted infection, pregnancy, cervical cancer screening).

Forcing Variable and Cut-off

A principal component of the RDD is the forcing variable, an observed continuous covariate that assigns exposure based on whether its value is above or below a fixed cut-off. Assignment to Ontario's Grade 8 HPV vaccination program was based on whether a girl was in Grade 8 before or after the September 2007 program implementation date. Since we defined Grade 8 year using birth date, girls born December 31, 1993 and earlier were ineligible for the program and girls born January 1, 1994 and later were eligible for the program (Table 4.1).

Therefore, the forcing variable was based on birth date, and the cut-off was January 1, 1994. To ensure there was a sufficient number of data points (i.e., values of the forcing variable) on either side of the cut-off to fit regression lines and to ensure each data point had a sample size high enough for these estimations, birth date was collapsed into three-month intervals, henceforth referred to as birth year quarters.

Table 4.1 Operationalization of Forcing Variable

	Grade 8 school year	Birth Year	Birth Year Quarter	Value of Forcing Variable
Ineligible	2005/06	1992	Mar 1992 – Jan 1992	-8
			Jun 1992 – Apr 1992	-7
			Sept 1992 – Jul 1992	-6
			Dec 1992 – Oct 1992	-5
	2006/07	1993	Mar 1993 – Jan 1993	-4
			Jun 1993 – Apr 1993	-3
			Sept 1993 – Jul 1993	-2
			Dec 1993 – Oct 1993	-1
Eligible	2007/08	1994	Jan 1994 – Mar 1994	0
			Apr 1994 – Jun 1994	1
			Jul 1994 – Sept 1994	2
			Oct 1994 – Dec 1994	3
	2008/09	1995	Jan 1995 – Mar 1995	4
			Apr 1995 – Jun 1995	5
			Jul 1995 – Sept 1995	6
			Oct 1995 – Dec 1995	7

Exposure

To illustrate both the sharp and fuzzy RDD setting, we used two approaches to defining exposure status. For the sharp RDD, exposure was based on program eligibility; that is, whether a girl was in Grade 8 before or after the September 2007 program implementation date. This definition was used because girls had no control over whether they were eligible for the program. It also represents an intention-to-treat definition of vaccination. For the fuzzy RDD, exposure was also defined based on actual HPV vaccination status, which was ascertained between

September 1 of Grade 8 and August 31 of Grade 9. The fuzzy setting was appropriate here since eligible and ineligible girls had the option of the receiving the vaccine, but the incentives to do so were very different between groups (free and school-based *vs.* $450 and three visits to a physician).

Outcome

In its traditional form, the RDD is applied when there is a continuous forcing variable and a continuous dependent variable. However, recent work in the RDD literature has expanded the design to also include dichotomous outcomes.[120-123] This development is particularly important for researchers wishing to apply the design to epidemiologic questions, as outcomes of interest are commonly categorical disease diagnoses. If fact, the outcome used in this paper is dichotomous – i.e., the detected presence of cervical dysplasia, a precursor to cervical cancer. To ensure temporality between exposure and outcomes, cases of cervical dysplasia were ascertained between September 1 of Grade 10 and March 31 of Grade 12.

RDD Assumptions

There are four fundamental assumptions of the RDD, each of which will be addressed in turn.

1. There is a discontinuity in the probability of exposure at the cut-off.
2. The forcing variable was not manipulated.
3. Exposure groups are exchangeable at the cut-off.
4. There is a discontinuity in the probability of the outcome at the cut-off.

Assumption 1 – There is a discontinuity in the probability of exposure at the cut-off

The RDD is founded first and foremost on the notion that there is a discontinuous change in the probability of exposure at an assignment cut-off. It is also important to assess whether there are additional discontinuities near the cut-off, as this could be indicative of other interventions or policy changes that might confound the results. Accordingly, continuity in the probability of exposure across values of the forcing variable with notable discontinuity at the cut-off provides evidence that this first assumption is satisfied. To evaluate this, we created line graphs to display the probability of each definition of exposure according to the forcing variable.

Figure 2-A clearly shows that program eligibility was a deterministic function of the forcing variable at the cut-off. In contrast, Figure 2-B shows that actual HPV vaccine exposure was only partially determined by the intervention, as evidenced by the jump from a probability of 0.03 to 0.46 between girls on either side of the eligibility cut-off. Moreover, there was continuity across values of the forcing variable on each side of the cut-off, with the exception of a slight jump between the 1994 and 1995 birth year cohorts (corresponding to the 2007/08 and 2008/09 program years). Although we generally seek continuity on either side of the cut-off, this jump is likely attributable to the increase in HPV vaccine acceptance between the first two years of the program, rather than to factors external to this study, such as the introduction of a new intervention that increased HPV vaccine use in the 1995 birth cohort *and* differentially affected their probability of dysplasia. Therefore, this assumption is satisfied.

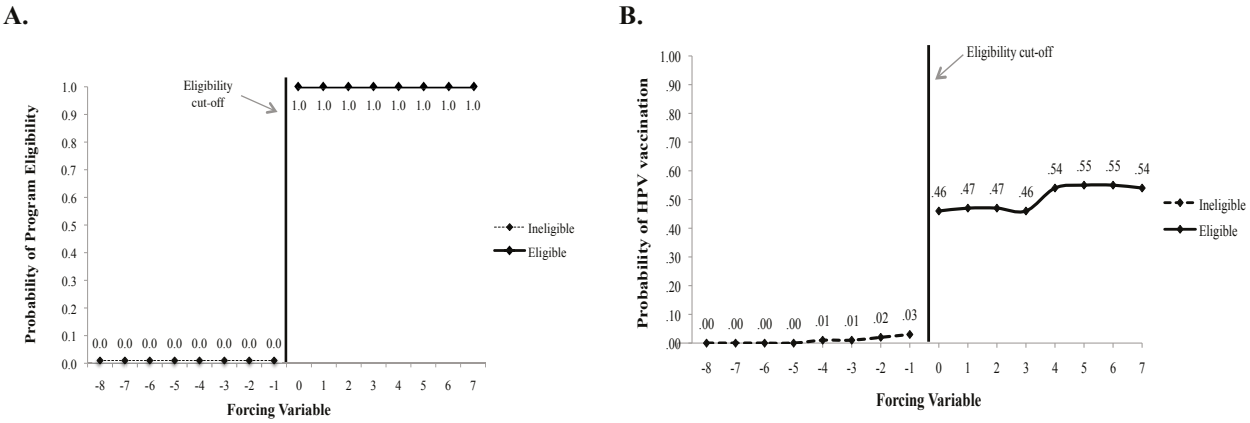


Figure 4.2 Probability of exposure, by the forcing variable*

A. Probability of qHPV vaccine program eligibility; B. Probability of qHPV vaccination

*See Table 4.1 for how values of the forcing variable were operationalized.

Assumption 2 – The forcing variable was not manipulated

Another important requirement of the RDD is that individuals did not have control over the value of their forcing variable, as this would violate the argument that groups were assigned to the intervention in a way that was analogous to randomization. For example, in a weight-loss program available only to those weighing at least 300 pounds, we might expect some individuals just below the cut-off to gain the few additional pounds required to be eligible. As a result, we would see relatively few participants with weights just below the cut-off and a relatively high

number of participants with weights at or just above the cut-off, creating a discontinuity in the frequency distribution of participants at the cut-off.

In our study, the forcing variable is based on birth date, which is difficult to manipulate. Even if it were manipulated, as would be the case if parents planned date of conception, it is unlikely that the reasons for manipulation would be related to the outcome of interest; therefore it would not introduce confounding. Similarly, it is unlikely that parents or students would take measures to manipulate something as important as school grade simply to receive free HPV vaccination. Nevertheless, to assess this assumption, we determined the percent of cohort members per forcing variable (Table 4.2) and created a histogram of the density of the forcing variable (Figure 4.3).

Table 4.2 Distribution of cohort members across birth year quarters

Value of the Forcing Variable	Frequency	Percent (N=260,493)
-8	16,309	6.26
-7	17,415	6.69
-6	17,126	6.57
-5	15,803	6.07
-4	15,766	6.05
-3	17,035	6.54
-2	16,697	6.41
-1	15,630	6.00
0	15,741	6.04
1	16,860	6.47
2	16,695	6.41
3	15,522	5.96
4	15,419	5.92
5	16,743	6.43
6	16,561	6.36
7	15,171	5.82

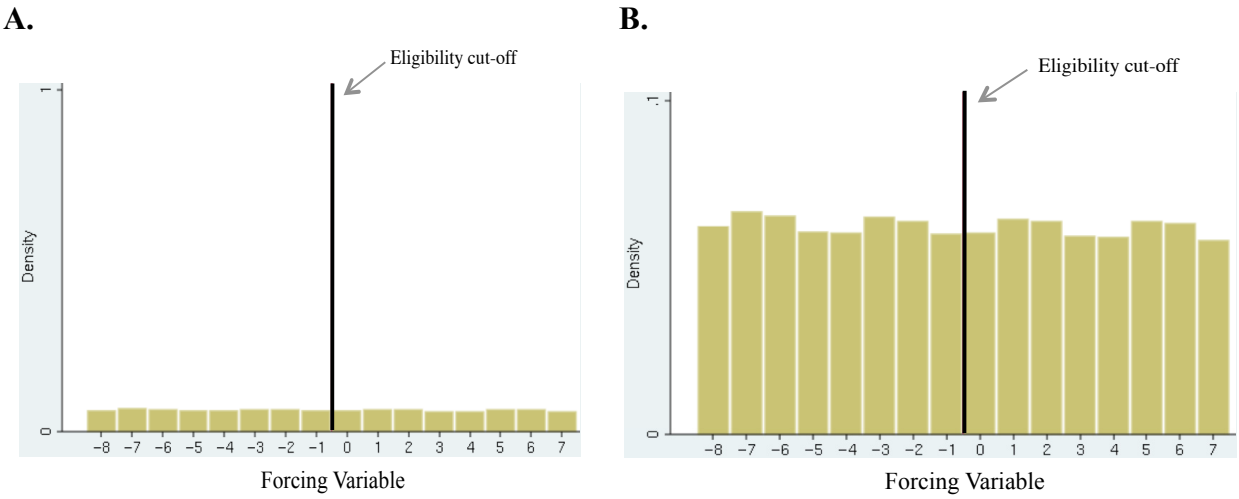


Figure 4.3 Density of the forcing variable*

A. Full scale (0-1); B. Reduced scale (0-0.1)

* See Table 4.1 for how values of the forcing variable were operationalized.

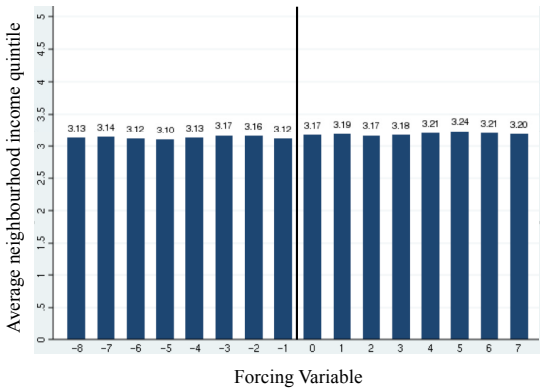
The percentage of cohort members per forcing variable (birth year quarter) ranged from 5.8% to 6.5% and appeared fairly evenly distributed. Moreover, Figure 4.3-A is flat, indicating continuity in the density of the forcing variable, and Figure 4.3-B, which provides a magnified view of the density, demonstrates that although there were slight variations in densities, there were no discontinuities. Continuity in the frequency and density across the cut-off is evidence that the forcing variable was not manipulated. Notably, a histogram was sufficient to assess this assumption in this context given the implausibility that the forcing variable had been manipulated and the clear continuity observed in the Table 4.2 and Figure 4.3, in other cases, McCrary's density test may be applied as it offers a more rigorous assessment of this assumption.[135]

Assumption 3 – Exposure groups are exchangeable at the cut-off

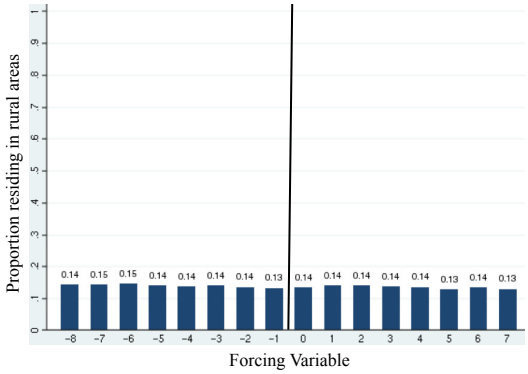
The quasi-experimental nature of the RDD implies that groups should be exchangeable with respect to all measured and unmeasured factors other than exposure. In classic epidemiological designs, this is assessed by directly comparing exposed and unexposed groups or cases and controls. In the RDD, however, the assumption of exchangeability is particularly important closest to the cut-off because differences at that location are the most likely to confound the analysis. Accordingly, the RDD assumes that individuals closest to the cut-off are

the most exchangeable with respect to measured and unmeasured confounders, and it is generally accepted that this exchangeability may decrease with increasing distance from the cut-off. To test this assumption, we plotted the probability of baseline characteristics for each value of the forcing variable. For variables with more than two categories, each category was assessed separately (Figure 4.4).

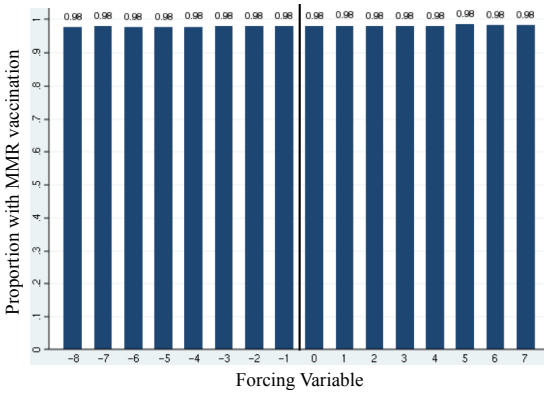
A. Average neighbourhood income quintile



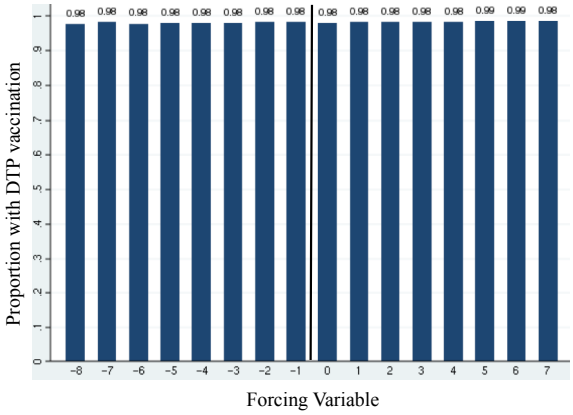
B. Rural residency



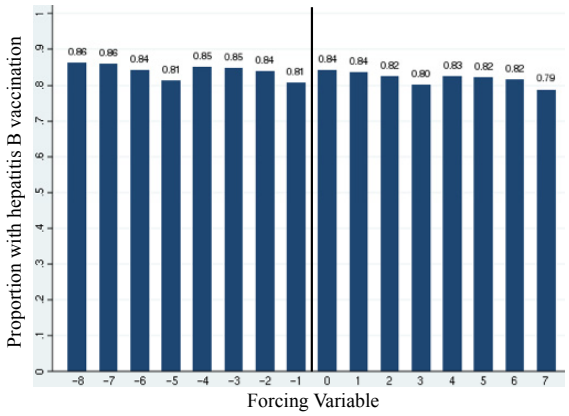
C. Previous MMR vaccination



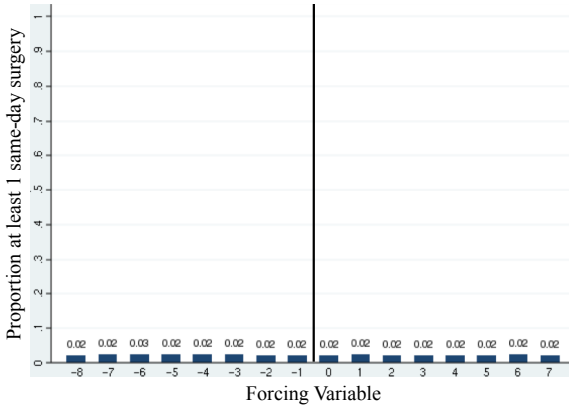
D. Previous DTP vaccination



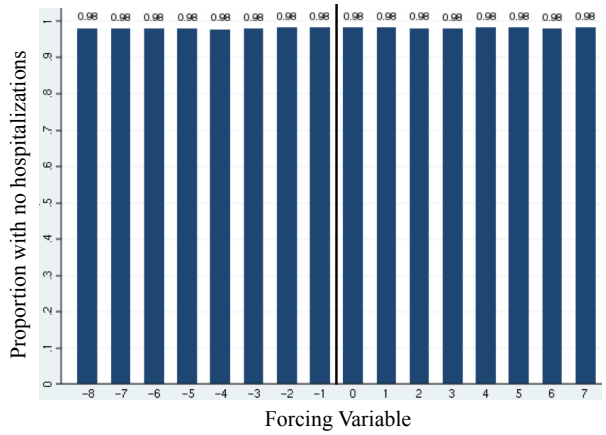
E. Previous HepB vaccination



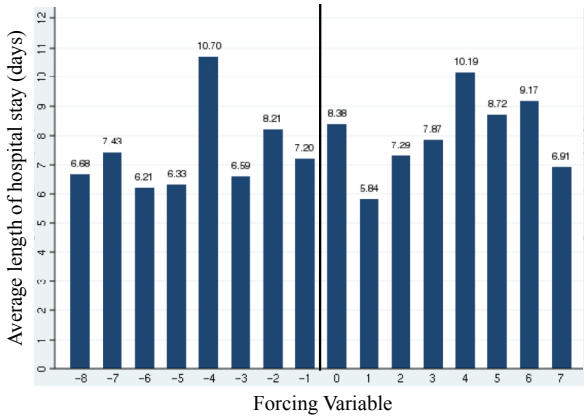
F. At least 1 same-day surgery



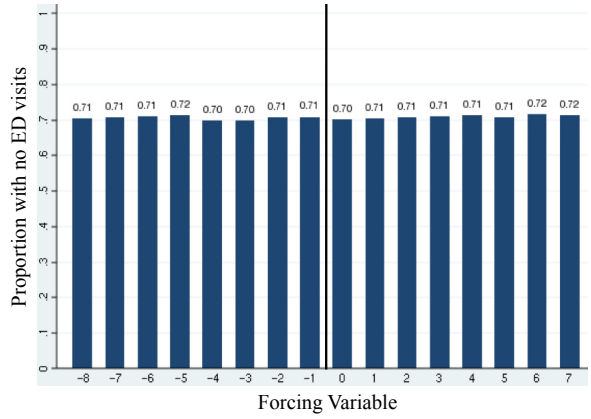
G. No hospitalizations



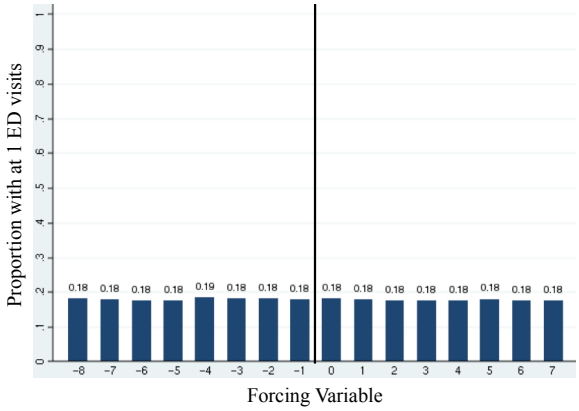
H. Average length of hospital stay



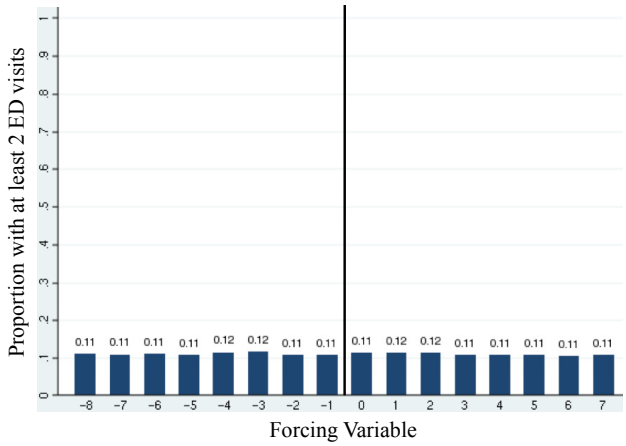
I. No emergency department visits



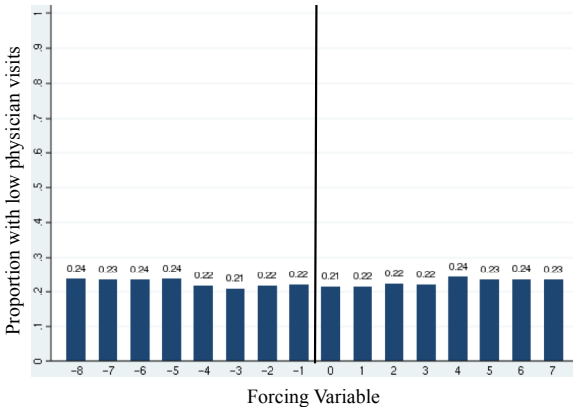
J. One emergency department visit



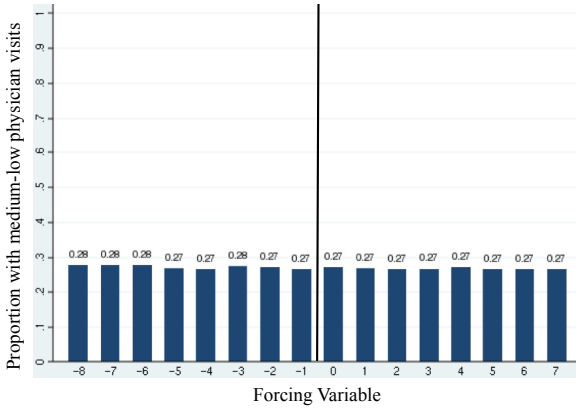
K. At least 2 emergency department visits



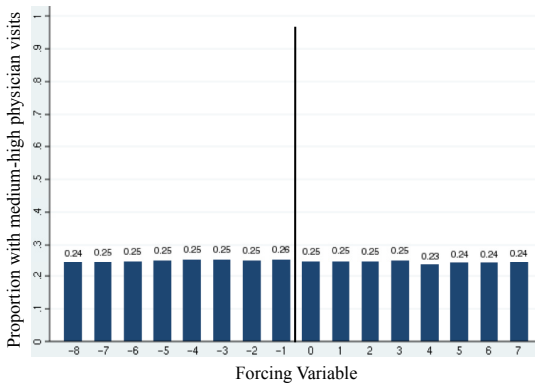
L. 0-1 physician visits



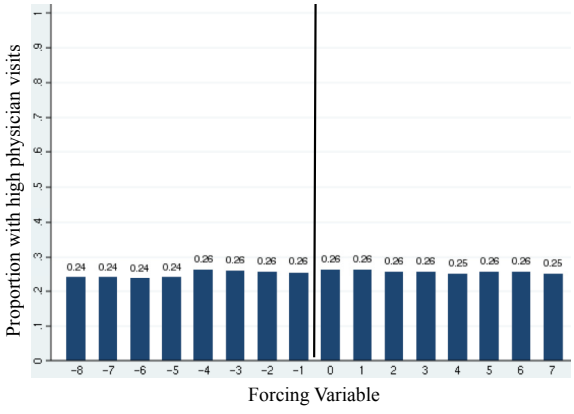
M. 2-5 physician visits



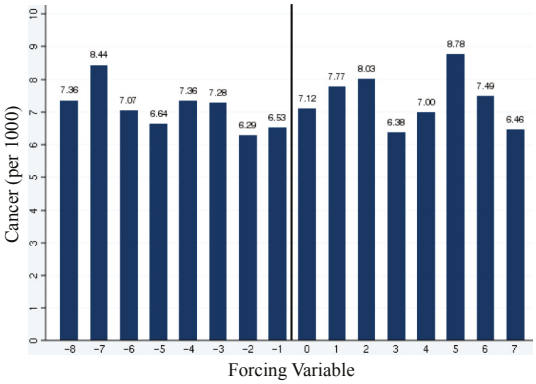
N. 6-12 physician visits



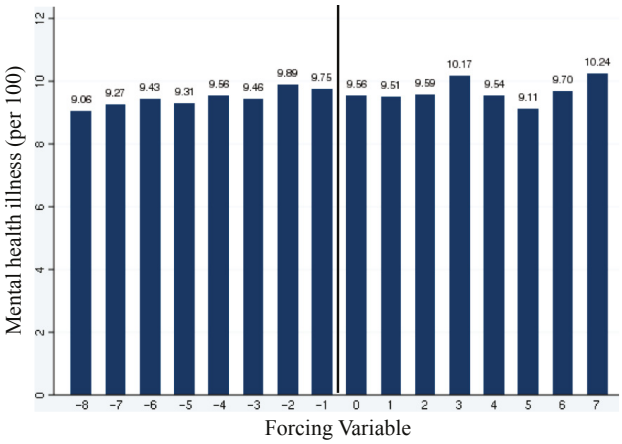
O. At least 13 physician visits



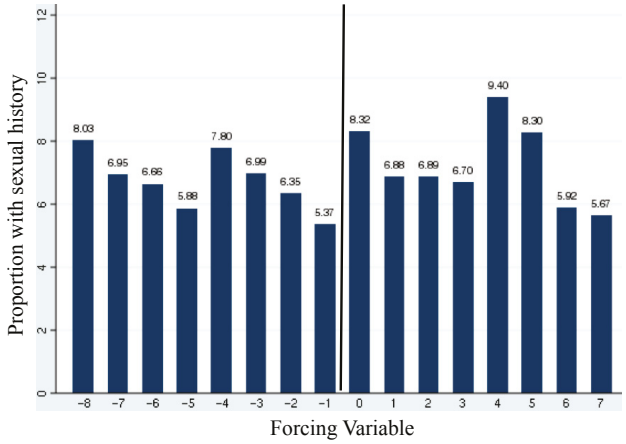
P. Cancer



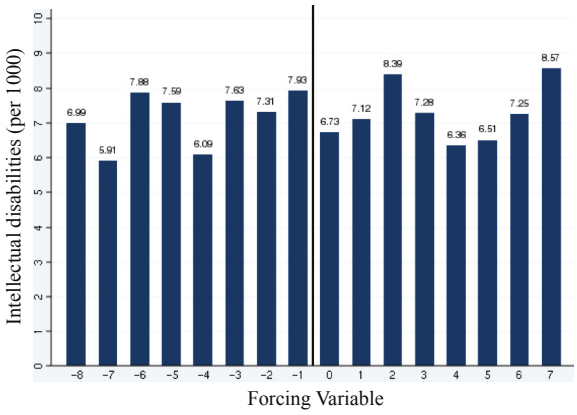
Q. Mental Health



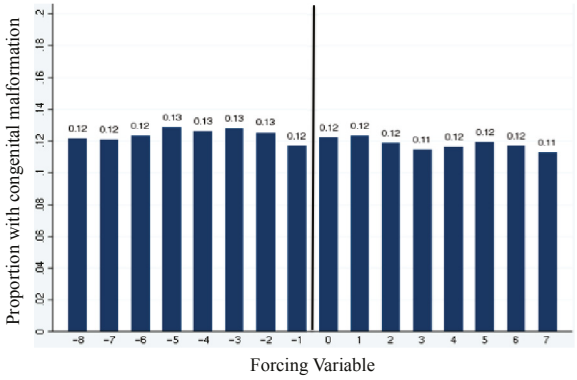
R. Sexual history



S. Intellectual disabilities



T. Congenital Malformations



U. Down's Syndrome

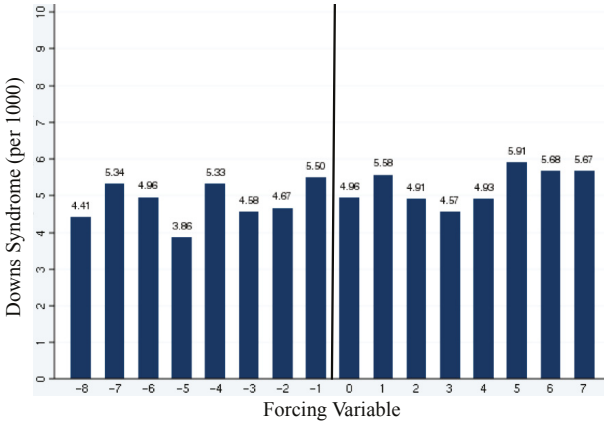


Figure 4.4 Distribution of baseline characteristics, by the forcing variable

Figure 4.4 provides evidence that, in general, socio-demographics (average neighbourhood income quintile, rural residency), vaccine history (MMR and DTP vaccination), and frequency of healthcare use (same-day surgeries, hospitalizations, emergency department visits, outpatient services) were evenly distributed across the forcing variable. Not surprisingly, there was greater variability in the distribution of characteristics with low baseline incidence risks, such as average length of hospital stay, cancer, mental health conditions, and intellectual disabilities. However, there were no discernable patterns in these data and differences at the cut-off were not of greater magnitude than those at locations other than the cut-off, suggesting the differences between values were attributable to random variation rather than to actual differences between groups. In contrast, hepatitis B vaccination (Figure 4.4-E) and a history of sexual health-related outcomes (Figure 4.4-R) revealed patterns in which, regardless of birth year, individuals born earlier in the calendar (January-March and April-June) were more likely to have the characteristic than those born later in the calendar year (July-September and October-December). These findings suggested the timing of a girl's birth relative to that of her grade-matched peers was associated with receipt of optional vaccines and indicators of sexual behaviour. Overall, Figure 4.4 provides evidence that cohort members were generally similar with respect to measured potential confounders across levels of the forcing variable, including at and around the eligibility cut-off, with some exceptions. In particular, birth timing (specifically, birth quarter) appeared to have a potentially confounding effect on the association of interest.

Assumption 4 – There is a discontinuity in the probability of the outcome at the cut-off

The RDD analysis is essentially a test of whether a discontinuous change in the probability of exposure at an assignment cut-off corresponds with a discontinuous change in the probability of the outcome at that same cut-off.[94] Therefore, examining whether there is a discontinuity in the outcome at the cut-off can provide great insight into the ultimate results of the analysis.

Since randomized controlled trials of the HPV vaccine have shown it to be highly efficacious in preventing cervical dysplasia,[48,49] we expected a drop in the risk of this outcome at the program eligibility cut-off. To assess this, we graphed the probability of the outcome for each value of the forcing variable (Figure 4.5-A). This graph also allowed us to determine whether there was continuity in the probability at locations other than the cut-off. These results suggested

that eligible girls had a lower risk of the outcome than ineligible girls, but it did not reveal a discontinuity at the cut-off as we had expected. However, as was observed with hepatitis B vaccination and sexual history, these findings also provided evidence that girls born earlier in the calendar year were at higher risk of this outcome than girls born later in the year. To control for this, we collapsed the probability of the outcome across birth quarter (Figure 4.5-B), which revealed a discontinuity between ineligible and eligible birth years at the cut-off. These findings confirmed that birth quarter was associated with cervical dysplasia and needed to be taken into account in the RDD analyses.

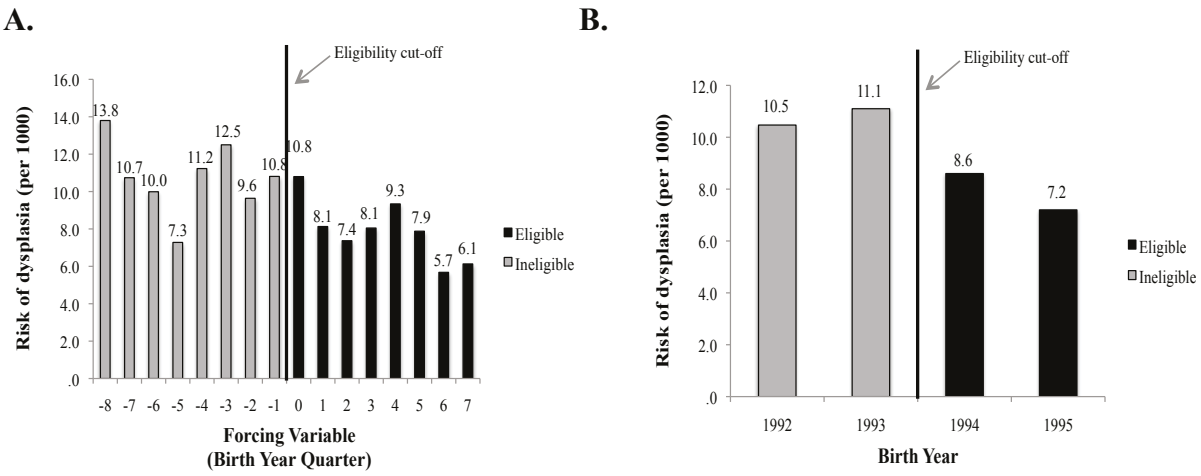


Figure 4.5 Risk of the outcome (cervical dysplasia)

A. By the forcing variable*; B. By birth year

*See Table 4.1 for how values of the forcing variable were operationalized.

Discussion

This study provides the first introduction to the regression discontinuity design for epidemiologists. Moreover, it describes four easy strategies researchers should use to assess the fundamental assumptions of the RDD and determine whether this design is appropriate to use for a given study question. By applying this approach to our question on the impact of HPV vaccination on cervical dysplasia, we found the four major assumptions of the RDD were generally satisfied, but that birth timing had the potential to confound our effect estimate.

Conceptually, our research question was well suited to the RDD – there was an observable continuous forcing variable, a clear assignment cut-off, strong incentives to accept

the treatment at the cut-off, and a high likelihood that program implementation would have an effect on our outcome. However, our evaluation of the RDD assumptions revealed an important effect of birth timing that suggested standard RDD analysis would not be appropriate in this context. Consequently, certain adjustments needed to be made to the RDD analysis to account for potential confounding effect of birth timing. As this effect was not anticipated *a priori*, it highlights the importance of assessing the RDD assumptions prior to using this design, even when the study question is conceptually ideal. More broadly, these findings highlight the need to test assumptions and undertake thorough descriptive analyses prior to the execution of any causal analysis, as they can provide crucial additional insight into the problem at hand.

To date, published papers describing the RDD have been largely limited to the economics literature.[94,124] A major strength of this study is that it offers an introduction to the RDD in the epidemiologic literature, thereby potentially broadening its application in this field, where it may be of particular value. Another strength of this paper is that it demonstrates how to assess the RDD assumptions in the context of an applied example. Importantly, the applied example was not a classic example of the RDD for a couple of different reasons. First, it was based on a dichotomous rather than continuous outcome. Given the prominence of dichotomous outcomes in health research, this helps illustrate that the RDD can be applied to these study questions. Second, we observed a confounding effect of birth timing that meant girls closest to the cut-off were *not* the most exchangeable, as is generally required for the RDD. Although not ideal, this finding reflects the reality of most studies in which the data are not perfectly suited to the rigid assumptions of the analysis. Understanding and accommodating such unique situations is often necessary.

Finally, this paper provides strategies to assess four fundamental assumptions that should be assessed before executing the RDD analysis; however, it is intended as an introduction only. Depending on the study question and initial findings, additional strategies may be required or desired. For example, we generally used bar and line graphs to assess the probability of each variable of interest (exposure, outcome, covariate) by the forcing variable, as we found these graphs provided the most detailed insight into the data. However, scatterplots are another popular tool used to assess these assumptions, as adding smoothed regression lines estimated separately on each side of the cut-off can improve visual presentation. Additional tests may also be

warranted, such as the previously mentioned McCrary's density test to assess for non-manipulability of the forcing variable.

Conclusion

Assessing assumptions are an integral component of any study, and this paper demonstrates that the RDD is no exception. Graphical analyses, in particular, can be a powerful tool for assessing whether a particular study question is suited to the RDD analysis. The findings presented here also highlight the importance of testing assumption and using descriptive analyses to fully understanding the intricacies of the study data, which is of the utmost important for executing appropriate, unbiased analyses. We hope this paper will encourage other health researchers to consider the RDD approach for evaluating policy changes and new interventions.

CHAPTER 5: THE EFFECTIVENESS OF HPV VACCINATION

5.1 Preface to Manuscript 2

The findings of Manuscript 1 provided important insight into the data that affected how I carried out the regression discontinuity design in this thesis. In particular, to account for the potential confounding effect of birth timing discovered in Manuscript 1, I made certain modifications to the standard RDD; the details of these modifications are described in section 3.4 ("Analysis") of this thesis. This modified RDD analysis is applied in the following manuscript (Manuscript 2) to assess the causal effects of the HPV vaccine and of Ontario's Grade 8 HPV vaccination program on cervical dysplasia and anogenital warts. This study was the first in Canada to assess the effectiveness of publicly funded HPV vaccination. Although a few other studies (including a small study of HPV vaccines received privately in Manitoba) have assessed the real-world effectiveness of the HPV vaccine, none have done so using a method that allows for causal inference. Additionally, the RDD allowed for estimation of the intention-to-treat effect for the first time outside of clinical trials, thereby enabling us to report on the population- or program-level impact of HPV vaccination.

Manuscript 2 will is currently being revised for re-submission to *Pediatrics.*

5.2 Manuscript 2 – The Impact of Human Papillomavirus (HPV) Vaccination on Cervical Dysplasia and Anogenital Warts Among Adolescent Girls: The Ontario Grade 8 HPV Vaccine Cohort Study

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ABSTRACT

Background: Despite widespread promotion of quadrivalent human papillomavirus (qHPV) vaccination for females, there is limited information on the real-world effectiveness of the vaccine, especially in the young age groups targeted for vaccination, and none on the impact of qHPV vaccination programs. We assessed the early health benefits of the qHPV vaccine and of Canada's largest qHPV vaccination program on cervical dysplasia and anogenital warts (AGW) among adolescent females.

Methods: Administrative health and immunization databases of Ontario, Canada, were used to identify a population-based retrospective cohort of girls in Grade 8 in the two years before (2005/06-2006/07) and after (2007/08-2008/09) implementation of Ontario's publicly funded Grade 8 qHPV vaccination program (ineligible *vs.* eligible cohorts). Vaccine exposure was ascertained during Grades 8-9 (program vaccination period) and outcomes from Grade 10 until March 31 of Grade 12. Using a quasi-experimental approach known as regression discontinuity, we estimated absolute risk differences (RD), relative risks (RR), and 95% confidence intervals (CI) attributable to program eligibility (intention-to-treat analysis) and vaccination.

Findings: The cohort comprised 260,493 girls (112,155 ineligible, 108,859 eligible). We identified 2,436 cases of dysplasia and 400 cases of AGW. HPV vaccination significantly reduced the incidence of dysplasia by 5.70 per 1,000 girls (95% CI -9.91, -1.50), corresponding to a relative reduction of 44% (RR=0.56; 95% CI 0.36, 0.87). Program eligibility also had a significant protective effect on this outcome: RD=-2.32 per 1,000 (95% CI -4.02, -0.61); RR=0.79; 95% CI 0.66, 0.94). Results also suggested possible decreases in AGW attributable to program vaccination (RD= -0.83 per 1000, 95% CI -2.54, 0.88; RR=0.57, 95% CI 0.20, 1.58) and eligibility (RD=-0.34 per 1000, 95% CI -1.03, 0.36; RR=0.81, 95% CI 0.52, 1.25).

Interpretation: This study provides strong evidence of the early benefits of qHPV vaccination on reductions in cervical dysplasia among females as young as 14-17 years. These findings offer additional justification for not delaying vaccination.

INTRODUCTION

The human papillomavirus (HPV) is considered the most common sexually transmitted infection in the world, affecting 50-75% of all sexually active individuals.[1-3] While the vast majority of infections are self-limiting and without clinical sequelae,[4] others can lead to important health consequences, including cervical cancer and anogenital warts (AGW).[5,6]

In 2006, a quadrivalent HPV (qHPV) vaccine designed to protect against HPV types 6 and 11, which cause >90% of cases of AGW and HPV types 16 and 18, which cause 70% of cases of cervical cancer, became commercially available.[7-9] Marketed as one of the world's first cancer-preventing vaccines, the qHPV vaccine received a great deal of attention from the scientific and medical communities, as well as from the general public.[43] Currently, the qHPV vaccine is available in over 100 countries, more than 40 of which have also introduced national qHPV immunization programs.[42]

The popularity of large-scale qHPV programs was supported by the results of randomized controlled trials (RCTs), which reported near-perfect efficacy for preventing vaccine type-specific pre-cancerous cervical lesions (i.e., cervical dysplasia) and AGW among per-protocol populations of compliant, HPV-naïve women.[48,49] As with most RCTs, however, the generalizability of these results to the general population and routine practice is limited given the highly selected nature of study participants and strictly controlled trial conditions.[63] Moreover, RCTs offer limited insight into the population-level impact of qHPV vaccination, which depends on a number of additional factors, including vaccine coverage, the baseline risk of disease, and the prevalence of HPV types not covered by the vaccine. Consequently, the value of population-based programs has been called into question.[13,44,46]

Currently, there are few non-ecologic studies on the real-world effects of the qHPV vaccine[51-54,62] and none on the population-level impact of qHPV vaccine programs on the burden of disease. Given the number and scale of qHPV vaccination programs currently offered around the world, there is a need for evidence on the program-level effects in addition to vaccine-level effects as both have important implications for the health impact and cost-effectiveness of these initiatives. Therefore, we undertook a population-based retrospective cohort study to assess the impact of qHPV vaccination on cervical dysplasia and AGW among adolescent girls, both at the population level (*program impact*) and the vaccine level (*vaccine impact*).

METHODS

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

Study Setting

Our study is based in Ontario, Canada's most populous province, which began offering population-based, publicly funded qHPV vaccination in September of 2007.[40] Specifically, Ontario's program offers all three doses of the qHPV vaccine, free of charge, to all Grade 8 girls in the province. Vaccine doses are administered primarily through school-based immunization clinics, but girls also have the option of receiving the vaccine from a physician or at their health unit at no cost. Since the qHPV vaccine is not mandatory in Ontario, program participation is voluntary. Prior to September 2012, eligible girls had until the end of their Grade 8 year to initiate the vaccine series and until the end of Grade 9 to complete it. As no catch-up program was available during the study period, girls who were not eligible for the program (e.g., in Grade 8 before 2007) could obtain the vaccine series from their physician or at their local health unit at a cost of approximately $400.

Data Sources

Data for this study were obtained from Ontario's population-based administrative health and immunization databases, access to which is available through the Institute for Clinical Evaluative Sciences (ICES) [103] In particular, we used the following six databases: (1) the Registered Persons Database (RPDB), Ontario's population registry of insured persons, for information on socio-demographics, (2) the Ontario Health Insurance Plan (OHIP) database for information on fee-for-service claims by physicians, (3) the Discharge Abstract Database (DAD) for information on hospitalizations, (4) the Same-Day Surgery (SDS) database for information on same-day surgeries, (5) the National Ambulatory Care Reporting System (NACRS) for information on emergency department visits, and (6) the Immunization Record Information System (IRIS) for information on vaccinations. Each resident is represented in these databases by a unique encrypted identifier, enabling complete, anonymized, individual-level record linkage across databases and time. These databases, which have been described elsewhere in detail,[99-102,109] are generated by Ontario's universal health insurance programs and have been used extensively in health research, including in the post-marketing evaluation of drug and vaccine effects.[85,105-107,136]

Study Population and Cohort Formation

We identified a population-based cohort of all girls in Grade 8 in Ontario during the 2005/06-2008/09 school years. This includes two years of girls who were eligible for publicly funded qHPV vaccination (i.e., in Grade 8 in 2007/08 and 2008/09) and two years of girls who were not eligible (i.e., in Grade 8 in 2005/06 and 2006/07). As school grade is not available in the databases, grade was based on birth year because the vast majority of girls enter Grade 8 in their thirteenth year of life. Specifically, we used the RPDB to identify all females born in 1992, 1993, 1994, and 1995 and, through record linkage with IRIS, restricted these birth cohorts to girls whose immunization records were available at the time of this study and who were residing in Ontario on September 1 of 2005, 2006, 2007, and 2008, respectively. A validation study showed this method correctly identified 96.4% of girls eligible for the 2007/08 and 2008/09 program years.[134] Cohort members were followed from September 1 of their Grade 8 year (*cohort entry*) until the earliest of: date of death, occurrence of a study outcome, or March 31 of Grade 12 (*end of follow-up*).

Measurement and Analysis

Approach – Observational studies of vaccine effects are particularly vulnerable to confounding bias, in large part because individuals who opt for vaccination tend to have a much different health profile than those who do not.[78-81] Indeed, evidence consistently suggests that health beliefs and behaviours are strongly associated with both the decision to receive the qHPV vaccine[76,85-87] and the outcomes of interest[18,88-91]. Since health beliefs and behaviours are difficult to identify and quantify, traditional methods of analyzing cohort data that compare vaccinated and unvaccinated girls are susceptible to irremediable biases. Therefore, we implemented an alternative method of analysis, known as the regression discontinuity design (RDD), that accounts for observed and unobserved confounding, thus permitting reliable causal inference in this context.[94,122,124]

The RDD is a quasi-experimental approach that is increasingly used to evaluate the causal effects of interventions in situations when assignment to a treatment is determined or affected by the value of an underlying continuous covariate (e.g., birth date), referred to as the forcing variable, being on one side of a fixed cut-off (e.g., program eligibility).[93,94,122,124,137] As a result, the probability of receiving the treatment changes discontinuously (i.e., jumps or drops) at the cut-off (Figure 5.1-A). Since the cut-off is based on an administrative decision (e.g., date of

program implementation), its exact location is random with respect to the characteristics of individual study participants, implying that observations on either side of the cut-off are exchangeable with respect to all measured and unmeasured factors other than treatment. The forcing variable may also be associated with the outcome of interest, but this association is assumed to be smooth; therefore, any discontinuity in the conditional distribution of the outcome at the cut-off is interpreted as the causal effect of the intervention (Figure 5.1-B).[94] Studies show that randomized experiments and RDDs produce similar estimates in regions close to the cut-off.[95]

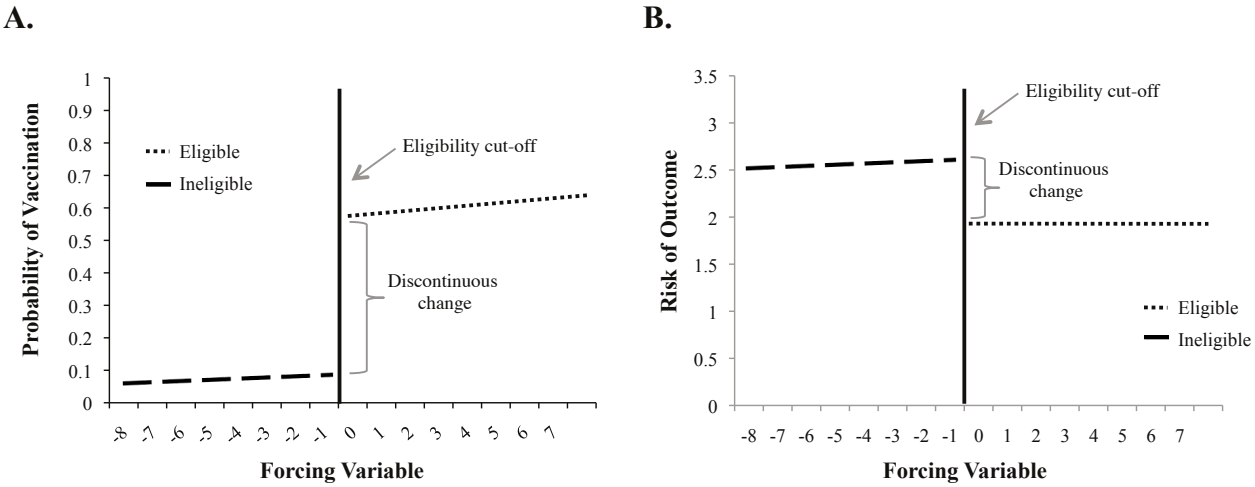

Figure 5.1 Hypothetical depiction of RDD scenario*

A. Discontinuity probability of exposure at the eligibility cut-off*; B. Discontinuity in the risk of the outcome at the eligibility cut-off*

*Please note that, in the context of this study, the x-axis represents birth quarter (the forcing variable) *not* the calendar time surrounding the policy intervention. As such, scenario A represents hypothetical vaccine exposure between September 1 of Grade 8 and August 31 of Grade 9 (by birth quarter) and scenario B represents the hypothetical cumulative incidence of the outcome (e.g., AGWs) between September 1 of Grade 10 and March 31 of Grade 12 (by birth quarter).

Forcing variable – Our study design exploits the fact that girls were eligible for free qHPV vaccination (i.e., assigned to treatment) based on whether they were in Grade 8 before or after the September 2007 program implementation date (i.e., born December 31, 1993 or earlier *vs.* January 1, 1994 or later), which induced a discontinuity in the probability of qHPV vaccination at the eligibility cut-off. Accordingly, the forcing variable was based on each girl's date of birth, and its value reflected the distance of the girl's birth date from the eligibility cut-off. Since we collapsed the forcing variable into three-month intervals, girls born October 1,

1993 to December 31, 1993 were directly on the "ineligible" side of the cut-off and girls born January 1, 1994 to March 31, 1994 were directly on the "eligible" side; girls born earlier/later than these dates were represented with increasing distance from the cut-off on the ineligible/eligible sides (Appendix 5-A).

Exposure – To evaluate the impact of the qHPV vaccination program, exposure status was based solely on program eligibility (i.e., "intention-to-treat" definition). To assess the impact of vaccination on our outcomes, actual qHPV vaccine exposure was also taken into account (i.e., "as-treated" definition). We defined qHPV vaccine exposure as receipt of all three doses between September 1 of Grade 8 and August 31 of Grade 9, as this was the program eligibility period.

Outcomes – Incident cases were identified between September 1 of Grade 10 and March 31 of Grade 12 using the OHIP, NACRS, DAD, and SDS databases. An incident case of cervical dysplasia was defined as a diagnosis or treatment of cervical dysplasia with no diagnosis or treatment in the previous 730 days (Appendix 5-B). An incident case of AGW was defined as a diagnosis or treatment of AGW with no diagnosis or treatment in the previous 365 days (Appendix 5-C). Since the algorithms for ascertaining these outcomes have not been validated, we created three definitions for each outcome (broad, possible, and probable) in consultation with substantive experts to reflect different degrees of potential misclassification.

Baseline Characteristics – To describe the study cohort, we identified a number of baseline characteristics relating to socio-demographics, vaccination history, healthcare utilization, and medical history.

Statistical Analyses – Each outcome was analyzed separately. To evaluate the program impact, local linear regression was used to model the association between program eligibility and the outcome.[94,124] Specifically, regression functions were fit on each side of the eligibility cut-off, and the magnitude of the difference (discontinuity) between the intercepts at the cut-off represented the absolute change in the outcome attributable to program eligibility (i.e., the intention-to-treat or population-level effect). To evaluate the vaccine impact, a second stage was added to the analysis that modeled the association between program eligibility and qHPV vaccine exposure. In this analysis, the ratio of the eligibility-outcome and eligibility-vaccine discontinuities represented the absolute effect of treatment for girls actually treated (i.e., as-treated or vaccine-level effect). Similarly, one- and two-stage log-binomial regression was used to estimate the relative impact of program eligibility and vaccination on the outcomes of interest.

The "number needed to treat" (NNT) of each outcome was estimated based on the reciprocal of the absolute risk difference and 95% confidence limits.[138] In all analyses, girls closest to the program eligibility cut-off (i.e., born in 1993 or 1994) were weighted twice as heavily as girls further away (i.e., born in 1992 and 1995) since girls closest to the cut-off are the most directly comparable. Similarly, we controlled for birth timing because we found girls born early (or late) in the year were most comparable between birth years. Similar relative effects of age have been documented on a number of different outcomes.[139-141]

A number of sensitivity analyses were performed to assess the robustness of our results. For one, in light of recent evidence suggesting two doses of the qHPV vaccine may be sufficient to confer benefit,[130,131] the primary vaccine impact analyses were repeated using an exposure definition of at least two doses. In a separate sensitivity analysis for vaccine impact, exposure and outcome ascertainment windows were modified such that qHPV vaccine exposure was ascertained between September 1 and August 31 of Grade 8 (since this is when most girls are vaccinated) and outcomes were ascertained between September 1 of Grade 9 and March 31 of Grade 12. We also conducted sensitivity analyses that controlled for additional baseline covariates, such as neighbourhood income quintile, hepatitis B vaccination, and a recent sexual health-related outcome (e.g., diagnosis of a sexually transmitted infection, cervical cancer screening, pregnancy).

Data management was carried out using SAS statistical software version 9.3 (SAS Institute Inc., Cary, North Carolina), and statistical analyses were executed using Stata version 12 (StataCorp, College Station, Texas).

RESULTS

We identified a cohort of 206,493 girls, 49.4% of whom were eligible for publicly funded qHPV vaccination (Figure 5.2).

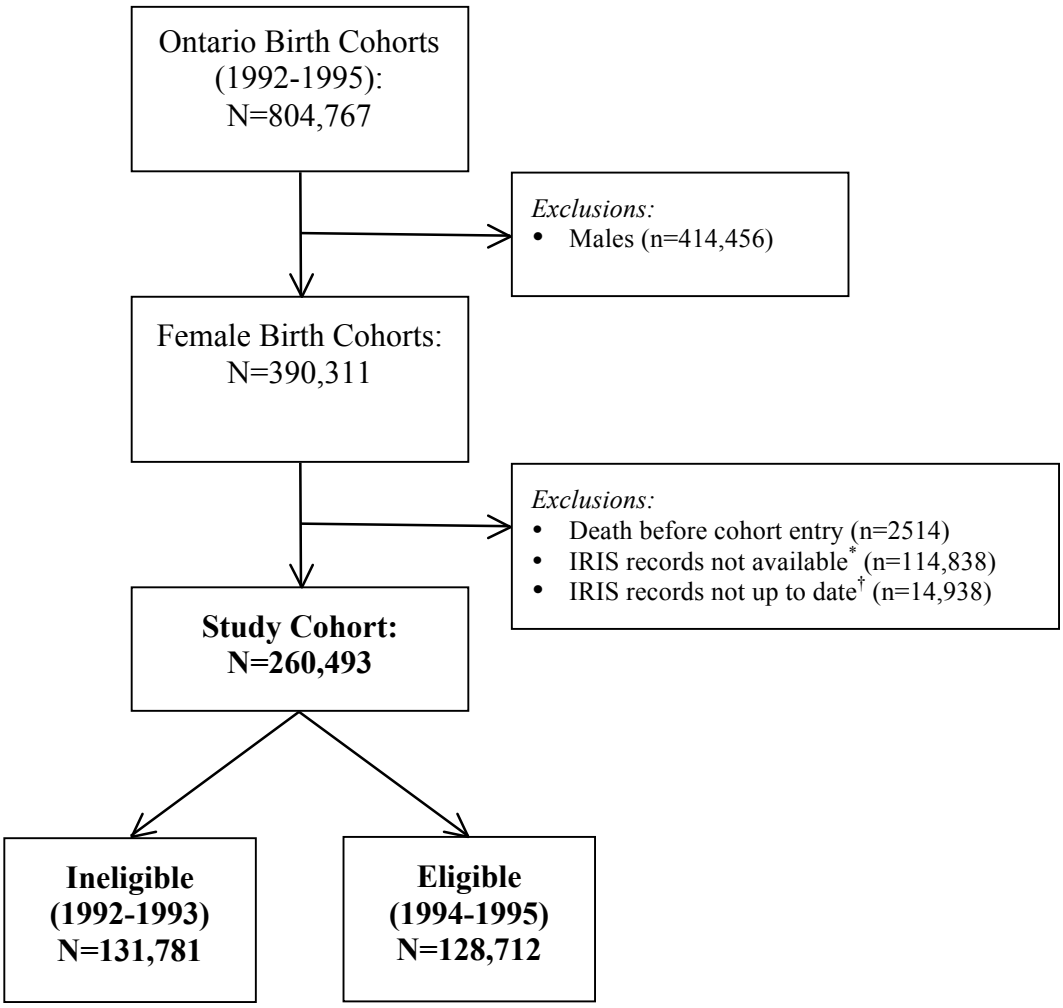

Figure 5.2 Cohort Flow Diagram

*At the time of this study, two of Ontario's 36 IRIS databases (representing approximately 22% of Ontario's population) had not yet been transferred to ICES and were therefore unavailable for use. IRIS records were also unavailable if the girl emigrated from Ontario before starting kindergarten or immigrated to Ontario after completing high school.

† A girl's IRIS record was defined as "up to date" if it had been modified 30 days before cohort entry or later. Otherwise, it was assumed the girl had moved out of our study area prior to cohort entry.

Girls were 12.7-13.7 years of age at cohort entry and were followed for an average of 4.6 years (standard deviation = 0.12). Eligibility groups were similar with respect to a number of baseline characteristics, including frequency of outpatient physician visits and previous receipt of the measles-mumps-rubella and diphtheria, tetanus, and pertussis vaccines. There were small differences for such characteristics as neighbourhood income quintile, hepatitis B vaccination, and a recent sexual health-related outcome (Table 5.1).

Table 5.1 Baseline characteristics of study cohort

Characteristic	Percentage[*]	
	Ineligible (n=131,781)	**Eligible (n=128,712)**
Socio-demographics[†]		
Mean age at cohort entry (SD)	13.17 (0.28)	13.17 (0.28)
Birth Quarter		
January-March	24.3	24.2
April-June	26.1	26.1
July-September	25.7	25.8
October-December	23.9	23.9
Residency		
Urban	85.3	85.8
Rural	14.0	13.5
Missing[‡]	0.7	0.6
Income quintile		
1st (lowest)	16.6	15.0
2nd	18.4	17.8
3rd	20.6	21.1
4th	22.0	23.1
5th (highest)	21.4	22.1
Missing[‡]	1.0	0.9
Vaccination History[§]		
MMR[‖]	97.9	98.2
DTP[‖]	98.0	98.3
Hepatitis B[‖]	84.1	82.0
All three vaccines	83.0	81.1
Health Services Use[¶**]		
Hospitalizations		
None	98.0	98.2

≥1	2.0	1.8
Days (mean, SD)	7.4, 15.6	8.0, 18.2
Same-day surgeries		
None	97.7	97.8
≥1	2.4	2.2
Emergency department visits		
None	70.7	71.1
1	18.1	17.8
≥2	11.2	11.1
Outpatient visits		
0-1	25.0	25.8
2-5	22.6	22.8
6-12	25.1	24.5
≥13	27.4	26.9
Medical History		
Cancer[¶]	0.71	0.74
Mental health diagnosis[¶]	9.5	9.7
Sexual health indicators[¶††]	0.68	0.73
Down's syndrome[§]	0.48	0.53
Congenital malformations[§]	12.4	11.8
Intellectual disabilities[§]	0.72	0.73

SD = standard deviation; MMR = measles-mumps-rubella; DTP = diphtheria, tetanus, and pertussis
* Figures are expressed as percentages except where indicated otherwise
† At cohort entry
‡ Missing due to missing or inaccurate postal code
§ Between birth and cohort entry
‖ At least one dose
¶ In the two years preceding cohort entry
** Categories determine based on the frequency of the distribution
†† Composite of sexually transmitted infections, cervical dysplasia, Papanicolaou smears, and pregnancy

Of the 75,848 girls who received at least one dose of the qHPV vaccine in Grades 8-9, 88% completed the vaccination series. As expected, vaccine exposure was largely influenced by program eligibility. In particular, 50.6% of eligible girls were classified as qHPV vaccine

exposed compared with only 0.92% of ineligible girls, creating clear discontinuity in the probability of exposure at the cut-off (Figure 5.3).

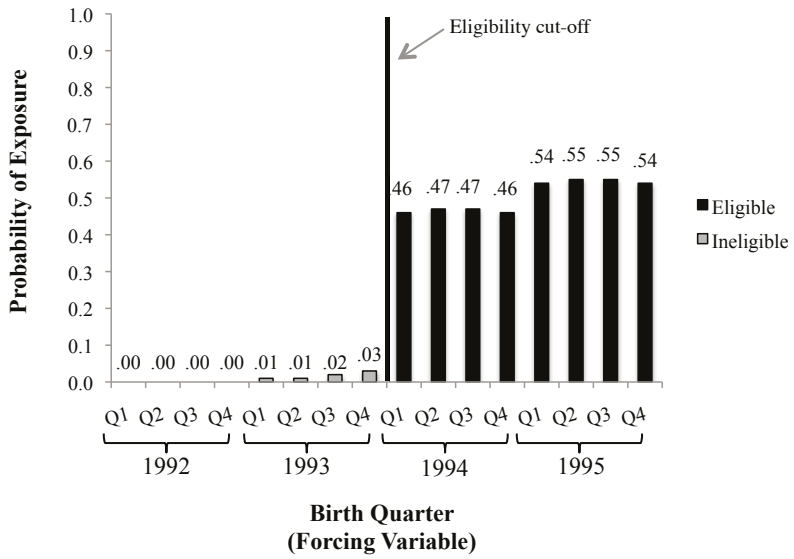

Figure 5.3 Probability of qHPV vaccine exposure*, by birth quarter

Q1: born January-March; Q2: born April-June; Q3: born July-September; Q4: born October-December

*Receipt of three doses of the qHPV vaccine between September 1 of Grade 8 and August 31 of Grade 9.

We identified 2,436 (0.94%) cohort members with incident cervical dysplasia (Table 5.2). Although there was no apparent discontinuity at the eligibility cut-off when assessed across birth quarters (Figure 5.4-A), collapsing into birth years revealed a clear drop in the risk of dysplasia between eligibility groups (Figure 5.4-B), demonstrating the importance of taking birth quarter into account in the analysis.

Table 5.2 Cumulative incidence of cervical dysplasia and anogenital warts*

Outcome	Frequency (percent)				
	Ineligible		Eligible		TOTAL (N=260,493)
	1992 (n=66,653)	1993 (n=65,128)	1994 (n=64,818)	1995 (n=63,894)	
Dysplasia					
Broad	698 (1.05)	720 (1.11)	555 (0.86)	463 (0.72)	2,436 (0.94)
Possible	444 (0.67)	478 (0.73)	358 (0.55)	277 (0.43)	1,557 (0.60)
Probable	232 (0.35)	229 (0.35)	161 (0.25)	121 (0.19)	743 (0.29)
Anogenital Warts					
Broad	119 (0.18)	120 (0.18)	91 (0.14)	70 (0.11)	400 (0.15)
Possible	68 (0.10)	59 (0.09)	32 (0.05)	31 (0.05)	190 (0.07)
Probable	62 (0.09)	54 (0.08)	30 (0.05)	27 (0.04)	173 (0.07)

*Ascertained between September 1 of Grade 10 and March 31 of Grade 12.

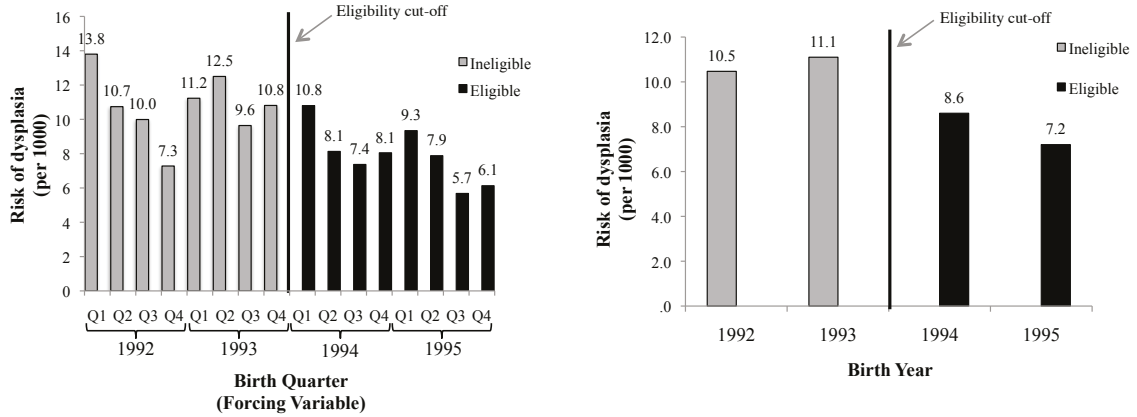

Figure 5.4 Risk of broad cervical dysplasia*

A. By birth quarter; B. By birth year
Q1: born January-March; Q2: born April-June; Q3: born July-September; Q4: born October-December
*Ascertained September 1 of Grade 10 to March

Indeed, the regression discontinuity analyses revealed a statistically significant reduction in dysplasia attributable to program eligibility: risk difference (RD) = -2.32 cases per 1000, 95% confidence interval (CI) -4.02 to -0.61. An even stronger effect was observed for girls who were vaccinated: RD = -5.70 per 1000, 95% CI -9.91 to -1.50. These results indicate that one case of

cervical dysplasia was prevented for every 431 (95% CI 248 to 1639) girls eligible for publicly funded vaccination, as well as for every 175 (95% CI 101 to 667) girls who received the vaccine. The absolute risk differences corresponded to a 21% (95% CI, 6% to 34%) and 44% (95% CI, 13% to 64%) relative risk reduction for program eligibility and vaccination, respectively. Relative risk reductions were similar for possible dysplasia and probable dysplasia, whereas absolute risks differences decreased and NNTs increased with increasing sensitivity of the dysplasia definition (Table 5.3).

Table 5.3 Impact of qHPV vaccination on risk of cervical dysplasia and anogenital warts*

	Risk Difference, per 1000 (95% CI)	Risk Ratio (95% CI)	NNT (95% CI)†
Dysplasia			
Program Impact			
Broad	-2.32 (-4.02, -0.61)	0.79 (0.66, 0.94)	431 (248, 1639)
Possible	-1.70 (-3.08, -0.32)	0.76 (0.61, 0.95)	588 (325, 3125)
Probable	-0.79 (-1.74, 0.16)	0.76 (0.56, 1.05)	1266 (575, ∞ to NNH 6250)
Vaccine Impact			
Broad	-5.70 (-9.91, -1.50)	0.56 (0.36, 0.87)	175 (101, 667)
Possible	-4.19 (-7.59, -0.80)	0.50 (0.30, 0.84)	239 (132, 1250)
Probable	-1.94 (-4.28, 0.39)	0.51 (0.21, 1.09)	515 (234, ∞ to NNH 2564)
Anogenital Warts			
Program Impact			
Broad	-0.34 (-1.03, 0.36)	0.81 (0.52, 1.25)	2941 (971, ∞ to NNH 2778)
Possible	-0.34 (-0.81, 0.13)	0.60 (0.31, 1.15)	2941 (1235, ∞ to NNH 7692)
Probable	-0.29 (-0.74, 0.16)	0.63 (0.32, 1.24)	3448 (1351, ∞ to NNH 6250)
Vaccine Impact			
Broad	-0.83 (-2.54, 0.88)	0.57 (0.20, 1.58)	1205 (394, ∞ to NNH 1136)
Possible	-0.84 (-1.99, 0.31)	0.31 (0.07, 1.41)	1190 (503, ∞ to NNH 3226)
Probable	-0.72 (-1.82, .0.38)	0.34 (0.07, 1.72)	1389 (549, ∞ to NNH 2632)

CI – confidence interval; NNT – number needed to treat; NNH – number needed to harm.
*To address the effect of birth timing we observed, we utilized the entire bandwidth of data (i.e., all observations in the 1992 to 1995 birth cohorts) and included birth timing as a covariate in the model. In all analyses, the birth cohorts closest to the cut-off (1993 and 1994) were weighting twice as heavily as those furthest from the cut-off (1992 and 1995).
† Reported as recommended by Altman (1998).[138] When absolute risk differences are not statistically significant, the limits of the confidence interval for the NNT reflect both the possibility of benefit (NNT) and the possibility of harm

(NNH). Moreover, the NNT is infinity (∞) when the absolute risk difference is 0. To convey the continuity of the confidence interval, Altman suggests that both the NNT and the NNH be represented in one interval and that 0 be represented by infinity.

Four hundred cohort members were diagnosed with or treated for AGW during the outcome ascertainment period (Table 5.2). Figures 5.5-A and 5.5-B depict this risk by birth quarter and by birth year, respectively. The results suggested reductions in the incidence of AGW attributable to program eligibility and vaccination, both on the absolute scale (RD=-0.34 per 1000, 95% CI -1.03, 0.36; RD= -0.83, 95% CI -2.54, 0.88) and the relative scale (RR=0.81, 95% CI 0.52, 1.25; RR=0.57, 95% CI 0.20 to 1.58); however, these results were not statistically significant. Findings indicated even greater relative risk reductions for more specific outcome definitions of AGW, while absolute risk reductions were similar across definitions (Table 5.3). Results for both cervical dysplasia and AGW were robust in sensitivity analyses.

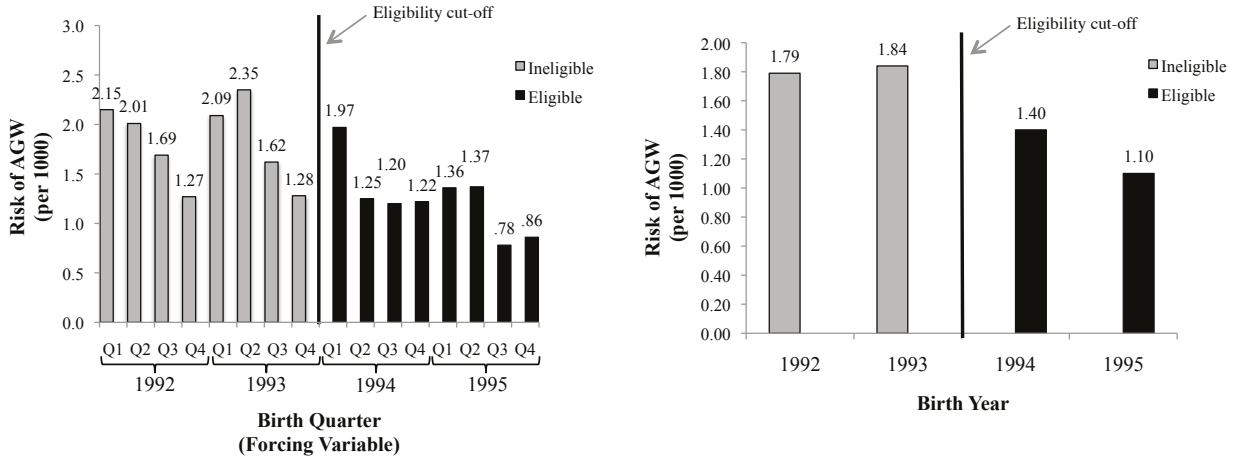

Figure 5.4 Risk of broad AGW*

A. By birth quarter; B. By birth year

Q1: born January-March; Q2: born April-June; Q3: born July-September; Q4: born October-December

*Ascertained September 1 of Grade 10 to March

DISCUSSION

This is the first study of the early benefits of the qHPV vaccine to use a methodological approach that permits causal inference. As such, it provides new, strong evidence of the positive health impact of population-based qHPV vaccination. In particular, our analyses revealed a strong, protective effect of the qHPV vaccine program on cervical dysplasia among girls aged 14-17 years and, although imprecise, we also observed an apparent reduction in the incidence of anogenital warts. Estimates of vaccine impact for both outcomes were even stronger than those

of program impact. All results speak to the value of offering qHPV vaccination to adolescent girls.

This study used an analytical approach that exploited the quasi-experimental situation that arose when a provincial policy made free qHPV vaccination accessible to a specific population (Grade 8 girls) after a specific point in time (September 2007 onward). As a result, we were able to evaluate the "intention-to-treat" (ITT) effects of qHPV vaccination for the first time outside of clinical trials. Our findings of such an early, positive program-level impact provide evidence of the value of offering large-scale qHPV vaccination and support current recommendations of vaccinating girls at a young age. Not surprisingly, estimates of the "as-treated" analysis (i.e., vaccine impact) were much stronger than estimates of the ITT analysis (i.e., program impact). For example, we observed almost 2.5 times greater absolute reductions in cervical dysplasia attributable to the vaccine compared with the program. A major reason for this difference is that program impact is a function of vaccine refusal, which was almost 50% among eligible girls. Such low vaccine coverage has been well documented in a number of Canadian provinces, particularly in the early years of program implementations.[10,85] These results highlight the important effect of factors like vaccine coverage, which has also been a challenge in regions outside of Canada,[42] on reducing the burden of HPV-related infections in the population. Indeed, a thorough appreciation of the interplay between the program- and vaccine-level effects in any region will be crucial to improving qHPV vaccine delivery and policy in ways that optimize the health and economic benefits of this public health intervention.

To date, observational studies of cervical dysplasia have reported relative estimates of vaccine impact by comparing vaccinated and unvaccinated girls. Our results are consistent with this previous research.[51-54] Importantly, observational studies have reported more conservative estimates of vaccine effectiveness than those reported in RCTs.[49] This not surprising given that trials estimated treatment effects under ideal conditions; it does, however, highlight the importance of observational studies in determining the real-world effects of health interventions. Only one of the previous observational studies also reported numbers needed to treat.[52] In particular, based on a nested case-control study of females aged 11-27 years followed for a median of two years in Queensland, Australia, Crowe et al. reported numbers needed to treat of 125 (95% CI 97 to 174) and 22 (95% CI 19 to 25) for preventing one case of high grade cervical dysplasia and "other" cervical dysplasia, respectively. While these number are smaller than those

reported in our study, this is expected given Crowe et al.'s older study population and correspondingly higher baseline incidence of cervical dysplasia.

The only non-ecologic observational study of anogenital warts published to date reported a magnitude of effect greater than we report here; however, the results generally fell within the range of our confidence intervals.[62] It is possible this discrepancy is, at least in part, attributable to residual confounding between vaccinated and unvaccinated girls in the previous study, which may have caused researchers to overestimate the protective effect of the vaccine. Regardless, given the low event rate of diagnosed AGW in our study's young age group and the resulting imprecision of our estimates, additional studies are needed to further elucidate these findings.

A major strength of our study is the use of population-based administrative databases, which enabled us to conduct a cohort study on a large group of individuals with limited potential for selection, recall, or response biases. An additional benefit is the use of validated vaccination data. In particular, a re-abstraction of a subset of the vaccination records indicated that sensitivity and specificity of individuals' qHPV vaccination status was 99.8% (95% confidence interval 99.3-99.9) and 97.7% (95% confidence interval 96.3-98.7), respectively, and that 98.6% of vaccination dates were accurate to the day.[110] Therefore, the impact of exposure misclassification would be negligible. Conversely, outcome misclassification is a potential source of error in our study, as these measures have not been validated. To address this at the design stage, we created three levels of each outcome, reflecting increasing levels of outcome sensitivity. Our results suggest our broad definition of anogenital warts was misclassified, as evidenced by the fact that the relative risk was biased toward the null compared with the more sensitive definitions. This is not surprising since this broad definition included a diagnostic code that could also be used to capture warts on other body sites. Conversely, the consistency in results across definitions of cervical dysplasia and between definitions possible and probable AGW suggest these definitions were not misclassified. Another limitation of our outcome data is they only captured girls who sought care following abnormal cervical cancer screening results and girls who sought physician care for anogenital warts. Consequently, our absolute estimates of effect are likely conservative. On the other hand, since under-ascertainment of outcomes would have affected both groups equally, it would not have had an impact on our relative estimates of effect. This is reinforced by the consistency of our results with those of previous studies reporting on the relative effect of qHPV vaccination. Finally, since we did not have access to cervical screening cytology, we

could not report on the stage of cervical dysplasia. Nevertheless, our results are consistent with those of studies that included staging.[51-54]

As previously mentioned, a major strength of our study is our use of the regression discontinuity design, a unique analytic approach for estimating causal effects that controls for confounding from potential imbalances between eligibility groups, whether measured or unmeasured. In addition, since all girls were followed over the same age range, we avoid the possibility of confounding by age. This design is conceptually vulnerable to external influences that might have differentially affected eligibility groups (e.g., another large-scale policy or intervention). However, we have no knowledge of any such occurrence during the study period, and given the considerable calendar year overlap between groups, especially closest to the cut-off, this source of bias seems unlikely.

Unlike most previous studies of HPV vaccine effectiveness, we provide both absolute and relative measures of effect because of the importance of the former in determining the public health impact and cost-effectiveness of this intervention. Nevertheless, since absolute risk differences are a function of the underlying baseline risk, their generalizability to other jurisdictions and other age groups remains unclear. For example, given the low event rate in our young population, the absolute benefits we observed were small. However, since the rates of these outcomes generally increase with age, we expect the absolute benefits to increase in this population over time. Correspondingly, while the numbers needed to treat are large in our adolescent population, these numbers will likely be smaller in more high-risk age groups, as was the case in the study by Crowe et al.[52] Therefore, our analyses should be repeated in a range of settings and over time. Readers should also exercise caution when interpreting our intention-to-treat estimates, as they must be taken in the context of the low qHPV vaccine coverage in our study population. Relative measures of vaccine impact, on the other hand, account for the probabilistic nature of qHPV vaccine receipt. As such, they are likely more generalizable to other jurisdictions offering free qHPV vaccination to girls who are largely sexually naïve, such as those offered, across Canada.

Conclusion

This observational study of the qHPV vaccine is the first to use a design that allows for causal inference. As such, it provides strong evidence of the impact of qHPV vaccination on reductions in cervical dysplasia among adolescent girls. Though imprecise, we also observed

reductions in anogenital warts. The fact that these benefits were observed in such a young age group strengthens current recommendations that vaccination should occur at an early age (e.g., 9-13 years) when the likelihood of previous infection is low. Additional studies are needed to further evaluate the impact of qHPV vaccination at the population-level and to assess the impact of this vaccine on cervical cancer morbidity and mortality. Furthermore, cost-effectiveness studies should be updated to incorporate real-world estimates of program- and vaccine-level effectiveness and vaccine coverage to provide more accurate assessments of the value of qHPV vaccination.

5.2.1 APPENDIX 5-A: Operationalization of the forcing variable

	Grade 8 school year	Birth Year	Birth Year Quarter	Value of Forcing Variable
Ineligible	2005/06	1992	Mar 1992 – Jan 1992	-8
			Jun 1992 – Apr 1992	-7
			Sept 1992 – Jul 1992	-6
			Dec 1992 – Oct 1992	-5
	2006/07	1993	Mar 1993 – Jan 1993	-4
			Jun 1993 – Apr 1993	-3
			Sept 1993 – Jul 1993	-2
			Dec 1993 – Oct 1993	-1
Eligible	2007/08	1994	Jan 1994 – Mar 1994	0
			Apr 1994 – Jun 1994	1
			Jul 1994 – Sept 1994	2
			Oct 1994 – Dec 1994	3
	2008/09	1995	Jan 1995 – Mar 1995	4
			Apr 1995 – Jun 1995	5
			Jul 1995 – Sept 1995	6
			Oct 1995 – Dec 1995	7

5.2.2 APPENDIX 5-B: Definitions of cervical dysplasia, by data source

CODE	DESCRIPTION	ALGORITHM
NACRS/CIHI		
ICD-10 code		
N86	Erosion and ectropion of cervix uteri	
N87	Dysplasia of cervix uteri	
N870	Mild cervical dysplasia	*Broad dysplasia*: Any ICD-10 OR fee code
N871	Moderate cervical dysplasia	
N872	Severe cervical dysplasia	*Possible dysplasia*: Any ICD-10 code
N879	Dysplasia of cervix uteri, unspecified	
D06	Cervical cancer	
Intervention Code		*Probable dysplasia*: At least one ICD-10 code AND any corresponding intervention code
1RN26	Brachytherapy (radiotherapy), cervix	
1RN27	Radiation, cervix	
1RN59	Destruction, cervix	
1RN87	Partial excision, cervix	
1RN89	Total excision, cervix	
2RN71	Biopsy, cervix	
4AH0277	Cytology screening, cervico-vaginal	
OHIP		*Broad dysplasia:* Any diagnostic code OR selected* fee code
Diagnostic Code		
622	Cervical erosion/dysplasia	
180	Cervical cancer	*Possible dysplasia:* Diagnosis code AND any corresponding fee code listed
Fee Code		
A203	Specific assessment - obs/gyn	
A204	Partial assessment - obs/gyn	
A205	Complete assessment - obs/gyn	*Probable dysplasia:* Diagnosis code AND selected* fee code
E430	Pap outside hospital	
G365	Papanicolaou smear	
G394	Follow-up Pap for abnormal or inadequate smear	

Z720*	Cervix uteri - biopsy
Z724*	Cervic uteri – cautery
Z729*	Cervic uteri – cryoconization, eclectronization/dysplasia
Z730*	colposcopy
Z731*	uterus/cervix investigate abnormal cytology
Z732*	uterus/cervix cautery cryotherapy

5.2.3 APPENDIX 5-C: Definition of anogenital warts, by data source

Code	Description	Algorithm
Treatment for warts (OHIP fee codes)		
Z701*	Cryotherapy for penile condylomata	
Z733*	Cryotherapy for vulvar condylomata	
Z736*	Excision/electrodes/CO2 for vulvar condylomata (local anesthetic)	*Broad AGW:* Code for treatment for warts (general) and corresponding diagnosis code related to the anogenital region OR code for treatment of anogenital warts OR code for diagnosis of AGW
Z549*	Destruction/fulguration of anal condylomata (local anesthetic)	
Z758*	Destruction/fulguration of anal condylomata (general anesthetic)	
Z769*	Excision/electrodes/CO2 laser for vulvar condylomata (general anesthetic)	
Z117†	Chemical and/or cryotherapy treatment of skin lesions	*Possible AGW:* Code for diagnosis OR treatment of anogenital warts
Associated Diagnoses (OHIP diagnostic codes)		
078	Warts	*Probable AGW:* Code for treatment for anogenital warts and any corresponding diagnosis code OR code for diagnosis of AGW
079	Other viral diseases	
099‡	Other venereal disease	
622‡	Cervical erosion/dysplasia	
616‡	Cervitis, vaginitis, cyst or abscess, vulvitis	
629‡	Other disorders of female genital tract	
Diagnosis of AGW (ICD-10 code, NACRS & CIHI)		
A630§	Venereal anogenital warts	

ICD-10 = International Classification of Diseases, version 10
* code for treatment of AGW
† general code for treatment of warts
‡ diagnostic code related to anogenital region
§ sufficient for identification of AGW in all definitions

5.3 Additional Results and Discussion

As indicated in Chapter 3 and Manuscript 2, a number of additional analyses were executed to assess the robustness of our various assumptions.

Appendix F displays the absolute risk reductions observed using the secondary exposure definitions. Evidently, the absolute and relative risk reductions were of slightly lower magnitude when girls who only received two doses of the vaccine were included in the primary exposure definition, suggesting a small reduction in vaccine effectiveness. These findings are consistent with previous studies on the effects of receiving two rather than three doses of the qHPV vaccine. For example, Herweijer et al.[131] report the incidence rate ratio for AGW was 0.18 (95% CI 0.15 to 0.22) among girls aged 10 16 years who received three doses of the qHPV vaccine compared with 0.29 (95% CI 0.21 to 0.40) among girls who received only two doses. Appendix F also displays the risk reductions when the primary exposure window was restricted to Grade 8 and the outcome ascertainment period was extended to include Grade 9. These findings suggest slight additional absolute reductions in risk, which is what is expected since adding the additional year of outcomes increases the baseline incidence of disease. These additional reductions in risk are also evidenced on the relative scale.

Results were also robust to additional variations to the exposure definition, as well as changes in the outcome definition, alternative weighting schemes, and the inclusion of additional covariates (Appendix G). Importantly, the unadjusted estimates of program and vaccine impact highlighted the importance of controlling for birth timing in these analyses. For example, the unadjusted relative estimates of probable dysplasia suggested *no* impact of program vaccination (1.01, 95% CI 0.51, 2.00) or eligibility (RR=1.01, 95% CI 0.76 to 1.35); point estimates for broad and possible dysplasia were 0.84 and 0.93, respectively, but were not statistically significant. Similarly, unadjusted estimates of broad AGW appeared confounded, as evidenced by a slight increase in risk, though statistically not significant (RR=1.09, 95% CI 0.44, 2.72). Estimates for possible and probable AGW were closer to the expected values (RR=0.41, 95% CI 0.10, 1.70 and RR=0.47, 95% CI 0.11, 2.07, respectively), but are nonetheless suspect to confounding bias. As the effect of birth timing was not anticipated *a priori,* the unadjusted findings reinforce the need to thoroughly assessing the assumptions of the RDD prior to executing the analyses, as was done in Manuscript 1.

Given the potential for misclassification of school grade discussed in Chapter 3 (subsection "Birth year as a proxy for school grade"), the primary analyses were re-run among girls for whom Grade 8 year could be confirmed (n=193,981). The effect of the program and the vaccine on cervical dysplasia were similar in this population and the entire thesis cohort. On the other hand, estimates of AGW in this sub-cohort suggested even greater risk reductions attributable to both program eligibility and program vaccination, though these findings were not statistically significant (Appendix H). As the estimates in the sub-cohort are closer to those suggested by randomized controlled trials[48] and the observational study of AGW[62], the difference in results may be partially attributed to reduced misclassification of school year. They are also likely attributable to increased HPV vaccine coverage of almost 6% in the subpopulation (56.4%) compared with the full cohort (50.6%). Regardless, as results were imprecise in both populations, analyses should be repeated when additional follow-up time is available in order to better understand the true magnitude of the effect of HPV vaccination on AGW in Ontario.

As mentioned in Chapter 3, ordinary least squares regression models yielded the same estimates of program impact as the regression discontinuity program (Appendix D). Results were also similar when the marginal absolute risk reductions were estimated using log-binomial regression, though the latter were slightly closer to the null. Two-stage least squares regression, which is a more traditional way of analyzing instrumental variable-based models, also yielded estimates of effect of similar magnitude to Stata's –rd– program (Appendix I). These findings suggest the primary method of analysis used in this thesis was robust to the assumptions of different methods.

Overall, the results of the additional analyses suggest the findings in Manuscript are robust to the various assumptions made.

CHAPTER 6: HPV VACCINATION AND SEXUAL BEHAVIOUR

6.1 Preface to Manuscript 3

Manuscript 2 provided evidence that HPV vaccination is having its intended effects in Ontario – that is, it is reducing the burden of cervical dysplasia and seems to also be reducing the burden of AGW. While monitoring the effectiveness of HPV vaccination is vital to the success of Ontario's program, understanding whether there are also any indirect or unintended effects of the vaccine or the program is also important. One area of particular controversy has been whether HPV vaccination would give girls a false sense of protection again *all* sexually transmitted infections that may encourage them to engage in more risky sexual behaviours (e.g., increased number of sexual partners, decreased condom use) than they would have otherwise. Studies have shown this fear has made some parents resistant to having their daughters vaccinated and is contributing to lowered HPV vaccine acceptance. As such, addressing this issue may help improve HPV vaccine coverage. This question is additionally important because risky sexual behaviour is a major risk factor for sexually transmitted diseases and teen pregnancy. From a public health perspective, increases in these outcomes would undermine the benefits of HPV vaccination observed in Manuscript 2. In the following study (Manuscript 3), the absolute and relative effects of HPV vaccination on non-sexually transmitted and pregnancy are estimated. The same study population is used in this study as in Manuscript 2, so the potential negative effects of HPV vaccination studied here can be interpreted alongside the benefits of HPV vaccination on cervical dysplasia and AGW previously discussed.

This manuscript in press at *Canadian Medical Association Journal.*

6.2 Manuscript 3 – The effect of human papillomavirus (HPV) vaccination on clinical indicators of sexual behaviour among adolescent females: The Ontario Grade 8 HPV Vaccine Cohort Study

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ABSTRACT

Background

Human papillomavirus (HPV) vaccination continues to be controversial, partly because of fears it may increase risky sexual behaviour. We assessed the impact of HPV vaccination and Ontario's Grade 8 HPV vaccination program on clinical indicators of sexual behaviour among adolescent girls.

Methods

Using Ontario's administrative health databases, we identified a population-based cohort of girls in Grade 8 in the two years before (2005/06-2006/07) and after (2007/08-2008/09) Ontario's HPV vaccination program began. Vaccine receipt was ascertained in Grades 8-9 and indicators of sexual behaviour (pregnancy and non-HPV-related sexually transmitted infections [STIs]) in Grades 10-12. Using a quasi-experimental methodology known as regression discontinuity, we estimated the absolute risk difference (ARD) and relative risk (RR) for each outcome (combined in the primary analysis) attributable to vaccination and program eligibility (intention-to-treat effect).

Results

The cohort comprised 260,493 girls (131,781 ineligible, 128,712 eligible). We identified 15,441(5.9%) cases of pregnancies and STIs and found no evidence that vaccination increased this risk: ARD per 1,000 girls= -0.61 (95% confidence interval [CI] -10.71, 9.49), RR=0.96 (95% CI 0.81, 1.14). Similarly, no discernible effect for program eligibility was identified: ARD per 1,000= -0.25 (95% CI -4.35, 3.85), RR=0.99 (95% CI 0.93, 1.06). Findings were similar when pregnancy and STIs were assessed separately.

Interpretation

This study provides strong evidence that HPV vaccination does not have a negative impact on clinical indicators of sexual behaviour among adolescent girls. These findings suggest concerns over increased promiscuity following HPV vaccination are unwarranted and should not deter from vaccinating young girls.

INTRODUCTION

The human papillomavirus (HPV) is one of the most common sexually transmitted infections (STIs) in Canada and around the world, affecting 50-75% of all sexually active individuals at some point during their lifetime.[1-3] While a number of conditions are associated with anogenital HPV, arguably the most widely recognized is anogenital warts (AGWs) and the most devastating is cervical cancer.

In 2006, Canada was among 49 countries to license Gardasil® (Merck, Whitehouse Station, New Jersey), a quadrivalent HPV (qHPV) vaccine designed to protect against four HPV types that cause 70% of cases of cervical cancer and >90% of cases of AGW.[7-9] Following randomized controlled trials of this vaccine, which showed it to be highly efficacious in preventing vaccine-type specific pre-cancerous cervical lesions and AGWs among young females,[48,49] it received expedited approval in a number of countries and was the subject of intensive marketing, lobbying, and public health campaigns around the world.[43] By 2012, the vaccine had been approved in almost 100 countries, many of which have also implemented nationwide HPV immunization programs.[42]

Despite the popularity of large-scale immunization programs, HPV vaccination also faced a great deal of controversy regarding, in large part, the many unanswered questions about the real-world effects of this vaccine.[11,44] A major topic of public debate has been the possibility that HPV vaccination might lead to sexual disinhibition;[142] that is, that vaccination may give females a false sense of protection against *all* STIs that may lead them to, for example, initiate sexual contact at an earlier age, be more promiscuous, and refrain from using condoms. Undoubtedly, these increases in risky sexual behaviour could have clinical consequences, such as increased risk of pregnancy and non-HPV-related STIs. Although there is little empirical support for the notion that sexual health interventions promote risky sexual behaviours,[68,143-146] this possible unintended effect of the HPV vaccine would undermine its value for reducing the burden of sexual health-related diseases. Moreover, fear of increased promiscuity following HPV vaccination has been reported as a major determinant of vaccine refusal among some parents[76] and school boards[147], which may help explain suboptimal HPV vaccine coverage in some jurisdictions.[10,77] Evidently, both actual and perceived sexual disinhibition can have a negative effect on the potential health benefits of HPV vaccination. Therefore, we conducted a population-based retrospective cohort study to assess the impact of HPV vaccination on clinical

indicators of sexual behaviour among adolescent girls in Ontario, both at the level of the vaccine and of the program (intention-to-treat effect).

METHODS

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

Ontario's Grade 8 QHPV Immunization Program

Ontario's Grade 8 HPV vaccination program began in September 2007. This publicly funded program offers the three recommended doses of the vaccine, free-of-charge, to all Grade 8 girls in the province.[40] Since the vaccine is not mandatory in Ontario, participation in the program is voluntary. The program is primarily delivered through school-based immunization clinics administered by the province's 36 public health units, but eligible females also have the option of receiving the vaccine at the their local health unit or through their family physician at no cost. During our study period, eligible females had until the end of their Grade 8 school year to initiate the vaccine series and until the end of Grade 9 to complete it under the publicly funded program. At that time, no catch-up program was offered; therefore, females who were not eligible for the program (e.g., completed Grade 8 before September 2007) would have had to pay for the vaccine at a cost of approximately $150 per dose. The bivalent HPV vaccine, which is designed to protect against HPV types 16 and 18, was not authorized for use in Canada until February of 2010[148] and is not the vaccine used for Ontario's publicly funded program.

Data Sources

Data for this study were obtained from Ontario's population-based administrative databases, which are generated by the province's universal health insurance programs. Specifically, we used the following databases: (1) Registered Persons Database (RPDB), Ontario's population registry of insured persons, for information on socio-demographics, (2) Ontario Health Insurance Plan (OHIP) database for information on fee-for-service claims by physicians, (3) Discharge Abstract Database (DAD) for information on hospitalizations, (4) Same-Day Surgery (SDS) database for information on procedures carried out during same-day

surgeries, and (5) National Ambulatory Care Reporting System (NACRS) for information on emergency department visits. These databases have been used extensively in health research, including in the post-marketing evaluation of drug and vaccine effects.[85,105-107,136] Details on these databases are available elsewhere.[99-102,109]

We also used the Immunization Records Information System (IRIS) for information on vaccinations, including qHPV vaccinations.[109] IRIS databases are maintained by each of Ontario's 36 health units to record and track the immunization status of all school-aged children in their jurisdiction. Although these database were originally developed for the six designated diseases (diphtheria, tetanus, polio, measles, mumps and rubella) for which immunization is mandated under the *Immunization of Schools Pupils Act (1982)*, they are currently used for other vaccines as well, particularly those that are publicly funded. Prior to centralizing the databases, we validated the qHPV vaccination data of a medium-sized health unit and found that it captured qHPV vaccination status with near-perfect sensitivity (99.8%, 95% confidence interval [CI] 99.3 to 99.9) and high specificity (97.7%, 95% CI 96.3 98.7). Moreover, 98.6% of qHPV vaccination dates were accurate.[110] Due to the rigorous and standardized procedures that have developed as a result of the requirements in the *Immunization of Schools Pupils Act,* we expect the qHPV vaccine data of other health units to be of similarly high quality.

All data were accessed through the Institute for Clinical Evaluative Sciences (ICES). Since residents of Ontario are represented in these databases by a unique encrypted identifier, individual-level record linkage is possible across databases and over time.

Study Population and Cohort Formation

We identified a population-based cohort of all females who entered Grade 8 in Ontario in the two years before (2005/06, 2006/07) and after (2007/08, 2008/09) implementation of the province's Grade 8 qHPV immunization program. Although we did not have a direct measure of school grade, Ontario school entry practices are such that children typically enter school (Kindergarten) in September of the calendar year during which they turn 5, meaning the vast majority of children in a given grade have the same birth year.[149] Since this means girls in Grade 8 typically turn 13 years of age by December 31 of that school year, we identified a cohort of all females born in 1992, 1993, 1994, and 1995 to correspond with Grade 8 years of 2005, 2006, 2007, and 2008, respectively. We then restricted the cohort to girls who were alive and residing

in Ontario on September 1 of their Grade 8 year and whose immunization records were available at the time of the analysis. Although using birth year to determine Grade 8 year misclassifies cohort members who were held back or advanced a grade, we found that this approach correctly identified 96.4% of girls eligible for the program's first two years (i.e., 2007/08 and 2008/09).[134] Cohort members were followed until the earliest of their date of death, occurrence of a study outcome, or March 31 of Grade 12 (i.e., March 31 of 2010, 2011, 2012, or 2013, depending on the girl's birth year).

Measurement and Analysis

The Regression Discontinuity Design – To address our objectives, we used the regression discontinuity design (RDD), a quasi-experimental approach that was specifically created to evaluate the causal effects of interventions.[93,94,122,124,137] The RDD is used in situations when assignment to an intervention (e.g., HPV vaccine program) is determined by the value of an observed continuous factor (e.g., birth date), referred to as the "forcing variable", being on one side of a fixed eligibility cut-off or the other, causing the probability of receiving the intervention (e.g., HPV vaccine) to increase discontinuously at this cut-off. In terms of Ontario's Grade 8 qHPV vaccination program, assignment to the intervention was based on whether individuals were in Grade 8 before or after the September 2007 program implementation date (i.e., born December 31, 1993 or earlier *vs.* January 1, 1994 or later), causing the probability of receiving the vaccine to jump at the eligibility cut-off (Figure 6.1-A). RDD analyses are used to measure any corresponding discontinuous change in the probability of the outcome at the same eligibility cut-off (Figure 6.1-B), which is interpreted as the causal effect of the intervention. Correspondingly, a null effect is reflected by *continuity* in the outcome across the cut-off (Figure 6.1-C).

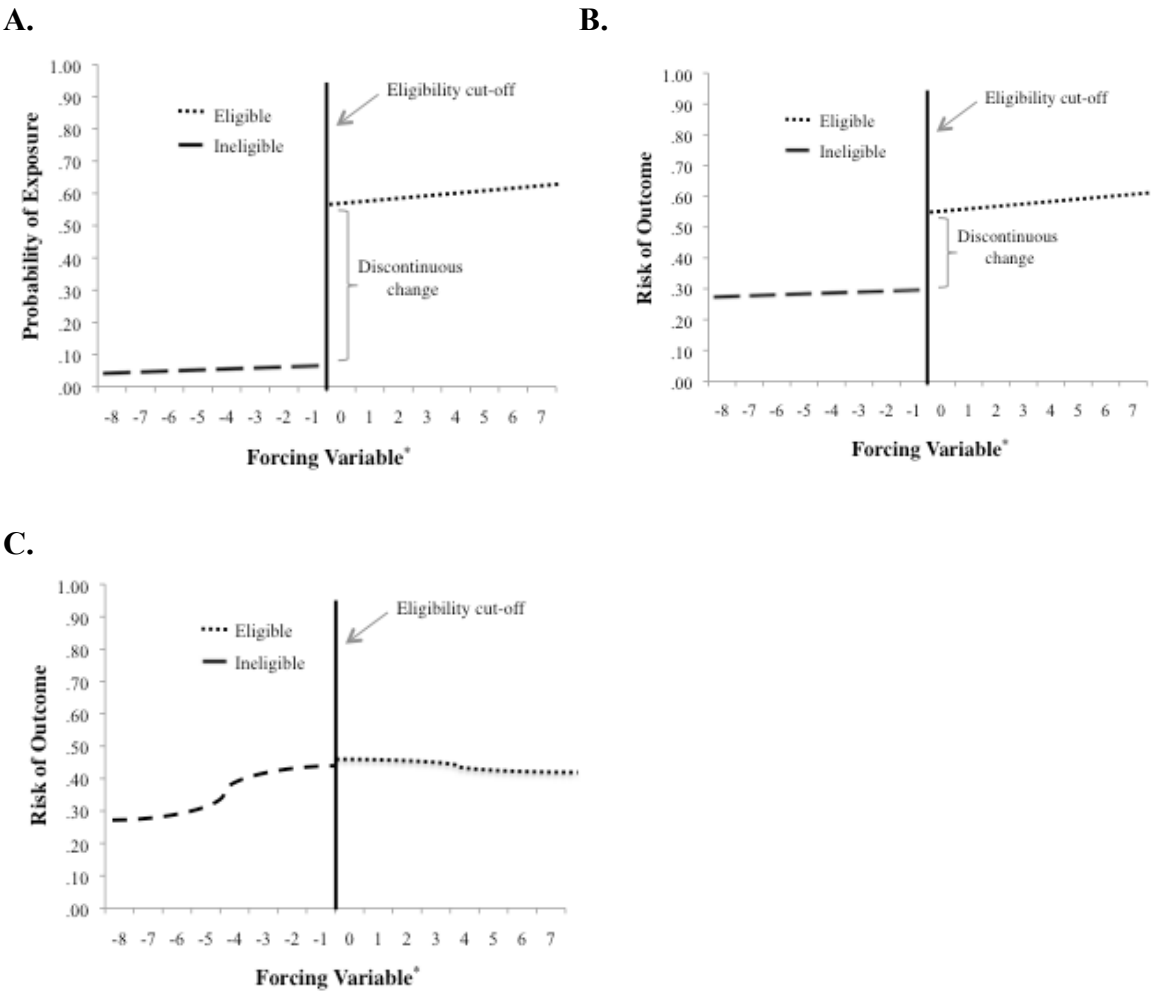

Figure 6.1 Hypothetical depictions of RDD scenarios*

A. Discontinuity in the probability of exposure; B. Discontinuity in the probability of outcome; C. Continuity in the risk of the outcome

The major advantage of the RDD rests on the notion that the eligibility criteria and implementation date, which determine the assignment cut-off, are based on administrative decisions, meaning, the exact location of the eligibility cut-off is random. Consequently, individuals falling directly on either side of the cut-off are comparable with respect to all measured and unmeasured confounders; the only factor that differentiates them is their probability of receiving the vaccine. This type of design is particularly valuable in studies of vaccine effects because individuals who opt for vaccination tend to have different health beliefs and behaviours than those who do not. Since health beliefs and behaviours are strongly

associated with health outcomes and are difficult to identify and quantify, traditional methods of analysis that directly compare vaccinated and unvaccinated individuals are prone to confounding bias.[78-81] Conversely, by controlling for this type of observed and unobserved confounding, the RDD facilitates reliable causal inference in this setting.[94,122,124]

Forcing variable and cut-off – As mentioned above, our study design exploits the fact that girls were eligible for the qHPV vaccination program based on when they were in Grade 8. Since school grade was estimated based on birth date, females born January 1 1992 to December 31, 1993 (corresponding with the 2005/06 and 2006/07 Grade 8 calendar years) were ineligible for the qHPV vaccination program, whereas females born January 1, 1994 to December 31, 1995 (corresponding with the 2006/07 and 2007/08 Grade 8 years) were eligible for this program. Accordingly, the forcing variable was based on birth date and December 31, 1993 *vs.* January 1, 1994 defined either side of the cut-off. For the purposes of analysis, the forcing variable was collapsed into three-month intervals (birth year quarters), meaning cohort members born October 1, 1993 to December 31, 1993 were directly on the ineligible side of the cut-off and cohort members born January 1, 1994 to March 31, 1994 were directly on the eligible side; cohort members born earlier/later than those dates were represented with increasing distance from the cut-off on the ineligible/eligible sides (Appendix 6-A).

Exposure Ascertainment – Two levels of exposure were analyzed. First**,** to evaluate the impact of the vaccination program, exposure was based solely on program eligibility. Therefore, cohort members who were in Grade 8 in the 2005/06 and 2006/07 school years were classified as *ineligible*, while those in Grade 8 in the 2007/08 and 2008/09 were classified as *eligible.* This approach is analogous to an "intention-to-treat" (ITT) definition of exposure. Second, to assess the impact of vaccination, actual qHPV vaccine receipt was also taken into account. A girl was classified as *vaccinated* if she received three doses of the vaccine between September 1 of Grade 8 and August 31 of Grade 9, which is the program vaccination period; otherwise, she was considered *unvaccinated.* The use of three doses for the primary exposure definition was based on the fact that this vaccine is administered as a three-dose series in Ontario. As such, girls were told they required three doses to be fully protected. However, we also conducted sensitivity analyses based on receipt of at least one dose to assess whether the act of vaccination may have been sufficient to induce disinhibition. Similarly, we defined HPV vaccination status based on two doses in light of recent evidence that suggests two doses provide adequate protection.[130,131]

Outcome Ascertainment – Our primary outcome was a composite measure of incident non-HPV-related STIs or pregnancy (Appendix 6-B). We also assessed each endpoint separately. We excluded HPV-related STIs (i.e., anogenital warts) from our measure of STIs because a decrease in this endpoint is an intended effect of the program and the vaccine. To ensure fixed follow-up time with equal probability of the outcomes for all cohort members, outcomes were ascertained between September 1 of Grade 10 and March 31 of Grade 12. A case was defined as incident if there was no indication of that event (STI or pregnancy) in the previous 365 days.

Baseline Characteristics – To describe the study cohort, we identified a number of baseline characteristics relating to socio-demographics, vaccination history, health service use, and medical history.

Statistical Analyses – To evaluate the program impact (i.e., intention-to-treat effect), linear regression was used to model the association between program eligibility and the outcome. To evaluate the vaccine impact, two-stage linear regression was used to estimate the association between program eligibility and the outcome *and* the association between program eligibility and qHPV vaccine exposure. In the two-stage analysis, the estimate of interest was the ratio of coefficients from the two regressions, which represents the absolute impact of qHPV vaccination on the outcome. Similarly, one- and two-stage log-binomial regressions were used to estimate the relative impact of program eligibility and vaccination on the outcomes of interest. In all analyses, cohort members born in 1993 or 1994 (i.e., closest to the cut-off) were weighted twice as heavily as those born in 1992 and 1995 because individuals closest to the cut-off are the most comparable. Moreover, analyses were conditioned on birth timing (i.e., birth quarter) because we found that, across birth years, females born early (or late) in the year were the most comparable (Appendix 6-C). Similar effects of relative age have been found in other studies as well.[139-141]

Sensitivity analyses were executed to test the robustness of our results to our various assumptions. For example, we assessed the impact of using different weights for birth year. Also, as previously mentioned, vaccination status was re-defined based on receipt of at least one and at least two doses. In addition, exposure and outcome ascertainment windows were altered to ascertain vaccine exposure in Grade 8 (since this is when most girls are vaccinated) and outcomes in Grades 9 to Grade 12. Furthermore, we conducted sensitivity analyses that controlled for neighbourhood income quintile, hepatitis B vaccination, and a recent sexual

health-related outcome (i.e., pregnancy, diagnosis of an STI, or cervical cancer screening) in addition to birth quarter.

Data management was carried out using SAS statistical software version 9.3 (SAS Institute Inc., Cary, North Carolina), and statistical analyses were executed using Stata version 13.1 (StataCorp, College Station, Texas).

RESULTS

We identified a cohort of 260,493 females entering Grade 8 between 2005 and 2008, 49.4% of who were eligible for publicly funded qHPV vaccination (Figure 6.1).

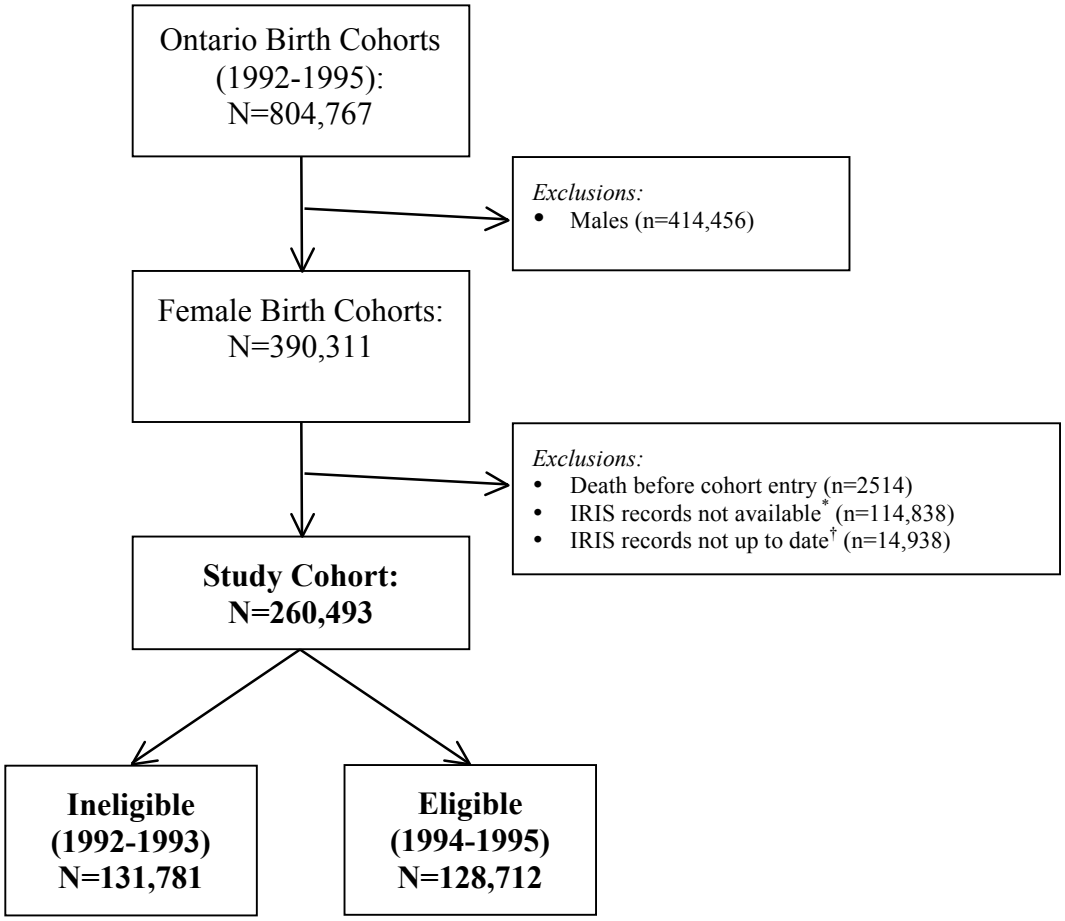

Figure 6.2 Cohort flow diagram

*At the time of this study, two of Ontario's 36 IRIS databases (representing approximately 22% of Ontario's population) had not yet been transferred to ICES and were therefore unavailable for use. IRIS records were also unavailable if the girl emigrated from Ontario before starting kindergarten or immigrated to Ontario after completing high school.

† A girl's IRIS record was defined as "up to date" if it had been modified 30 days before cohort entry or later. Otherwise, it was assumed the girl had moved out of our study area prior to cohort entry.

The mean age at cohort entry was 13.2 (standard deviation=0.3), and cohort members were followed for an average of 4.5 years (standard deviation=0.3). Eligible and ineligible groups were similar, with the possible exception of small differences in income quintile, hepatitis B vaccination history, and the prevalence of some medical conditions (Table 6.1).

Table 6.1 Baseline characteristics of study cohort

Characteristic	Percentage[*]	
	Ineligible (n=131,781)	**Eligible (n=128,712)**
Socio-demographics[†]		
Mean age at cohort entry (SD)	13.17 (0.28)	13.17 (0.28)
Birth Quarter		
January-March	24.3	24.2
April-June	26.1	26.1
July-September	25.7	25.8
October-December	23.9	23.9
Residency		
Urban	85.3	85.8
Rural	14.0	13.5
Missing[‡]	0.7	0.6
Income quintile		
1st (lowest)	16.6	15.0
2nd	18.4	17.8
3rd	20.6	21.1
4th	22.0	23.1
5th (highest)	21.4	22.1
Missing[‡]	1.0	0.9
Vaccination History[§]		
MMR[‖]	97.9	98.2
DTP[‖]	98.0	98.3

Hepatitis B[‖]	84.1	82.0
All three vaccines	83.0	81.1
Health Services Use[¶]**		
Hospitalizations		
None	98.0	98.2
≥1	2.0	1.8
Days (mean, SD)	7.4, 15.6	8.0, 18.2
Same-day surgeries		
None	97.7	97.8
≥1	2.4	2.2
Emergency department visits		
None	70.7	71.1
1	18.1	17.8
≥2	11.2	11.1
Outpatient visits		
0-1	25.0	25.8
2-5	22.6	22.8
6-12	25.1	24.5
≥13	27.4	26.9
Medical History		
Cancer[¶]	0.71	0.74
Mental health diagnosis[¶]	9.5	9.7
Sexual health indicators[¶††]	0.68	0.73
Down's syndrome[§]	0.48	0.53
Congenital malformations[§]	12.4	11.8
Intellectual disabilities[§]	0.72	0.73

SD = standard deviation; MMR = measles-mumps-rubella; DTP = diphtheria, tetanus, and pertussis
* Figures are expressed as percentages except where indicated otherwise
† At cohort entry
‡ Missing due to missing or inaccurate postal code
§ Between birth and cohort entry
‖ At least one dose
¶ In the two years preceding cohort entry
** Categories determine based on the frequency of the distribution
†† Composite of sexually transmitted infections, cervical dysplasia, Papanicolaou smears, and pregnancy

Of the 75,848 (29.1%) of cohort members who initiated the vaccination series during he program eligibility period, 87.5% (n=66,395) went on to receive three doses and were therefore classified as *vaccinated* in the primary analysis. As expected, eligible girls were considerably more likely to receive the vaccine (50.6%) than ineligible girls (0.92%), resulting in clear discontinuity in the probability of vaccination at the eligibility cut-off (Figure 6.3).

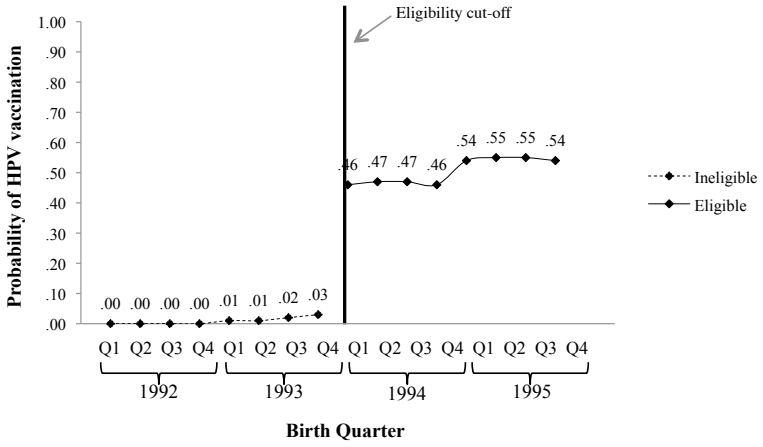

Figure 6.3 Probability of qHPV vaccine exposure according to birth quarter and program eligibility.
Q1: born January-March; Q2: born April-June; Q3: born July-September; Q4: born October-December

Just under 6% of cohort members had an outcome of interest during the primary outcome ascertainment period – 10,187 with pregnancies and 6,259 with a non-HPV STI (Table 6.2).

Table 6.2 Cumulative risk of outcomes according to qHPV vaccination program eligibility and birth year

Clinical indicator(s) of sexual behaviour	Frequency (percent)				
	Ineligible		Eligible		TOTAL (N=260,493)
	1992 (n=66,653)	1993 (n=65,128)	1994 (n=64,818)	1995 (n=63,894)	
Composite endpoint	4,203 (6.3)	4,032 (6.2)	3,801 (5.9)	3,405 (5.3)	15,441* (5.9)
Pregnancy	2,854 (4.3)	2,658 (4.1)	2,476 (3.8)	2,199 (3.4)	10,187 (3.9)
STIs	1,609 (2.4)	1,653 (2.5)	1,541 (2.4)	1,456 (2.3)	6,259 (2.4)

*This number is smaller than the sum of pregnancy and non-HPV-related STIs because some cohort members had both outcomes.

Figure 6.4, which depicts the risk of each endpoint by birth quarter, illustrates that girls born during the first quarter of each year (January to March) were consistently at higher risk of pregnancy and non-HPV-related STIs than girls born later in the year, demonstrating the importance of controlling for birth timing in the analyses.

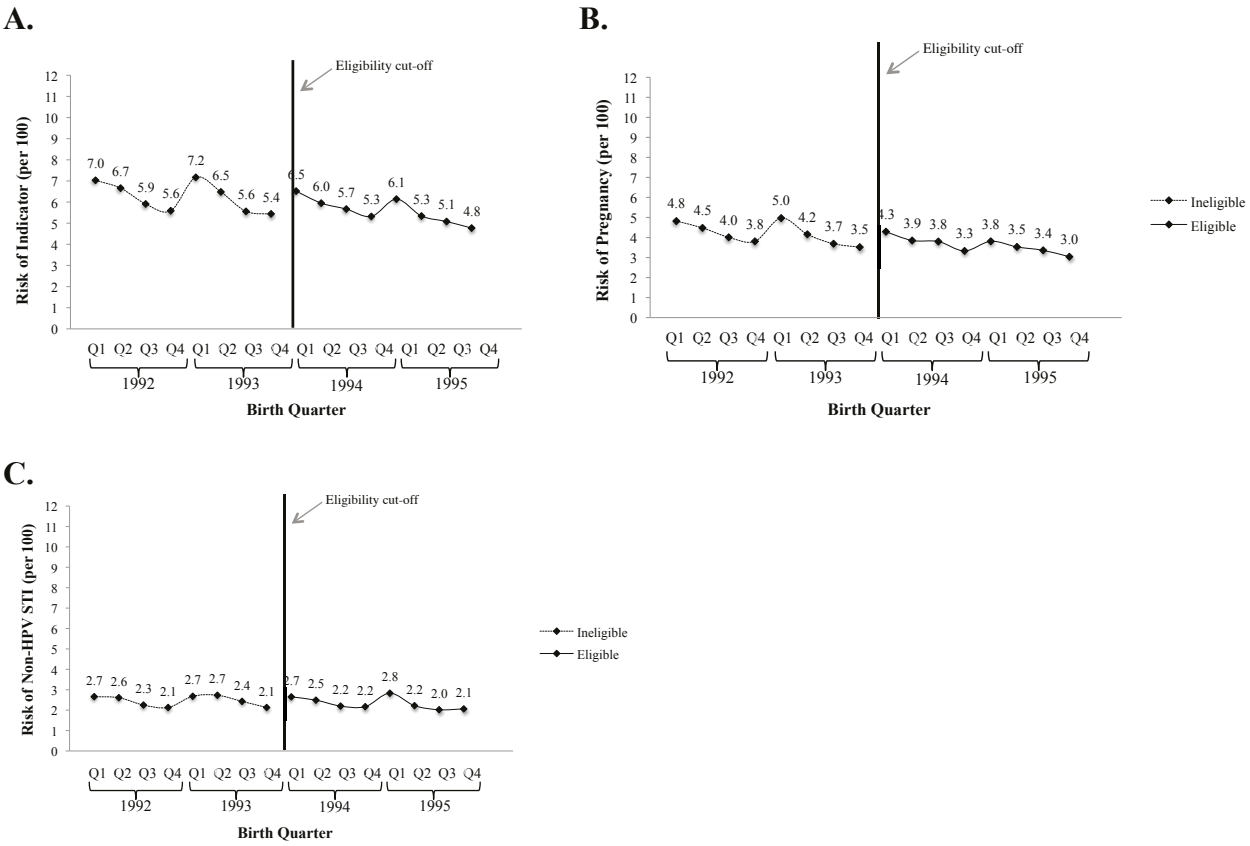

Figure 6.4 Risk of clinical indicators of sexual behaviour according to birth quarter and program eligibility.

A. Composite endpoint of pregnancy and non-HPV-related sexually transmitted infections (STIs); B. Pregnancy; C. Non-HPV-related sexually transmitted infections (STIs).

Q1: born January-March; Q2: born April-June; Q3: born July-September; Q4: born October-December

Indeed, no increase in risk was observed between qHPV vaccination and clinical indicators of sexual behaviour, as evidenced both on the absolute and relative scale: absolute risk difference (ARD) per 1000 girls = -0.61 (95% confidence interval [CI] -10.71 to 9.49), relative risk (RR) = 0.96 (95% CI 0.81 to 1.14). In addition, no discernable effect of program eligible on this outcome was identified: ARD = -0.25 (95% CI -4.35 to 3.85), RR=0.99 (95% CI 0.93 to 1.06) (Table 6.3). Findings were similar when pregnancy and non-HPV-related STIs were assessed separately. These results were unchanged after controlling for neighbourhood income quintile, hepatitis B vaccination, and history of sexual health-related outcomes, supporting the absence of confounding with the RDD approach. Our results were also robust to the other sensitivity analyses, including those using one and two doses to classify vaccination status.

Table 6.3 Impact of qHPV vaccination on clinical indicators of sexual behaviour*

Outcome	Absolute Risk Reduction per 1000 population (95% CI)	Relative Risk (95% CI)	Adjusted† Relative Risk (95% CI)
Vaccine Impact			
Composite endpoint	-0.61 (-10.71, 9.49)	0.96 (0.81, 1.14)	0.98 (0.84, 1.14)
Pregnancy	0.70 (-7.57, 8.97)	0.99 (0.79, 1.23)	1.00 (0.83, 1.21)
STIs	-4.92 (-11.49, 1.65)	0.81 (0.62, 1.05)	0.81 (0.63, 1.04)
Program Impact			
Composite endpoint	-0.25 (-4.35, 3.85)	0.99 (0.93, 1.06)	1.00 (0.93, 1.07)
Pregnancy	0.29 (-3.07, 3.64)	1.00 (0.92, 1.09)	1.01 (0.93, 1.10)
STIs	-2.00 (-4.67, 0.67)	0.92 (0.83, 1.03)	0.92 (0.83, 1.03)

*To address the effect of birth timing we observed, we utilized the entire bandwidth of data (i.e., all observations in the 1992 to 1995 birth cohorts) and included birth quarter as a covariate in the model. In all analyses, the birth cohorts closest to the cut-off (1993 and 1994) were weighting twice as heavily as those furthest from the cut-off (1992 and 1995).

†In this sensitivity analysis, we adjusted for neighbourhood income quintile, hepatitis B vaccination, and history of sexual health-related indictor in addition to birth quarter

INTERPRETATION

This large, population-based cohort study provides strong evidence that publicly funded HPV vaccination does not have a negative impact on clinical indicators of sexual behaviour among adolescent girls. In particular, we demonstrate that neither qHPV vaccination nor program eligibility increased the risk of pregnancy or non-HPV-related sexually transmitted infections among females aged 14-17 years.

To date, only one other study has reported on the association between HPV vaccination and clinical indicators of risky sexual behaviour. Bednarczyk et al.[69] compared sexual behaviour-related outcomes (i.e., contraceptive counseling, pregnancy, or STI testing or diagnosis) between vaccinated and unvaccinated females and reported that HPV vaccination was not associated with this outcome (ARD 1.6 per 100 person-years, 95% CI -0.03 to 3.24; RR 1.29, 95% CI 0.92 to 1.80). Since its publication in October 2012, this article has been frequently cited as evidence of a lack of association between qHPV vaccination and risky sexual behaviours; however, the small sample size (N=1,398) and corresponding wide confidence intervals resulted in uncertainty, especially since the point estimates were suggestive of a potential increased risk. Moreover, because this study directly compared vaccinated and unvaccinated individuals, the results may have been confounded by health behaviours affecting both the probability of the outcome and the decision to vaccinate. The few additional studies on HPV vaccination and sexual disinhibition have focused on perceptions of increased risk following vaccination, rather than actual risk[70,71] or have relied on self-reports of sexual behaviour,[72,73] which are notoriously vulnerable to the recall bias, response bias, and social desirability bias[74,75]; furthermore, all were based on small samples (range: 193-1243 females). Our study, which is based on a sample size of 260,493, addresses the uncertainty that remained, providing strong evidence against a meaningful association between HPV vaccination and clinical indicators of risky sexual behaviours.

Our findings are also consistent with studies assessing the impact of school-based sexual health interventions on adolescent behaviour. For example, empirical evidence indicates that programs aimed at improving access to condoms and providing sexual health education for teens do not increase sexual activity and, among individuals who are or become sexual active, actually results in less risky behaviours (e.g., delayed age of sexual initiation, increased use of contraception).[68,143-146] Akin to the controversy surrounding the HPV vaccine, such interventions

have faced heated debate and strong opposition. Our study contributes to the body of evidence that sexual health interventions do not promote risky sexual behaviour.

We also observed that indicators of sexual activity were highest among girls born earliest in calendar year (i.e., oldest in their birth cohort) and lowest among girls born latest (i.e., youngest in their birth cohort), despite equal follow-up time. This effect was present for indicators that occurred in the two years before cohort entry, as well as those that occurred during our outcome ascertainment period, and was relatively consistent across birth cohort. These findings are in line with previous studies that found season of birth and/or relative age are associated with a number of outcomes related to health, athletic success, educational achievements, and income, and mortality.[139-141]

A major advantage of our study is the use of an analytic approach specifically designed to assess the effects of policy changes in a way that minimizes confounding bias. In particular, by exploiting the quasi-experimental situation that arose when a clearly defined population was offered HPV vaccination at a specific point in time, we were able to avoid the potential for bias that arises when directly comparing vaccinated and unvaccinated individuals.[79,81] Circumventing this type of bias is particularly important when studying factors related to risky sexual behaviour since these outcomes are likely strongly associated with the same unmeasured and unidentifiable health beliefs and behaviours that influence the decision to receive the qHPV vaccine.[76,85-87] Theoretically, residual confounding could have arisen in the presence of an intervention that differentially affected eligibility groups, such as a sexual health education programs being paired with the HPV vaccination program. However, no such program was implemented in Ontario and, to the best of our knowledge, any sex education provided through the Ontario school system was offered similarly across birth cohorts. Another advantage of using the RDD is that it permits the assessment of the population-level impact of the vaccination program (intention-to-treat effect), in addition to the vaccine-level impact, which is particularly valuable given the population-based nature of so many HPV vaccination programs. Moreover, the consistency of our results between these two measures provides additional support for our conclusions. In addition, an earlier study using the same study population and design reported a statistically significant protective effect of the qHPV vaccine and Ontario's Grade 8 vaccination program on the risk of cervical dysplasia[150], demonstrating the ability of this design to detect meaningful differences when they exist. Another strength of this study is the use of population-based databases, which enabled us

to identify a large cohort of females with little concern for recall bias or selection bias. Also, since losses to follow-up would only occur secondary to emigration from Ontario, this proportion is expected to be extremely low and to be non-differential between eligible and ineligible girls. Finally, our study benefits from validated qHPV vaccination data, which greatly minimized the potential for exposure misclassification.

Conversely, a limitation of our study is that our outcome measures have not been validated. Of particular concern is the potential impact of misclassification on our measure of non-HPV-related STIs. Specifically, as there is no specific diagnostic code for anogenital warts in the OHIP database, physicians may code for "other venereal disease" when diagnosing anogenital warts. Since both the vaccine and the program are intended to reduce the risk of AGW, we would expect this source of misclassification to bias results toward a protective effect. Indeed, this source of bias could explain why the point estimate for non-HPV-related STIs was slightly below 1.0. Consequently, we believe that pregnancy, which is unaffected by this potential source of bias, is a valid clinical indicator of risky sexual behaviour. Another limitation is that we did not have direct measures of sexual behaviour, such as number of sexual partners, age of sexual onset and condom use, which have been the focus of public controversy. Instead, our study used STIs and pregnancy as clinical manifestations of disinhibition, as these represent direct measures of the health *consequences* of risky sexual behaviour (e.g., not using condoms). While these two outcomes do not encompass all facets of disinhibition, there are nonetheless objective measures of certain manifestations of risky sexual behaviour that are not susceptible to the biases that plague direct measures of sexual behaviour, such as selection bias from non-participation, self-reporting bias, and social desirability bias.[74,75] Moreover, from a public health perspective, changes in pregnancy and STIs are arguably of equal, if not greater, importance given their direct impact on the health of adolescents and use of healthcare services.

The generalizability of our results to other populations and jurisdictions is not yet known. However, the consistency of our findings with the existing evidence discussed above provides support for the absence sexual disinhibition following HPV vaccination in a range of populations. In addition, since the quadrivalent vaccine protects against anogenital warts in addition to cervical dysplasia, it is reasonable to assume the potential for sexual disinhibition could be greater for the quadrivalent vaccine than the bivalent vaccine; therefore, our results are likely generalizable to the bivalent HPV vaccine and bivalent HPV vaccination programs.

CONCLUSION

This large, population-based cohort study provides strong evidence that HPV vaccination does not have a negative impact on clinical indicators of risky sexual behaviour among adolescent girls. These findings suggest fears of increased risky sexual behaviour following HPV vaccination are unwarranted and should not be a barrier to vaccinating at a young age. The results of this study can be used by physician, public health providers, and policy makers to help address public and parental concerns about HPV vaccination and promiscuity.

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Authors' Contributions

LMS was involved in acquiring study data, played a major role in the conception, design, and interpretation of the study, carried out the statistical analyses, and drafted the manuscript. ECS and JSK played a major role in the conception, design, analysis, and interpretation of the study and critically reviewed the manuscript. LEL played the principal role in acquiring the study data, played a major role in the conception, design, analysis, and interpretation of the study, and critically reviewed the manuscript. All authors were involved in obtaining funding for this study, have given final approval of the manuscript, and agree to be accountable for all aspects of the work.

Competing Interests

The authors have no competing interests to declare.

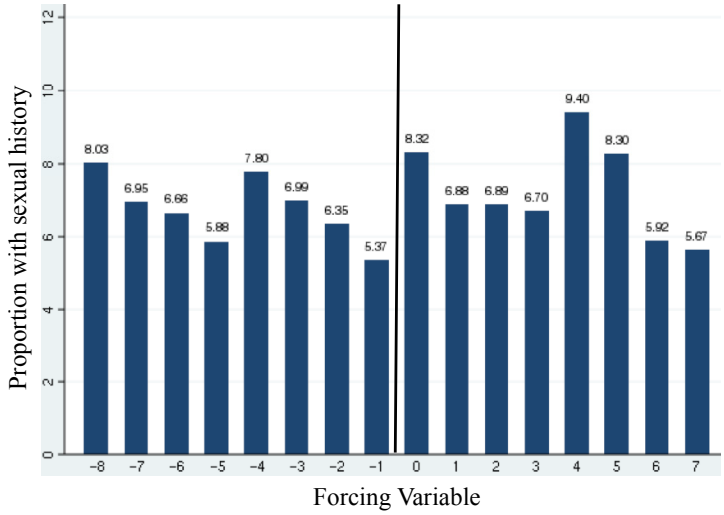
6.2.1 APPENDIX 6-A: Operationalization of the forcing variable

	Grade 8 school year	Birth Year	Birth Year Quarter	Value of Forcing Variable
Ineligible	2005/06	1992	Mar 1992 – Jan 1992	-8
			Jun 1992 – Apr 1992	-7
			Sept 1992 – Jul 1992	-6
			Dec 1992 – Oct 1992	-5
	2006/07	1993	Mar 1993 – Jan 1993	-4
			Jun 1993 – Apr 1993	-3
			Sept 1993 – Jul 1993	-2
			Dec 1993 – Oct 1993	-1
Eligible	2007/08	1994	Jan 1994 – Mar 1994	0
			Apr 1994 – Jun 1994	1
			Jul 1994 – Sept 1994	2
			Oct 1994 – Dec 1994	3
	2008/09	1995	Jan 1995 – Mar 1995	4
			Apr 1995 – Jun 1995	5
			Jul 1995 – Sept 1995	6
			Oct 1995 – Dec 1995	7

6.2.2 APPENDIX 6-B: Outcome Definition

Outcome		OHIP codes	ICD-10 codes	Description
Clinical indicators of sexual behaviour	**Non-HPV-related STIs**	097, 098, 099	A51-A60, A638, A64	Syphilis, gonococcal infections, or "other" venereal diseases (e.g., herpes, chlamydia, trichomoniasis)
	Pregnancy	632-635, 640-646, 650-653, 656, 658, 660-662	000-008, 010-048, 060, 080-084	Pregnancy, spontaneous abortion, therapeutic abortion, or delivery

6.2.3 APPENDIX 6-C: Sexual history* by the forcing variable



* Defined based on pregnancy, sexually transmitted infection, or cervical cancer screening in the two years before cohort entry

6.3 Additional Results and Discussion

All additional analyses performed for cervical dysplasia and AGW (discussed in section 5.3) were also performed for pregnancy and non-HPV-related STIs. In this study, results were also robust to changes in the exposure definition and time window (Appendix F). For example, the relative risk of the composite endpoint was 0.96 (95% CI 0.82, 1.11) in the primary analysis, 0.96 (95% CI 0.82, 1.12) when girls who only received two doses in Grades 8-9 were also classified as exposed, and 0.93 (95% CI 0.79,1.10) when the exposure status was ascertained in Grade 8 and outcomes in Grades 9 through 12. Results were also robust to various other sensitivity analyses (Appendix G). As with cervical dysplasia and AGW, unadjusted estimates of vaccine and program impact provided additional evidence of the need to account for the confounding effect of birth timing discovered in Manuscript 1. Furthermore, estimates of program impact and vaccine impact were similar in the full cohort compared with the sub-cohort for whom Grade 8 school year was verified, suggesting the effect of any misclassification of school grade was negligible (Appendix H). Results were also robust to the different methods of estimating program impact (Appendix D) and vaccine impact (Appendix I).

CHAPTER 7: DISCUSSION

7.1 Summary of Research

The goal of my thesis work was to assess the effects of Ontario's publicly funded, school-based HPV vaccination program on adolescent health outcomes. The first challenge was to determine an analytic approach that would allow for causal inference in this setting. Since the regression discontinuity design (RDD) was conceptually optimal, the first objective of this thesis was to assess whether the assumptions of the RDD were met in this study context. Once the assumptions of the RDD has been verified, the second objective was to apply the RDD to assess the effectiveness of the HPV vaccine and of Ontario's Grade 8 HPV vaccination program on reducing cervical dysplasia and anogenital warts among adolescent girls. Finally, to evaluate the potential unintended effects of HPV vaccination, the RDD was used to determine whether HPV vaccination had an impact on clinical indicators of sexual behaviour in this population.

In the first manuscript entitled, "Strategies for Evaluating the Fundamental Assumptions of the Regression Discontinuity Design: A Case Study Using a Human Papillomavirus Vaccination Program", background on the RDD and a discussion of its potential applicability to epidemiologic questions are provided. My study of the effect of HPV vaccination on cervical dysplasia is used as a worked example of how the four fundamental assumptions of the RDD can be assessed. Strategies are provided so researchers can apply these concepts to their own study questions. This manuscript helps contribute to the advancement of epidemiologic methodology as it helps introduce a new design (i.e., the RDD) to the epidemiologic literature. Furthermore, the results of these analyses had important implications for how the RDD analyses were executed in this thesis. In particular, while the assumptions of the RDD were generally met, I identified an effect of birth timing in which girls born earliest in a calendar year (January to March) were considerably more likely to have been previously sexually active (as indicated by increased incidence of pregnancy, cervical cancer screening, and sexually transmitted infections) than their grade-matched peers. As this effect had the potential to confound the effect estimates, I made a number of adjustments to the standard RDD analyses to accommodate this unique setting. Overall, the findings from this manuscript highlighted the importance of assessing the assumptions of the RDD prior to executing the analyses and, more broadly, pointed to the need for thorough descriptive analyses before the execution of any study.

In the second manuscript entitled, "The Impact of Human Papillomavirus (HPV) Vaccination on Cervical Dysplasia and Anogenital Warts Among Adolescent Girls: The Ontario Grade 8 HPV Vaccine Cohort Study", the RDD was applied to assess how effective Ontario's HPV vaccination program has been in its goal to reduce the burden of cervical dysplasia (a precursor to cervical cancer) and anogenital warts (AGW). The application of the RDD to this study question represents a significant methodological advancement over previous studies, which used more traditional methods of analysis (e.g., Cox proportional hazards) that directly compared vaccinated and unvaccinated populations and were therefore vulnerable to irremediable confounding bias. The RDD also allowed me to assess the intention-to-treat effect of vaccination for the first time outside of clinical trials, thereby yielding an estimate of the program impact or population-level effect of vaccination. The findings revealed that, despite relatively low HPV vaccine coverage in Ontario (~50%), the program has caused statistically significant reductions in cervical dysplasia among females aged 14-17 years. Reductions in risk attributable to the vaccine were of even greater magnitude. Results were also suggestive of early decreases in anogenital warts. Although the effects on AGW were not statistically significant, this is likely due to the low baseline incidence of disease in this study population (i.e., lack of statistical power) rather than to an actual absence of effect. In fact, relative estimates of effect were of even greater magnitude for anogenital warts than for cervical dysplasia, which is exactly what would be expected based on results from clinical trials. These findings have important public health implications as they provide the first evidence of the success of publicly funded HPV vaccination in Canada and provide evidence to support the benefits of vaccinating at a young age.

In the third and final manuscript entitled, "The effect of human papillomavirus (HPV) vaccination on clinical indicators of sexual behaviour among adolescent females: The Ontario Grade 8 HPV Vaccine Cohort Study," the RDD was applied to address the controversial topic of the effects of HPV vaccination on sexual behaviour using two clinical indicators of sexual behaviour (i.e., pregnancy and sexually transmitted infections) as proxies for this outcome. All absolute risk estimates were slightly below 0 and none were statistically significant, providing no evidence of an increase in risk attributable to the vaccine or the vaccination program. Similarly, the relative risk estimates for vaccine and program impact were 0.98 and 1.00, respectively, providing further support for an absence of effect. It is highly unlikely the null effect is attributable to a lack of statistical power, as the number of outcomes was more than six times

greater for this outcome than for cervical dysplasia. As previous studies on this controversial topic have been weak and inconclusive, these findings provide important information physicians and public health workers can use to reassure parents that fears of increased risky sexual behaviour following HPV vaccination are unfounded.

7.2 Limitations

A number of limitations of the three thesis studies are presented in each of the three manuscripts (Chapters 4-6). Although the limitations of the outcome measures are introduced therein, given their important implications, they are given additional attention in this section.

As the outcomes of interest in this thesis have not been validated, a major concern was outcome misclassification. As previously mentioned, in an effort to address this issue for cervical dysplasia and AGW, three definitions of each outcome were created in consultation with Drs. Aisha Lofters and Michael Schwandt, both of whom have extensive clinical and research experience in sexual health. In particular, "broad", "possible", and "probable" definitions were created to reflect increasing levels of outcome specificity, with the potential drawback of decreasing levels of sensitivity. To illustrate, the broad definition of anogenital warts included treatment of any type of warts provided there was a corresponding diagnosis related to the anogenital region. This definition was incorporated because, according to our experts, physicians often use the generic code for warts when diagnosing anogenital warts. However, in theory, a girl presenting with a plantar wart on her foot and a urinary tract infection may have been a case in the "broad" definition of anogenital warts. Since this type of misclassification likely occurred non-differentially between eligibility groups, it would have biased results toward the null. In contrast, the "probable" definition of AGW misses cases of AGW that were coded using the generic definition of warts. Although this source of misclassification would also be non-differential between eligibility groups, its impact is dependent on the effect of vaccination. Therefore, it would likely underestimate the absolute risk reductions, but not have an effect on the relative risks. The value of using the three definitions was reflected in the results from Chapter 5 (Table 5.3). For example, as expected, the relative estimates for the broad definition of AGW are much closer to the null than those for the possible and probable definitions, which tend to be similar, suggesting the broad definition was misclassified. On the other hand, the absolute differences for the broad and possible definitions were similar, suggesting fewer missed cases

with these definitions. Taken together, these findings suggest the "possible" definition for AGW is the most valid. The relative risk of dysplasia was also closest to the null for the broad definition, but there were only slights variations in estimates between definitions, suggesting less misclassification among definitions of dysplasia. The absolute difference for the probable definition, however, was considerably closer to the null than the broad and possible definitions, suggesting a high proportion of missed case with this definition. Accordingly, the broad or possible definitions of dysplasia are likely the most accurate. Undoubtedly, this and future studies would benefit from validating the definitions of cervical dysplasia and AGW. Nevertheless, the use of varying algorithms provided important insight into the definitions that was crucial to the appropriate interpretation of study results.

Outcome measures of pregnancy and STIs had also not been validated; however, given the nature of the coding for these outcomes, creating a range of outcome definitions did not seem beneficial. It was important that the primary measure be the composite endpoint as this provided the most statistical power and a more comprehensive proxy for sexual behaviour. However, to gain additional insight into the definitions use, pregnancies and STIs were also assessed separately. Indeed, as discussed in Chapter 6, the individual assessments revealed that the measure of STIs likely also included AGW, as indicated by the protective effect estimate.

Given the public health implications of the null findings in Manuscript 3, it is also important to consider the possibility that the results reflected a Type II error. There are two theoretical causes of this type of error in this study – outcome misclassification or insufficient statistical power. First, as demonstrated with the broad definition of AGW applied in Manuscript 2, if outcomes unrelated to sexual behaviour *and* HPV vaccination had been included in the definition, the measures of effect would have been biased toward the null. However, given the specificity of codes used to ascertain this outcome, it is difficult to envision scenarios in which such bias would have arisen. Second, more than six times the number of outcomes of pregnancy and STIs were identified compared with outcomes of cervical dysplasia. Since a statistically significant effect was observed for the latter, it is highly unlikely the non-significant effects observed for indicators of sexual behaviour were attributable to statistical imprecision.

It is also important to note that all outcomes studied in this thesis were restricted to detected cases. In particular, as data were obtained entirely from administrative health databases, only cases that presented for medical care were identified. Given the psychological morbidity

associated with AGW, many or most people with visual AGW seek treatment[22] and would therefore have been ascertained in this study; nevertheless, cases that did not present went undetected. In addition, some warts, such as those that present in the vagina, may go undetected even by the afflicted individual. Similarly, under-ascertainment of cervical dysplasia was expected as not all girls who receive results of an abnormal smear seek follow-up.[151] Importantly, this under-ascertainment would have under-estimated the true absolute effects of the vaccine and the program. While it would have been ideal to study all cases of dysplasia and AGW, since detected cases are the only outcomes that affect the healthcare system, they are arguably those of greatest public health interest.

It is also necessary to consider the potential for detection bias in this study. Specifically, it can be argued that the decrease in cervical dysplasia observed was a result of decreased cervical cancer screening among vaccinated individuals. However, given the highly publicized need for continued cervical cancer screening following HPV vaccination, this is unlikely.[152] Furthermore, until recently, a high proportion of physicians required that their patient receive a Pap test in order to receive a prescription for the oral contraceptive pill,[153] leaving little choice to the patient. Conceivably, changes in cervical cancer screening guidelines could have also impacted the detection of dysplasia. In particular, although it had long been common practice in North America to begin screening for cervical cancer at the start of sexual activity (e.g., upon request for birth control), in 2012 Cancer Care Ontario changed its guidelines to recommend screening be delayed until at least 21 years of age. Since evidence consistently suggests physicians are reluctant to change practice based on new guidelines,[154] especially when such practices are as ingrained as early cervical cancer screening, it is unlikely changes in guidelines alone would have had a major impact on screening. Conversely, on January 1, 2013, the OHIP reimbursement schedule changed in support of these guidelines, meaning physicians are no longer paid for Pap tests administered to girls under the age of 21. This change may have dramatically influenced practice; however, study follow-up for the 1992, 1993, and 1994 birth cohorts terminated prior to this date, meaning the discontinuity observed between the 1993 and 1994 birth cohorts could not have been influenced by this change. Furthermore, as the new reimbursement policy affected only three months of the outcome ascertainment for the 1995 birth cohort, its impact was likely negligible.

Another limitation to the outcome data is that we did not have access to information on cervical cytology to identify the stage of the dysplasia. Given the young age of the study cohort and the long latency between HPV infection and cervical cancer,[47] it is fair to assume the vast majority of detected cases represent atypical squamous cells or low-grade squamous intraepithelial lesions (i.e., mild dysplasia). However, cytology data would be needed confirm this. Gaining access to such data will become increasingly important as cohort members age, as it will provide more insight into the likely impact of HPV vaccination on cancer outcomes.

Despite the various limitations of our outcomes data, the results this thesis were consistent with what had been expected based on biological plausibility, clinical trial data,[48,49] and previous observational evidence,[51-54,62,69,144] suggesting the impact of potential biases were minimal. Consequently, the findings of this thesis are nonetheless of important clinical and public health value.

7.3 Implications of Research

The Regression Discontinuity Design

A major contribution of this thesis is its use of the regression discontinuity design. Importantly, the first manuscript of this thesis (section 4.2) helps introduce the RDD to the epidemiologic literature, where it is currently relatively unknown. In this manuscript, an overview of the design is presented and specific strategies are provided that will enable other researchers to assess whether their research questions are suited to the RDD analyses. In addition, in the second and third manuscripts (Chapters 5 and 6), the RDD is applied to important epidemiologic questions in a way that helps highlight its value and flexibility. As a result of these three papers, I hope other researchers will consider the RDD as a potential approach to assessing their questions on the impact of policy changes or interventions.

This thesis also helped to broaden the functionality of the RDD. In particular, certain modifications and extensions were made to the standard RDD analyses to optimize its value for health research. For example, the traditional linear regression-based analyses of the RDD were applied to dichotomous outcomes, thereby helping to dispel the myth that such analyses should be applied only to continuous outcomes.[113,114] Furthermore, while RDD analyses traditionally estimate absolute measures of effect, I used the design to estimate relative measures as well. To the best of my knowledge, few RDD studies have reported relative risks,[120,122,123] and none have

done so in the context of a two-stage/fuzzy design. These extensions may be crucial to helping the RDD gain traction in epidemiology, as dichotomous outcomes are often the outcomes of interest in health research. At this point, additional research is needed to promote these notions within the RDD literature. For example, information on how and when to apply the standard –rd– program in Stata to dichotomous outcomes may be beneficial; modifications to this program may be required to accommodate a broader range of situations. Furthermore, though a standard two-stage log binomial approach was suitable for this study context, alternative approaches of estimating relative risks for the fuzzy RDD may also be valid, such as generalized method of moments and g-estimation. Accordingly, studies are needed to investigate the relative advantages and disadvantages of the various potential approaches to estimating relative risks in different RDD settings.

Public Health and Economic Considerations

This thesis provides important evidence that, despite relatively low HPV vaccine coverage in Ontario, the vaccination program is already demonstrating reductions in the burden of cervical dysplasia and anogenital warts. These reductions likely have important health and economic benefits for Canadians and the Canadian healthcare system.

As previously mentioned, it is likely that most cases of dysplasia detected represent mild dysplasia. As the vast majority of these cases (>90%) clear without clinical sequelae,[47] their prevention may be perceived as inconsequential. However, it is important to note the impact even one abnormal Pap test result can have on both the individual and the healthcare system. For example, Drolet et al.[155] demonstrated that receiving news of an abnormal Pap test had a clinically meaningful negative impact on symptoms of anxiety among Canadian females for up to 12 weeks. Studies have also shown that positive Pap results are associated with feelings of worry and depression and can have an impact on the daily activities, self-esteem, sexual interest, and sleep patterns of those afflicted.[156-158] Although these symptoms are generally acute, they are undeniably disruptive to the well being of young girls. Furthermore, though the true annual cost of cervical screening in Canada is unclear, there is no doubt the cost and physician power associated with cytology, colposcopy, and follow-up care for abnormal Pap results is significant.[159-161] Accordingly, reductions in dysplasia help free up both healthcare dollars and physician time. Although the ultimate goal of the HPV vaccination programs is to prevent

cervical cancer, these intermediate benefits should not be undervalued.

The psycho-social, psycho-sexual, and economic burden of anogenital warts has been well documented.[19,20,23-25] Based on the literature, it is expected the reductions in AGW observed in this thesis have corresponded with prevention of the anxiety, stress, pain, discomfort, and negative self-image associated with the diagnosis and treatment of anogenital warts. Furthermore, based on the estimated cost per episode of AGW among women in British Columbia[20], each case of AGW prevented is expected to correspond with healthcare savings of over $200.

While the potential psychological and economic benefits of decreases in dysplasia and AGW presented here appear promising, they undoubtedly provide an incomplete picture of the impact of HPV vaccination. In order to assess the true value of HPV vaccination for adolescents and the healthcare system, studies are needed to qualify and quantify the benefits observed in this thesis relative to the resources required to deliver the HPV vaccination program.

Implications for Policy Makers, Physicians, and Parents

This thesis provides strong evidence that HPV vaccination in Ontario is decreasing cervical dysplasia and AGW and is *not* increasing risky sexual behaviour. Although these findings are likely not surprising to public health officials or physicians, they have broad applications. Furthermore, the complementary nature of these findings is valuable as it simultaneously addresses two major public concerns about the intended and unintended effects HPV vaccination for young girls.

The findings that the intended benefits of the vaccination program are being realized at the program/population level are particularly important to places like Ontario, where concerns over low HPV vaccine coverage have threatened the perceived value of the program. Accordingly, public health officials can use these findings to support the continuation of publicly funded, school-based HPV vaccination and to guide future HPV vaccine policy decision-making. Furthermore, both public health workers and physician can use the findings on vaccine impact in their efforts to educate the public about the benefits of HPV vaccination observed in the real world, as well as to support arguments against delaying vaccination until girls are older. The additional finding that HPV vaccination is not having a negative impact on clinical indicators of sexual behaviour should be reassuring to public health officials since increases in these endpoints

would have undermined the value of HPV vaccine programs and would likely have required that additional programs, such as sexual health education programs, be implemented alongside HPV vaccine programs. Healthcare providers can also use these findings when speaking with parents and guardians who have concerns over sexual disinhibition following HPV vaccination.

Combined, the findings in Manuscripts 2 and 3 can be used in efforts to promote HPV vaccination in Ontario and across Canada, with the aim of increasing acceptance and use of the vaccine and the vaccination programs. Since increased coverage of the vaccine plays a big part in optimizing the health benefits and cost-effectiveness of HPV vaccination, the dissemination of these results is of particular importance.

Optimizing the Program's Benefits

While increasing use of the HPV vaccine would help optimize the benefits of Ontario's HPV vaccination program, alternative strategies to improve program effectiveness should also be considered. For example, studies are needed to identify whether certain subgroups are benefitting less from this program, as disparities may exist despite the publicly funded, school-based nature of the vaccination program. In fact, an earlier study indicated that while uptake of the HPV vaccine did not differ by income status, series completion was lowest among girls of low-income,[85] suggesting subgroup analyses might reveal that the impact of the program is also lowest in this population. This is particularly important as women of low income report greater sexual activity and lower cervical cancer screening[162] and are at increased risk of cervical cancer.[163,164] As such, public health strategies that target these vulnerable girls may be required to ensure the early benefits in cervical dysplasia observed here ultimately translate into the desired reductions in cervical cancer.

Future Policy Decision-Making

Studies on the cost-effectiveness of HPV vaccination to date have focused on clinical trial data and hypothetical scenarios.[160,165,166] As the results of this study provide real-world information on HPV vaccine coverage and corresponding reductions in HPV-related illnesses, they should be used in future economic and policy analyses of HPV vaccine programs to help guide policy decision-making. For example, currently a major topic of debate surrounding the HPV vaccine is whether provincial/territorial HPV vaccination programs should be expanded to

also include boys. As Alberta and Prince Edward Island have recently confirmed they will begin offering HPV vaccination to boys, there is increased pressure on other provinces to follow suit. An updated cost-effectiveness analysis of this topic may help policy makers come to more informed decisions about this and other HPV vaccine policy issues.

Continued Surveillance

This thesis provides strong evidence of the early health effects of HPV vaccination in Canada's most populous province. While these findings are promising, the success of any vaccination program relies on continued monitoring and surveillance of the intended and potential unintended effects of the policy;[167] therefore, we must continue to study the effects of Ontario's Grade 8 HPV vaccination program over the years. Furthermore, while the findings of this thesis are likely generalizable to other provinces/territories, they should be confirmed. Indeed, cross-country comparisons may help illuminate the strengths and limitations of the various HPV vaccine programs, thereby helping improve HPV vaccine policy across the country.

7.4 Conclusion

This thesis provides the first evidence of the health effects of Canada's publicly, school-based HPV vaccination program. In particular, these studies suggest that Ontario's program is effectively reducing the incidence of cervical dysplasia and anogenital warts in the population and is not inadvertently leading to an increase in teen pregnancies or non-HPV related sexually transmitted infections. Taken together, these results can be used by physicians and public health officials to help guide future HPV vaccine decision-making and to address parental concerns over the real-world effects of HPV vaccination. In turn, this may help improve HPV vaccine coverage, which is important for maximizing the health benefits and cost-effectiveness of this vaccine. Additional research is needed to promote continued success of HPV vaccination in Canada.

APPENDIX A: Description of Databases

Database	Description	Original Source	Data elements	Diagnostic record
RPDB: Registered Persons' Database	Basic information about anyone who has ever been covered by Ontario health insurance	MOHLTC	• Demographic information (e.g., sex, date of birth, income quintile) • Geographic information (e.g., city/town, urban/rural) • Data of death (if applicable)	• N/A
OHIP: Ontario Health Insurance Plan	Record of services from health care providers that claim under OHIP	MOHLTC	• Clinical data (e.g. diagnoses, procedures) • Administrative data (e.g. date of admission, fee paid) • Physician information (e.g., specialty)	• 1 diagnosis per visit • 1 fee code per visit • 3-digit diagnosis code (variant of ICD-9) • physician specialty
DAD: Discharge Abstract Database	Record on inpatient hospital activity	CIHI	• Clinical data (e.g. diagnoses, procedures) • Administrative data (e.g. date of admission, date of discharge)	• 1-25 diagnoses per admission • 3-4 character ICD-9 codes (before 2002) • 3-4 character ICD-10 codes (2002 onward)
SDS: Same-Day-Surgeries	Record on same-day surgeries	CIHI	• Clinical data (e.g. procedures) • Administrative data (e.g. date of admission, date of discharge)	• 1-16 diagnoses per admission • 3-4 character ICD-9 codes (before 2002) • 3-4 character ICD-10 codes (2002 onward)
NACRS: National Ambulatory Care Reporting System	Record on patient visits to emergency departments	CIHI	• Clinical data (e.g. diagnoses, procedures) • Administrative data (e.g. date of admission)	• 1-10 diagnoses per consultation • 3-4 character ICD-9 codes • 3-4 character ICD-10 codes
IRIS: Immunization Record Information System	Record of the immunizations of school-aged children	LPHAs*	• Demographic information (e.g. health region) • Vaccine data (e.g., type, date)	• N/A

MOHTC: Ministry of Health and Long-Term Care; CIHI: Canadian Institutes of Health Information; LPHA: Local Public Health Agency; ICD: International Classfication of Diseases; N/A: Not applicable

*At the time of this study, IRIS data from 34 of Ontario's 36 LPHAs were available for our use.

APPENDIX B: Description of Baseline Characteristics

CHARACTERISTIC	DESCRIPTION
Sociodemographics	
Age at cohort entry	Age on September 1 of Grade 8. Defined based on true date of birth.
Birth Quarter	Indicates time of birth within calendar year. Categorized based on birth in January 1 – March 31, April 1 – June 30, July 1 – September 31, or October 1 – December 31.
Urban/Rural residency	Indicates urban/rural residency. Defined using postal codes and 2006 Census to identify residency in area of >10,000 people. Obtained from the RPDB postal year (pstyear) file.
Income quintile	Provincial neighbourhood income quintile. Defined based on postal codes and 2006 Census. Obtained from the RPDB postal year (pstyear) file.
Vaccine History	
Measles-mumps-rubella (MMR)	Receipt of at least one dose of MMR before cohort entry
Diphtheria, tetanus, pertussis (DTP)	Receipt of at least one dose of DTP before cohort entry
Hepatitis B	Receipt of at least one dose of hepatitis B before cohort entry
All of the above	Receipt of at least one dose of hepatitis B *and* MMR *and* DTP before cohort entry
Healthcare Use	
Emergency department (ED) visits	Categories created based on frequency distribution of number of ED visits in the two years before cohort entry. Ascertained based on unique episodes of care in NACRS.
Hospitalizations	Categories created based on frequency distribution of number of hospitalization in the two years before cohort entry. Ascertained based on unique episodes of care in CIHI-DAD where source= 'I'.
Length of inpatient stay	Among those with at least one hospitalization, number of days spent hospitalized in the two years before cohort entry. Ascertained based on unique episodes of care in CIHI-DAD where source= 'I'.
Same-Day-Surgeries (SDS)	Categories created based on frequency distribution of number of same-day surgeries in the two years before cohort entry. Ascertained based on unique episodes of care in CIHI-DAD where source= 'S'.
Outpatient physician	Categories created based on frequency distribution of number of unique records in OHIP in the two years before cohort entry that

visits	were not attributable to hospitalization, ED visits, or SDSs.
Medical History	
Recent cancer	Any code relating to a cancer diagnosis in the two years before cohort entry. Note: These can represent prevalent cases.
Recent mental illness	Any code relating to a mental health diagnosis in the 2 years before cohort entry. Note: These can represent prevalent cases.
Recent sexual health-related outcome	Composite endpoint of anogenital wart, non-HPV-related STIs, cervical dysplasia, Pap smears, or pregnancy in the two years before cohort entry
Down's syndrome	Any code relating to Down's syndrome between birth and cohort entry
Congenital anomalies	Any code relating to congenital anomalies (excluding chromosomal anomalies) between birth and cohort entry
Intellectual disabilities	Any code relating to intellectual disabilities between birth and cohort entry

RPDB: Registered Persons Database; MMR: measles, mumps, rubella; DTP: diphtheria, tetanus, pertussis; NACRS: National Ambulatory Care Recording System; CIHI: Canadian Institutes of Health Information; DAD: Discharge Abstracts Database; ED: Emergency Department; I: inpatient; SDS: Same-Day Surgery; S: same-day surgery; OHIP: Ontario Health Insurance Plan

APPENDIX C: Operationalization of Medical History

Condition	OHIP code	ICD-10 code	ICD-9 code	Description
In the two years before cohort entry				
Cancer	140-209, 230-239	C00-C97	N/A	Malignant neoplasms
Mental health-related condition	295-314	F10-F63	N/A	Mental health disorders, including affective disorders (excludes mental retardation and delays in development)
	078, 079, 099, 616, 622, 629, 999	A630	N/A	Anogenital warts: Diagnosis of venereal warts
	Z117, Z733, Z736, Z769, Z549, Z758	N/A	N/A	Anogenital warts: Treatment for anal or vulvar condylomata
Indicator of sexual history	097, 098, 099	A51-A60, A638, A64	N/A	Non-HPV-related STI: Syphilis, gonococcal infections, or "other" venereal diseases (e.g., herpes, chlamydia, trichomoniasis)
	632-635, 640-646, 650-653, 656, 658, 660-662	O00-O99	N/A	Pregnancy: Pregnancy, spontaneous abortion, therapeutic abortion, or delivery
Papanicolaou test	A203, A204, A205, E430, G365, G394, Z730, Z731	N/A	N/A	Cervical cancer screening
Between birth and cohort entry				
Down syndrome	758	Q90	7580	Down Syndome
Congenital anomalies	741-756	QOO-Q89	740-757	Congenital malformations and deformations, excluding chromosomal anomalies
Intellectual Disabilities	319	F70-F79	317-318	Mild mental retardation

APPENDIX D: Comparison of Approaches for Estimating Program Impact

OUTCOME	Regression Discontinuity program (–rd–)	Ordinary Least Squares*	Log-Binomial Regression with –margins– command
Cervical Dysplasia			
Broad	-.00232 (-.00402, -.00061)	-.00232 (-.00402, -.00061)	-.00195 (-.00387, -.00004)
Possible	-.00170 (-.00308, -.00032)	-.00170 (-.00308, -.00032)	-.00142 (-.00301, .00018)
Probable	-.00079 (-.00174, .00016)	-.00079 (-.00174, .00016)	-.00065 (-.00170, .00040)
Anogenital Warts			
Broad	-.00034 (-.00103, .00036)	-.00034 (-.00103,.00036)	-.00026 (-.00106, .00053)
Possible	-.00034 (-.00081, .00013)	-.00034 (-.00081, .00013)	-.00035 (-.00080, .00010)
Probable	-.00029 (-.00074, .00016)	-.00029 (-.00074, .00016)	-.00026 (-.00076, .00024)
Indicators of Sexual Activity			
Composite endpoint	-.00025 (-.00435, .00385)	-.00025 (-.00435, .00385)	.00013 (-.00407, .00434)
Non-HPV STIs	-.00200 (-.00467, .00067)	-.00200 (-.00467, .00067)	-.00173 (-.00455, .00109)
Pregnancy	-.00029 (-.00307, .00364)	-.00028 (-.00307, .00364)	.00082 (-.00277, .00442)

*with robust standard errors

APPENDIX E: Estimate of School Grade Misclassification*

Birth Year Quarter	Frequency	% behind a grade (misclassified)	% on schedule (correctly classified)	% ahead a grade (misclassified)
JAN-MAR 1992	13,431	2.8	95.4	1.9
APR-JUN 1992	14,414	3.3	95.3	0.9
JUL-SEP 1992	13,905	4.6	94.1	0.7
SEP-DEC 1992	12,666	7.4	91.9	0.6
JAN-MAR 1993	12,702	2.9	94.5	1.9
APR-JUN 1993	13,699	3.4	95.7	0.9
JUL-SEP 1993	13,291	4.3	95.0	0.8
SEP-DEC 1993	12,314	7.8	91.4	0.7
JAN-MAR 1994	12,382	3.0	94.9	2.2
APR-JUN 1994	13,270	3.5	95.6	0.9
JUL-SEP 1994	12,917	4.3	94.9	0.8
SEP-DEC 1994	11,905	7.1	92.4	0.5
JAN-MAR 1995	11,673	2.4	95.8	1.8
APR-JUN 1995	12,722	3.1	95.8	1.1
JUL-SEP 1995	12,591	4.2	95.0	0.8
SEP-DEC 1995	11,304	7.1	92.3	0.7
TOTAL	**205,186**	**4.4**	**94.5†**	**1.1**

*Based on 205,186 girls who received the hepatitis B vaccine during the relevant time frame (i.e., 730 days before to 365 days after cohort entry).
† This percentage comprises 193,981 girls and therefore represent 74.5% of the entire study cohort of 260,493.

APPENDIX F: Secondary Analyses

OUTCOME	Primary Analysis	Secondary Analyses	
	Exposure Window: Gr8-9, Outcome Window: Gr10-12 Exposure definition: 3 doses	*Exposure Window: Gr8-9, Outcome Window: Gr10-12 Exposure definition: 2 doses*	*Exposure Window: Gr8, Outcome Window: Gr9-12 Exposure definition: 3 doses*
Absolute Risks			
Dysplasia			
Program Impact			
Broad	-.00232 (-.00402, -.00061)	-.00232 (-.00402, -.00061)*	-.00255 (-.00431, -.00079)
Possible	-.00170 (-.00308, -.00032)	-.00170 (-.00308, -.00032)*	-.00169 (-.00309, -.00030)
Probable	-.00079 (-.00174, .00016)	-.00079 (-.00174, .00016)*	-.00075 (-.00171, .00021)
Vaccine Impact			
Broad	-.00570 (-.00991, -.00150)	-.00523 (-.00915, -.00138)	-.00660 (-.01117, -.00203)
Possible	-.00419 (-.00759, -.00080)	-.00387 (-.00701, -.00074)	-.00439 (-.00801, -.00077)
Probable	-.00194 (-.00428, .00039)	-.00179 (-.00394, .00036)	-.00195 (-.00428, .00039)
Anogenital Warts			
Program Impact			
Broad	-.00034 (-.00103, .00036)	-.00034 (-.00103, .00036)*	-.00041 (-.00115 , .00032)
Possible	-.00034 (-.00081, .00013)	-.00034 (-.00081, .00013)*	-.00033 (-.00082, .00015)
Probable	-.00029 (-.00074, .00016)	-.00029 (-.00074, .00016)*	-.00028 (-.00074, .00018)
Vaccine Impact			
Broad	-.00083 (-.00254, .00088)	-.00077 (-.00235, .00081)	-.00107 (-.00298, .00084)
Possible	-.00084 (-.00200, .00031)	-.00078 (-.00184, .00029)	-.00086 (-.00212, .00040)
Probable	-.00072 (-.0018, .00038)	-.00067 (-.00168, .00035)	-.00073 (-.00192, .00047)
Indicators of Sexual Behaviour			
Program Impact			
Composite endpoint	-.00025 (-.00435, .00385)	-.00025 (-.00435, .00385)*	-.00082 (-.00505, .00340)
Non-HPV STIs	-.00200 (-.00467, .00067)	-.00200 (-.00467, .00067)*	-.00221 (-.00500, .00059)
Pregnancy	.00029 (-.00307, .00364)	.00029 (-.00307, .00364)*	.00015 (-.00330, .00359)
Vaccine Impact			
Composite endpoint	.00061 (-.01071, .00949)	-.00056 (-.00989, .00876)	-.002125 (-.01307, .00881)
Non-HPV STIs	-.00492 (-.01149, .00165)	-.00454 (-.01061, .00152)	-.00572 (-.01295, .00152)
Pregnancy	.00070 (-.00757, .00897)	.000648 (-.00699, .00828)	.00038 (-.00854, 00931)

Relative Risks			
Dysplasia			
Program Impact			
Broad	0.79 (0.66, 0.94)	0.79 (0.66, 0.94)*	0.79 (0.66, 0.93)
Possible	0.76 (0.61, 0.95)	0.76 (0.61, 0.95)*	0.77 (0.62, 0.95)
Probable	0.76 (0.55, 1.04)	0.76 (0.55, 1.04)*	0.78 (0.57, 1.06)
Vaccine Impact			
Broad	0.56 (0.37, 0.85)	0.59 (0.40, 0.86)	0.53 (0.35, 0.80)
Possible	0.49 (0.30, 0.82)	0.52 (0.33, 0.85)	0.48 (0.28, 0.81)
Probable	0.51 (0.23, 1.12)	0.53 (0.27, 1.07)	0.50 (0.23, 1.08)
Anogenital Warts			
Program Impact			
Broad	0.81 (0.52, 1.25)	0.81 (0.52, 1.25)*	0.80 (0.53, 1.20)
Possible	0.60 (0.31, 1.15)	0.60 (0.31, 1.15)*	0.64 (0.34, 1.19)
Probable	0.63 (0.32, 1.23)	0.63 (0.32, 1.23)*	0.66 (0.35, 1.27)
Vaccine Impact			
Broad	0.57 (0.20, 1.59)	0.59 (0.23, 1.53)	0.52 (0.19, 1.42)
Possible	0.31 (0.07, 1.41)	0.34 (0.08, 1.39)	0.33 (0.07, 1.50)
Probable	0.34 (0.07, 1.72)	0.37 (0.09, 1.62)	0.36 (0.07, 1.78)
Indicators of Sexual Behaviour			
Program Impact			
Composite endpoint	0.99 (0.93, 1.06)	0.99 (0.93, 1.06)*	0.99 (.92, 1.05)
Non-HPV STIs	0.92 (0.83, 1.03)	0.92 (0.83, 1.03)*	0.92 (0.83, 1.02)
Pregnancy	1.00 (0.92, 1.09)	1.00 (0.92, 1.09)*	1.00 (0.92, 1.09)
Vaccine Impact			
Composite endpoint	0.96 (0.83, 1.11)	0.96 (0.82, 1.12)	0.93 (0.79, 1.10)
Non-HPV STIs	0.80 (0.63, 1.04)	0.82 (0.64, 1.05)	0.78 (0.61, 1.03)
Pregnancy	0.99 (0.80, 1.21)	0.99 (0.82, 1.19)	0.97 (0.79, 1.20)

APPENDIX G: Sensitivity Analyses

The following analyses are based on alterations of the primary regression discontinuity analyses. Unless otherwise specified, analyses were carried out using Stata's –rd– program, and results are presented as cumulative risk differences (and 95% confidence intervals).

Alternative exposure definitions. Only results for vaccine impact are presented.

1. Time windows: exposure Grade 8, outcome Grades 9-12; Exposure: two doses
2. Exposure: at least one between birth and cohort exit
3. Time window: outcome Grades 9-12; Exposure: at least one dose birth and cohort exit
4. Include potentially problematic doses in primary exposure definition

OUTCOME	**1**	**2**	**3**	**4**
Broad dysplasia	-.00573 (-.00969, -.00177)	-.00525 (-.00912, -.00138)	-.00578 (-.00978, -.00178)	-.00570 (-.00991, -.00150)
Possible dysplasia	-.00381 (-.00695, -.00067)	-.00386 (-.00699, -.00073)	-.00384 (-.00701,-.00067)	-.00419 (-.00759, -.00080)
Probable dysplasia	-.00169 (-.00384, .00046)	-.00179 (-.00394. .00036)	-.00170 (-.00387, .00047)	-.00194 (-.00427, .00039)
Broad AGW	-.00093 (-.00258, .00073)	-.00077 (-.00234, .00081)	-.00094 (-.00261, .00073)	-.00083 (-.00254, .00086)
Possible AGW	-.00075 (-.00184, .00034)	-.00078 (-.00184, .00029)	-.00076 (-.00186, .00035)	-.00084 (-.00199, .00031)
Probable AGW	-.00063 (-.00167, .00041)	-.00066 (-.00168, .00035)	-.00064 (-.00168, .00041)	-.00072 (-.00182, .00038)
STIs & pregnancy	-.00184 (-.01134, .00765)	-.00056 (-.00986, .00873)	-.00186 (-.01144, .00772)	-.00061 (-.01070, .00948)
Non-HPV STIs	-.00496 (-.01124, .00132)	-.00453 (-.01058, .00152)	-.00500 (-.01134, .00133)	-.00492 (-.01148, .00165)
Pregnancy	.00033 (-.00741, .00808)	.00065 (-.00700, .00826)	.00034 (-.00748, .00815)	.00070 (-.00756, .00897)

Alternative outcome definition – i.e., outcome as count rather than dichotomy

1. Regression Discontinuity
2. Poisson Regression (estimates incidence risk ratio)

OUTCOME	1. Program Impact	1. Vaccine Impact	2. Program Impact	2. Vaccine Impact
Broad dysplasia	-.00229 (-.00400, -.00058)	-.00565 (-.00985, -.00144)	0.79 (0.67, 0.94)	0.56 (0.37, 0.86)
Possible dysplasia	-.00168 (-.00306, -.00030)	-.00414 (-.00754, -.00074)	0.77 (0.62, 0.95)	0.50 (0.30, 0.84)
Probable dysplasia	-.00077 (-.00172, -.00018)	-.00189 (-.00423, .00045)	0.77 (0.56, 1.06)	0.52 (0.24, 1.09)
Broad AGW	-.00030 (-.00100, .00040)	-.00075 (-.00247, .00098)	0.83 (0.54, 1.28)	0.60 (0.21, 1.68)
Possible AGW	-.00032 (-.00079, .00015)	-.00079 (-.00196, .00037)	0.63 (0.33, 1.20)	0.34 (0.72, 1.59)
Probable AGW	-.00027 (-.00073, .00018)	-.00067 (-.00179, .00044)	0.66 (0.33, 1.30)	0.38 (0.08, 1.89)
STIs & pregnancy	-.00140 (-.00661, .00381)	-.00345 (-.01628, .00939)	0.98 (0.91, 1.05)	0.93 (0.78, 1.11)
Non-HPV STIs	-.00263 (-.00567, .00040)	-.00648 (-.01396, .00099)	0.90 (0.80, 1.01)	0.77 (0.59, 1.02)
Pregnancy	.00123 (.00272, .00519)	.00304 (-.00670, .01277)	1.03 (0.94, 1.12)	1.03 (0.83, 1.28)

Alternative definition of forcing variable

1. birth halves (6-month intervals)
2. birth month (1-month intervals)

OUTCOME	1. Program Impact	1. Vaccine Impact	2. Program Impact	2. Vaccine Impact
Broad dysplasia	-.00248 (-.00422,-.00073)	-.00602 (-.01025, -.00178)	.00284 (-.00667, .01236)	.00689 (-.01615, .02993)
Possible dysplasia	-.00183 (-.00324-.00042)	-.00445 (-.00788, -.00103)	.00349 (-.00414, .01112)	.00845 (-.01004, .02695)
Probable dysplasia	-.00084 (-.00181, .00012)	-.00204 (-.00440, .00031)	.00113 (-.00429, .00655)	.00273 (-.01039, .01586)
Broad AGW	-.00036 (-.00107, .00035)	-.00087 (-.00259, .00085)	-.00104 (-.00502, .00294)	-.00252 (-.01216, .00712)
Possible AGW	-.00031 (-.00079. .00018)	-.00074 (-.00191, .00043)	.00023 (-.00242, .00288)	.00056 (-.00586, .00698)
Probable AGW	-.00026 (-.00072, .00020)	-.00064 (-.00176, .00048)	.00042 (-.00213, .00298)	.00103 (-.00516, .00721)
STIs & pregnancy	-.00040 (-.00457, .00376)	-.00098 (-.01109, .00912)	.02862 (.00560, .05164)	.06930 (.01321, .12539)
Non-HPV STIs	-.00222 (-.00493, .00049)	-.00539 (-.01196, .00118)	.00573 (-.00934, .02081)	.01388 (-.02265, .05041)
Pregnancy	.00033 (-.00308, .00374)	.00080 (-.00748, .00909)	.02386 (.00509, .04262)	.05777 (.01205, .10349)

Alternative covariate adjustment

1. unadjusted
2. unadjusted using log binomial to estimate relative risks
3. adjusted for birth category + recent indicator of sexual behaviour
4. adjusted for birth category + neighbourhood income quintile (missing excluded)
5. adjusted for birth category + neighbourhood income quintile (missing as category)
6. adjusted for birth category + hepatitis B vaccination
7. adjusted for birth category + recent indicator of sexual behaviour + neighbourhood income quintile (missing excluded) + hepatitis B vaccination

OUTCOME	**1**	**2**
Program Impact		
Broad dysplasia	-.00080 (-.00238, .00078)	.93 (.79, 1.09)
Possible dysplasia	-.00025 (-.00151, .00102)	.98 (.80, 1.19)
Probable dysplasia	.00001 (-.00085, .00088)	1.01 (.76, 1.35)
Broad AGW	.00006 (-.00056, .00069)	1.05 (0.71, 1.55)
Possible AGW	-.00025 (-.00068, .00019)	0.68 (0.37, 1.26)
Probable AGW	-.00020 (-.00062, .00022)	0.73 (0.39, 1.37)
STIs & pregnancy	.00669 (.00300, .01041)	1.12 (1.05, 1.19)
Non-HPV STIs	.00113 (-.00130, .00356)	1.05 (1.95, 1.16)
Pregnancy	.00513 (.00209, .00816)	1.14 (1.05, 1.23)
Vaccine Impact		
Broad dysplasia	-.00189 (-.00561, .00184)	0.84 (0.58, 1.23)
Possible dysplasia	-.00058 (-.00356, .00240)	0.93 (0.58, 1.48)
Probable dysplasia	.00004 (-.00200, .00207)	1.01 (0.51, 2.00)
Broad AGW	.00015 (-.00133, .00163)	1.09 (.44, 2.72)
Possible AGW	-.00059 (-.00161 .00044)	.41 (.10, 1.70)
Probable AGW	-.00047 (-.00146, .00051)	.47 (0.11, 2.07)
STIs & pregnancy	.01579 (.00702, .02456)	1.29 (1.11, 1.49)
Non-HPV STIs	.00267 (-.00308, .00841)	1.34 (1.12, 1.61)
Pregnancy	.01210 (.00493, .01927)	1.11 (0.88, 1.40)

OUTCOME	3	4	5	6
Program Impact				
Broad dysplasia	-.00232 (-.00403, -.00062)	-.00235 (-.00406, -.00063)	-.00231 (-.00402, -.00060)	-.00232 (-.00402, -.00061)
Possible dysplasia	-.00171 (-.00309, -.00033)	-.00172 (-.00310, -.00033)	-.00170 (-.00308, -.00032)	-.00170 (-.00308, -.00032)
Probable dysplasia	-.00079 (-.00174, .00015)	-.00076 (-.00171, .00019)	-.00079 (-.00173, .00016)	-.00079 (-.00174, .00016)
Broad AGW	-.00034 (-.00104, .00035)	-.00033 (-.00103, .00036)	-.00034 (-.00103, .00036)	-.00034 (-.00103, .00036)
Possible AGW	-.00034 (-.00081, .00012)	-.00035 (-.00082, .00012)	-.00034 (-.00081, .00013)	-.00034 (-.00081, .00012)
Probable AGW	-.00029 (-.00074, .00015)	-.00030 (-.00075, .00015)	-.00029 (-.00074, .00016)	-.00030 (-.00074, .00016)
STIs & pregnancy	-.00027 (-.00437, .00383)	.00021 (-.00390, .00432)	-.00017 (-.00425, .00392)	-.00025 (-.00435, .00385)
Non-HPV STIs	-.00201 (-.00467, .00066)	-.00187 (-.00455, .00082)	-.00198 (-.00465, .00068)	-.00200 (-.00467, .00067)
Pregnancy	.00027 (-.00309, .00363)	.00066 (-.00270, .00402)	.00036 (-.00300, .00371)	.00028 (-.00308, .00364)
Vaccine Impact				
Broad dysplasia	-.00572 (-.00992, -.00152)	-.00573 (-.00992, -.00154)	-.00570 (-.00989, -.00149)	-.00480 (-.00833, -.00126)
Possible dysplasia	-.00420 (-.00760, -.00081)	-.00420 (-.00760, -.00081)	-.00418 (-.00758, -.00079)	-.00352 (-.00638, -.00067)
Probable dysplasia	-.00195 (-.00428, .00038)	-.00186 (-.00418, .00047)	-.00194 (-.00427, .00039)	-.00163 (-.00360, .00033)
Broad AGW	-.00084 (-.00255, .00087)	-.00082 (-.00252 .00088)	-.00083 (-.00254, .00088)	-.00070 (-.00214, .00074)
Possible AGW	-.00085 (-.00200, .00031)	-.00086 (-.00200, .00029)	-.00084 (-.00199 .00031)	-.00071 (-.00168, .00026)
Probable AGW	-.00073 (-.00183, .00038)	-.00073 (-.00183, .00036)	-.00072 (-.00182, .00038)	-.00061 (-.00153, .00032)
STIs & pregnancy	-.00067 (-.01076, .00943)	.00051 (-.00953, .01055)	-.00041 (-.01047, .00966)	-.00052 (-.00901, .00796)
Non-HPV STIs	-.00494 (-.01151, .00163)	-.00457 (-.01112, .00199)	-.00489 (-.01145, .00168)	-.00414 (-.00966, .00138)
Pregnancy	.00067 (-.00760, .00894)	.00161 (-.00660, .00982)	.00089 (-.00735, .00912)	.00058 (-.00637, .00753)

OUTCOME	7
Program Impact	
Broad dysplasia	-.00235 (-.00407, -.00064)
Possible dysplasia	-.00172 (-.00311, -.00033)
Probable dysplasia	-.00076 (-.00172, .00019)
Broad AGW	-.00034 (-.00103, .00036)
Possible AGW	-.00035 (-.00082, .00012)
Probable AGW	-.00030 (-.00075, .00015)
STIs & pregnancy	.00020 (-.00391, .00430)
Non-HPV STIs	-.00187 (-.00456, .00081)

Pregnancy	.00065 (-.00271, .00401)
Vaccine Impact	
Broad dysplasia	-.00484 (-.00837, -.00131)
Possible dysplasia	-.00354 (-.00640 -.00069)
Probable dysplasia	-.00157 (-.00353, .00039)
Broad AGW	-.00069 (-.00212 .00074)
Possible AGW	-.00072 (-.00169, .00024)
Probable AGW	-.00062 (-.00154, .00030)
STIs & pregnancy	.00040 (-.00805, .00886)
Non-HPV STIs	-.00386 (-.00938, .00166)
Pregnancy	.00134 (-.00557, .00825)

Alternative population weights

1. equal weighting (same as no weighting)
2. cut-off weighted 3 times as heavily (1.5 vs. 0.5)
3. cut-off weighted 5 times as heavily (1 vs. 0.2)
4. cut-off weighted 10 times as heavily (1 vs. 0.1)

OUTCOME	**1**	**2**	**3**	**4**
Vaccine Impact				
Broad dysplasia	-.00230 (-.00401, -.00060)	-.00232 (-.00403, -.00062)	-.00233 (-.00403, -.00063)	-.00234 (-.00404, -.00064)
Possible dysplasia	-.00170 (-.00308, -.00031)	-.00170 (-.00308, -.00032)	-.00169 (-.00306, -.00031)	-.00166 (-.00750, -.00072)
Probable dysplasia	-.00079 (-.00174, .00016)	-.00079 (-.00173, .00016)	-.00078 (-.00172, .00016)	-.00077 (-.00170, .00017)
Broad AGW	-.00034 (-.00104, .00036)	-.00034 (-.00103, .00036)	-.00033 (-.00102, .00036)	-.00032 (-.00101, .00037)
Possible AGW	-.00034 (-.00081, .00013)	-.00034 (-.00081, .00012)	-.00035 (-.00081, .00012)	-.00035 (-.00082, .00011)
Probable AGW	-.00029 (-.00074, .00016)	-.00029 (-.00074, .00015)	-.00030 (-.00074, .00015)	-.00030 (-.00075, .00014)
STIs & pregnancy	-.00030 (-.00440, .00381)	-.00019 (-.00429, .00391)	-.00009 (-.00418, .00400)	.00011 (-.00398, .00420)
Non-HPV STIs	-.00200 (-.00468, .00067)	-.00199 (-.00466, .00067)	-.00198 (-.00464, .00068)	-.00196 (-.00463, .00070)
Pregnancy	.00025 (-.00311, .00362)	.00033 (-.00303, .00368)	.00040 (-.00295, .00375)	.00054 (-.00280, .00389)
Vaccine Impact				
Broad dysplasia	-.00565 (-.00986, -.00145)	-.00571 (-.00993, -.00152)	-.00576 (-.00996, -.00155)	-.00580 (-.01001, -.00159)
Possible dysplasia	-.00418 (-.00758, -.00077)	-.00419 (-.00758, -.00079)	-.00417 (-.00756, -.00078)	-.00411 (-.00750, -.00072)
Probable dysplasia	-.00194 (-.00427, .00040)	-.00194 (-.00427, .00039)	-.00193 (-.00425, .00040)	-.00190 (-.00421, .00042)

Broad AGW	-.00084 (-.00255, .00088)	-.00083 (-.00253, .00088)	-.00082 (-.00252 .00089)	-.00079 (-.00249 .00091)
Possible AGW	-.00083 (-.00199, .00032)	-.00085 (-.00200, .00030)	-.00086 (-.00201, .00029)	-.00088 (-.00203, .00028)
Probable AGW	-.00071 (-.00182, .00039)	-.00073 (-.00183, .00038)	-.00073 (-.00184, .00037)	-.00075 (-.00185, .00035)
STIs & pregnancy	-.00073 (-.01084, .00937)	-.00047 (-.01057, .00963)	-.00022 (-.01032, .00990)	.00026 (-.00987, .01039)
Non-HPV STIs	-.00493 (-.01150, .00164)	-.00491 (-.01148, .00166)	-.00490 (-.01147, .00169)	-.00486 (-.01146, .00173)
Pregnancy	.00062 (-.00766, .00890)	.00080 (-.00747, .00907)	.00099 (-.00728, .00925)	-.00134 (-.00694, .00693)

Alternative kernel

1. triangular kernel with population weights
2. triangular kernel without population weights

OUTCOME	**1. Program Impact**	**1. Vaccine Impact**	**2. Program Impact**	**2. Vaccine Impact**
Broad dysplasia	-.00304 (-.00482, -.00127)	-.00763 (-.01209, -.00318)	-.00307 (-.00484, -.00130)	-.00764 (-.01205, -.00323)
Possible dysplasia	-.00194 (-.00335, -.00053)	-.00487 (-.00841, -.00134)	-.00202 (-.00343, -.00061)	-.00503 (-.00854, -.00152)
Probable dysplasia	-.00085 (-.00180, .00011)	-.00212 (-.00452, .00028)	-.00088 (-.00184, .00008)	-.00220 (-.00459, .00019)
Broad AGW	-.00028 (-.00098, .00042)	-.00070 (-.00246, .00106)	-.00030 (-.00010, .00040)	-.00075 (-.00250, .00100)
Possible AGW	-.00042 (-.00091, .00070)	-.00105 (-.00227, .00017)	-.00041 (-.00090, .00078)	-.00102 (-.00223, .000179
Probable AGW	-.00033 (-.00079, .00014)	-.00082 (-.00199, .00035)	-.00032 (-.00079, .00015)	-.00079 (-.00196, .00035)
STIs & pregnancy	.00072 (-.00353, .00497)	.00181 (-.00884, .01246)	.00037 (-.00386, .00460)	.00092 (-.00961, .01145)
Non-HPV STIs	-.00233 (-.00511, .00045)	-.00584 (-.01282, .00113)	-.00236 (-.00513, .00040)	-.00589 (-.01278, .00100)
Pregnancy	.00144 (-.00203, .00490)	.00350 (-.00509, .01229)	.00118 (-.00227, .00463)	.00294 (-.00566, .01154)

Alternative bandwidth

1. 4.1; no covariates*
2. Only include 1993 and 1994 birth years; no covariates*
3. Optimal bandwidth†, no covariates*

* Model could not be estimated within this bandwidth when birth quarter was included as a covariate.

† As determined in: Imbens G, Kalyanaraman K. Optimal bandwidth choice for the regression discontinuity estimator. *Review of Economic Studies* 2012;79(3):933-59.

OUTCOME	1. Program Impact	1. Vaccine Impact	2. Program Impact	2. Vaccine Impact
Broad dysplasia	-.00380 (-.00688, -.00072)	-.01190 (-.02156, -.00224)	-.00007 (-.00242, .00227)	-.00017 (-.00556, .00522)
Possible dysplasia	-.00077 (-.00319, .00165)	-.00240 (-.00998, .00517)	.00130 (-.000570, .00316)	.00298 (-.00131, .00727)
Probable dysplasia	.00039 (-.00123, .00200)	.00121 (-.00384, .00626)	.00100 (-.00028, .00229)	.00231 (-.00064, .00525)
Broad AGW	-.00001 (-.00134, .00113)	-.00033 (-.00120, .00354)	.000704 (-.00021, .00161)	.00162 (-.00048, .00371)
Possible AGW	-.00074 (-.00016, .00010)	-.00231 (-.00492, .00030)	-.00027 (-.00091, .00038)	-.00061 (-.00209, .00087)
Probable AGW	-.00053 (-.00013, .00025)	-.00165 (-.00409, .00079)	-.00013 (-.00076, .00049)	-.00031 (-.00174, .00113)
STIs & pregnancy	.00611 (-.00130, .01354)	.01915 (-.00410, .04240)	.01766 (.01221, .02311)	.04058 (.02804, .05313)
Non-HPV STIs	-.00456 (-.00954, .00041)	-.01429 (-.02986, .00129)	.00463 (.00107, .00820)	.01065 (.00245, .01884)
Pregnancy	.00810 (.00211, .01410)	.02536 (.00656, .04417)	.01379 (.00932, .01825)	.03168 (.02141, .04195)

OUTCOME	3. Program Impact	3. Vaccine Impact
Broad dysplasia	-.00001 (-.00230, .00228)	-.00003 (-.00532, .00526)
Possible dysplasia	--	--
Probable dysplasia	--	--
Broad AGW	--	
Possible AGW	--	--
Probable AGW	--	--
STIs & pregnancy	.01080 (.00556, .01604)	.02495 (.01282, .03708)
Non-HPV STIs	.00346 (.00002, .00690)	.00800 (.00004, .01594)
Pregnancy	.00770 (.00341, .01198)	.01778 (.00787, .02768)

-- could not be estimated

APPENDIX H: Effect in Sub-Cohort (Grade 8 Year Verified)*

OUTCOME	Risk Difference per 1000 (95% CIs)	Risk Ratio (95% CIs)
Dysplasia		
Program Impact		
Broad	-.00261 (-.00464, -.00059)	0.78 (0.64, 0.95)
Possible	-.00190 (-.00354, -.00035)	0.76 (0.59, 0.97)
Probable	-.00090 (-.00202, .00023)	0.74 (0.52, 1.07)
Vaccine Impact		
Broad	-.00547 (-.00970, -.00123)	0.54 (0.34, 0.86)
Possible	-.00400 (-.00741, -.00053)	0.49 (0.27, 0.87)
Probable	-.00188 (-.00423, .00047)	0.47 (0.20, 1.10)
Anogenital Warts		
Program Impact		
Broad	-.00064 (-.00146, .00019)	0.68 (0.42, 1.11)
Possible	-.00053 (-.00011, >.00001)	0.46 (0.22, 0.98)
Probable	-.00048 (-.00100, .00005)	0.48 (0.22, 1.05)
Vaccine Impact		
Broad	-.00133 (-.00305, .00040)	0.38 (0.12, 1.22)
Possible	-.00112 (-.00225, .00002)	0.17 (0.29, 0.99)
Probable	-.00099 (-.00209, .00010)	0.18 (0.03, 1.14)
Indicators of Sexual Behaviour		
Program Impact		
Composite endpoint	.00093 (-.00384, .00570)	1.01 (0.94, 1.10)
Non-HPV STIs	.00138 (-.00451, .00176)	0.94 (0.84, 1.07)
Pregnancy	.0008675 (-.00301, .00475)	1.02 (0.92, 1.13)
Vaccine Impact		
Composite endpoint	.00194 (-.00803, .01192)	1.00 (0.82, 1.21)
Non-HPV STIs	-.00288 (-.00942, .00357)	0.85 (0.63, 1.15)
Pregnancy	.00070 (-.00757, .00897)	1.01 (0.80, 1.29)

CI: confidence interval

*N=193,981

APPENDIX I: Comparison of Approaches for Estimating Vaccine Impact

OUTCOME	Regression Discontinuity program (–rd–)*	Two Stage Least Squares*
Cervical Dysplasia		
Broad	-5.70 (-9.91, -1.50)	-5.26 (-10.00, -4.91)
Possible	-4.19 (-7.59, -0.80)	-3.89 (-7.74, -0.34)
Probable	-1.94 (-4.28, 0.39)	-1.78 (-4.43, 0.86)
Anogenital Warts		
Broad	-0.83 (-2.54, 0.88)	-0.73 (-2.68, 0.12)
Possible	-0.84 (-1.99, 0.31)	-0.86 (-2.51, 0.43)
Probable	-0.72 (-1.82, .0.38)	-0.71 (-1.95, 0.53)
Indicators of Sexual Activity		
Composite endpoint	-0.25 (-4.35, 3.85)	1.90 (-9.66, 13.45)
Pregnancy	0.29 (-3.07, 3.64)	2.48 (-6.99, 11.94)
Non-HPV STIs	-2.00 (-4.67, 0.67)	-4.57 (-12.01, 2.95)

*risk difference per 1000 girls (95% confidence interval)

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