Child Health in the Province of Ontario: Establishing baselines for reproductive health and vaccine preventable diseases

by

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ABSTRACT

CHILD HEALTH IN THE PROVINCE OF ONTARIO: ESTABLISHING BASELINES FOR REPRODUCTIVE HEALTH AND VACCINE PREVENTABLE DISEASES

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This thesis was an investigation of child health in the province of Ontario through the lens of reproductive health, and vaccine preventable diseases (VPD). Two studies were conducted; the first examined the association between pre-pregnancy BMI and the risk of developing gestational diabetes mellitus (GDM) and gestational hypertension (GH) in a rural Southern Ontario community hospital. In multivariable logistic regression, pre-pregnancy BMI was significantly associated with the risk of developing both GDM and GH. The second study examined immunization compliance for measles, mumps, and rubella among children seven years of age residing in the city of Guelph. A significant difference was identified in overall immunization compliance to National Advisory Committee on Immunization Standards (NACI) between the city of Guelph's priority neighbourhoods, and non-priority neighbourhoods. These findings will aid in identifying populations at risk for the development of poor child health outcomes, for whom public health initiatives should be targeted.

DEDICATION

My thesis is dedicated to my grandma, Loula, who demonstrated through example how to persevere with a positive attitude through the many curvatures of your individual journey.

Arrivederci xo

"Make big plans; aim high in hope and work, remembering that a noble, logical diagram once recorded will never die, but long after we are gone will be a living thing, asserting itself with ever-growing insistency. Think big."

Daniel Burnham, Chicago architect (1846–1912)

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STATEMENT OF WORK

Adele Carty developed the study protocols, cleaned and manipulated the data, performed data analysis, interpreted the results and wrote the manuscripts.

Dr. Andrew Papadopoulos, Dr. Jan Sargeant, and Jennifer MacLeod provided consultation and guidance on the design of the studies. Drs. Andrew Papadopoulos and Jan Sargeant assisted with all statistical methodology. Input for the interpretation of results, as well as the review and editing for the entirety of the thesis, was provided by Dr. Andrew Papadopoulos, Dr. Jan Sargeant, and Jennifer MacLeod.

For the Better Outcomes Registry and Network (BORN) study (Chapter 2), data were procured and extracted on-site at our collaborating hospital by a nurse and analyst, respectively. William Sears provided technical support with data coding for the use of statistical analysis software (SAS). Dr. Sarah Gower provided her medical opinion and expertise which aided in the design of the study, and interpretation of results.

Data for the immunization compliance study (Chapter 3) were collected and entered into the Immunization Records Information System (IRIS) by data clerks at Wellington-Dufferin-Guelph Public Health (WDGPH). The extraction of data was completed by Adele Carty in conjunction with Jillian Dixon and Mai Miner, data analysts at WDGPH. Jillian Dixon assisted Adele Carty with the geo-mapping of results using ArcGIS Software. On-site at WDGPH, Jillian Dixon, Mai Miner and Dr. Patrick Seliske provided technical support to Adele Carty.

LIST OF ABBREVIATIONS

ANOVA: analysis of variance

BOH: board of health

BORN: Better Outcomes Registry and Network

BMI: body mass index

CDA: Canadian Diabetes Association

CDC: Centers for Disease Control and Prevention

CI: confidence interval

CIHI: Canadian Institute for Health Information

CPSS: Canadian Perinatal Surveillance System

FSA: forward selection area code

GDM: gestational diabetes mellitus

GH: gestational hypertension

GIS: geographic information system

HELLP: hemolysis, elevated liver enzymes and low platelet count

IOM: Institute of Medicine

IRIS: Immunization Records Information System

ISPA: Immunization of School Pupils Act

MMR: measles, mumps, and rubella (German measles)

MMRV: measles, mumps, rubella (German measles), and varicella

NACI: National Advisory Committee on Immunizations

OPHS: Ontario Public Health Standards

OR: odds ratio

ORG: Office of the Registrar General

PHAC: Public Health Agency of Canada

REB: Research Ethics Board

SOGC: Society of Obstetrics and Gynaecology of Canada

VPD: vaccine preventable disease

WDGPH: Wellington-Dufferin-Guelph Public Health

WHO: World Health Organization

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CHAPTER ONE

Introduction, Literature Review, Thesis Rationale, and Objectives

1.1. Introduction

As of 2014, the province of Ontario is home to 2.19 million children between the ages of zero to 14 years, representing 16% of the province's overall population.[1] Clinical and population health assessment is critical for this age group as early childhood experiences have an immediate and long lasting impact upon one's health.[2] Children are launched on trajectories of health before birth during pre-conception, laying the foundation for later health and well-being.[3] Early life exposure to health risks and preventive medicine affect how biological, cognitive, emotional, behavioural and social capabilities develop throughout childhood and across the life course.[4,5] Identifying populations that are at risk for the development of poor child health outcomes can contribute to the improvement of individual and population health.

The Ontario Ministry of Health and Long-Term Care established the Ontario Public Health Standards (OPHS) to outline the requirements for fundamental public health programs that are delivered by Boards of Health (BOH) throughout Ontario.[2] The standards consist of five domains of health: family health, infectious diseases, emergency preparedness, chronic diseases and injuries, and environmental health (Figure 1.1.). These domains are used to identify child health indicators for the measure of health disparities among children.[5]

Underpinning the OPHS domains of health are foundational standards (Figure 1.1.). These standards consist of population health assessment, surveillance, program evaluation, and research and knowledge exchange.[2] The premise is to use the best available evidence to address emerging needs of a population, and inform evidence-based health practices.[2] Evidence that is

generated through foundational standards ultimately contribute to improved health programs and interventions.

The OPHS requires BOH to work with community partners to conduct epidemiological analyses of data to: (1) develop services, and programs for the promotion of preconception health, and healthy pregnancy, and (2) prevent and reduce the burden of infectious diseases.[2] The research reported in this thesis sought to explore child health through the lens of two OPHS domains of health: family health (reproductive health), and infectious diseases (vaccine preventable diseases (VPD)). Data were obtained from secondary health databases, representing two populations located in Southern Ontario. Epidemiological methods were performed to identify populations most at risk for adverse maternal pregnancy outcomes, and potential VPD outbreaks.

The literature review that follows is intended to provide an introduction to the following areas: Ontario child health record systems, the epidemiology of adverse maternal pregnancy outcomes, and the epidemiology of VPDs.

1.2. Literature Review

1.2.1. Ontario Child Health Record Systems

In recent years, there has been a surge in the development of health databases and registries as a result of the progress in information technology.[6–8] This has led to data being accumulated faster, and in larger volumes compared to earlier years when data were collected manually.[8–10] Registries and databases are being funded to facilitate health research to inform clinical programs, health system management, and disease prevention.[6,10] Funding agencies range from academic peer-reviewed granting councils, federally and provincially sponsored

initiatives, and the private sector.[6] These data sources provide a mechanism to assess the health of populations, acting as a resource for the conduct of epidemiological research.[7,11]

Secondary data are data which have not been collected to address specific hypotheses but are now being used to answer research questions.[8,10,12] A growing challenge in the Canadian health system is doing 'more with less', as reported by the Canadian Institute of Health Information (CIHI).[10] The use of secondary data can afford health researchers the opportunity to obtain a large sample from existing and established databases which in turn can lead to the optimal utilization of time and research funds.[8,10,13] Researchers can capitalize on these data to readily assess the health needs of a population, and to identify priority populations for whom programs and interventions should be targeted.

Two health databases that promote child health surveillance were employed for this thesis; Ontario's Better Outcomes Registry and Network (BORN), and the Immunization Records Information System (IRIS).

Ontario's Better Outcomes Registry and Network (BORN)

In the province of Ontario, data about each birth are able to be collected and entered into Ontario's Better Outcomes Registry and Network (BORN) which is funded by the Ontario Ministry of Health and Long-Term Care, and administered by the Children's Hospital of Eastern Ontario.[14,15] Established in 2009, BORN is Ontario's pregnancy, birth, and childhood registry and network that enables the collection and sharing of prenatal data, and is a prescribed registry under Ontario's Personal Health Information Protection Act. [15,16] It was created in an effort to improve upon the quality of pregnancy, birth, and childhood data that are collected in the province of Ontario, which has been sub-optimal in the past.

Data are collected from all Ontario hospitals and midwifery practices that provide maternal and newborn services; 109 hospitals, and approximately 80 midwifery practices.[14,15,17] From across Ontario, subject matter experts participate in establishing the variables collected by BORN, advising on relevance, content, and terminology.[18] In total, more than 100 variables are collected by BORN which include data related to the following topics: fertility, prenatal screening, interventions and outcomes in labour and birth, maternal demographics, maternal morbidities, place of birth, and newborn screening.[18]

After birth, maternal and newborn data are retrieved from medical records, clinical forms, and the mother, and are then entered into BORN by manual entry performed by clinicians or data technicians, or direct upload from health record systems.[19] Every day, more than 3,000 data entries are submitted to BORN.[18] Each contributing site has access to their data, and to aggregated regional, and provincial level data.[14] A high level of data quality is maintained by an ongoing program of data verification, automated quality checks, and data procuring/entry training.[14] The accuracy of data collection, and quality control/maintenance of health databases are of paramount importance to enable the analyses and reporting of data.

The Canadian Perinatal Surveillance System (CPSS) is an ongoing national health surveillance program aimed at improving the health of pregnant women, mothers, and infants.[20] The program reports on perinatal outcomes using data obtained from provincial, territorial, and national databases.[20,21] Reports published by the CPSS have historically excluded Ontario from analyses as a consequence of data quality issues that occurred in the 1990's.[21–24] There is a number of widely acknowledged data quality issues within Ontario including under-registration of births, truncation of birth weights, and inaccurate gestational age recorded for births.[21,23,25,26]

In 1995, Statistics Canada reported an increase in the Canadian infant mortality rate after successive annual declines over more than three decades.[21] CPSS attributed the unexpected rise to Ontario's change in birth registration law which allowed municipalities to introduce an administration fee for the processing of birth registration documentation.[23,27] The fee ranged in value from $10.00 to $27.50.[23] Birth registration at the Office of the Registrar General (ORG) is required by law in all provinces and territories; however the inception of an administration fee discouraged some parents/guardians from registering their children's birth.[23,27] As of the year 2000, it was approximated that up to 4,000 Ontarian births were not registered.[28] Between 2006 and 2009, Ontario phased-in an electronic birth registration system while simultaneously eliminating the birth registration fee.[25]

During the early and mid-1990's, inaccurate data transcription of Ontario birth weights led to an artificial increase in the proportion of low birth weights.[21] A researcher from the Bureau of Reproductive and Child Health in Ottawa led an investigation to identify spatial patterns of reported changes in proportions of low birth weights.[29] The researcher gained access to live-birth files from Statistics Canada, and found that the increased proportions were due to data transcription errors. The 1993 and 1994 birth weight variable had been truncated by one digit in the recording of ounces.[29] Researchers reported the finding to the appropriate authority for rectification.[29]

Gestational age at birth is transcribed and collected by both the parents/guardians and the attending health care provider.[25] Until 1990, the attending health care provider information was used as the gold standard for reporting of gestational age to the Ontario ORG.[25] However, from 1990 to 2008 parents/guardians transcription of gestational age was utilized as the gold standard.[25] This change in gold standard led to an over-estimation of reported pre-term births in

Ontario as a result of incorrect gestational age calculation by parents/guardians.[25] In June 2008, the attending health care provider information was once again utilized as the gold standard, and the ORG rectified the incorrect gestational age data that was transcribed from 1990 to 1998.[25]

The most recent CPSS report on perinatal outcomes in 2013 excluded Ontario from most analyses, again due to poor data quality.[30] The CPSS has acknowledged Ontario's efforts to respond to their data quality issues, and hopes to be able to include Ontario in future national perinatal statistical analyses.[21] The continued efforts made by BORN to collect accurate and trusted perinatal data is contributing to the improvement of data quality standards in the province of Ontario.

Immunization Records Information System (IRIS)

Across Canada, immunization programs are in place for the routine administration of childhood vaccinations.[31] Historically, childhood vaccination records for Ontario school-aged children have been recorded and maintained in the provincial Immunization Records Information System (IRIS). IRIS was developed by the Ministry of Health and Long-Term Care in 1992 for Ontario's 36 BOH to monitor childhood vaccinations for their respective jurisdictions.[32–34] The data entered into IRIS belongs to each individual BOH, and it is their responsibility to ensure that collected immunization records are promptly entered into IRIS to enable the assessment of pupil immunization coverage for their area.[35]

Vaccination programs are meant to guard children and communities against VPDs.[33] Vaccines work by generating an immune response which allows the immune system to respond more efficiently to future infection, thereby providing immunity and individual protection against disease.[20] When a high proportion of a population is vaccinated, a threshold is met, providing protection to susceptible individuals by establishing herd immunity.[33] As a result of

the development and uptake of vaccines, infectious diseases that were once common are now rare or eradicated. One such disease is smallpox, which was globally eradicated in 1977.[36] It is imperative for jurisdictions to have registers that accurately and timely maintain immunization records for their population to enable the estimation of vaccine coverage such that optimal protection against VPDs is achieved.[37]

In Canada, recommendations for the use of vaccines in humans are governed by the National Advisory Committee on Immunizations (NACI).[38,39] The committee is comprised of national experts in the fields of pediatrics, infectious diseases, immunology, medical microbiology, internal medicine, and public health.[38] The delivery of immunization programs is a provincial/territorial mandate.[37] Each province and territory is heterogeneous in their immunization schedule, as is their implementation of immunization registers.[31,37] Based on recommendations set forth by NACI, each province and territory determines which vaccines they can afford to publicly fund, and the extent to which they capture immunization data.[37,40,41]

Immunization registers are repositories that have the capacity to capture individual record-level data on the receipt of vaccine doses.[37] They support the opportunity for immunization surveillance, which can be used to assess the effectiveness of immunization programs by estimating vaccine compliance and the proportions of populations that are adequately protected against VPDs.[37] Depending upon the availability of registers and the data collected, provinces and territories use varying methods to assess immunization compliance.[37] To date, there exists no network for the national surveillance of immunization in Canada.[36,37] Moreover, the current registers operating within Canada are not interoperable between jurisdictions.[37]

In 2003, the Canadian National Immunization Strategy was accepted by the Conference of Federal, Provincial, and Territorial Deputy Ministers of Health.[37,40] The strategy was designed to address challenges to immunization, consisting of five core components. One of the components was the development of a national immunization registry network, with the objective to improve national immunization surveillance by establishing and maintaining a national immunization registry.[36] The strategy received a 45 million dollar contribution over a five year period, from the 2003 federal budget.[40,41] However, a national immunization registry is yet to be employed.[40]

In lieu of the absence of a national immunization registry to facilitate the assessment of childhood immunization compliance, the Public Health Agency of Canada (PHAC) conducts telephone surveys to assess coverage throughout Canada.[37] The surveys, known as the Childhood National Immunization Coverage Surveys, are conducted biennially using a random digit dialling framework.[37] Their purpose is to collect immunization history for children at 2, 7, and 17 years of age by way of telephone interviews with parents/guardians to monitor and report on national childhood immunization coverage.[37,42] The results obtained from the surveys are used to develop public vaccine strategies, and also to report immunization coverage estimates to national organizations such as the World Health Organization (WHO).[37] Until a national immunization registry is implemented in Canada, the PHAC will continue to employ the Childhood National Immunization Coverage Surveys.[37]

Immunization has, and continues to be, one of the most prominent achievements of medicine and public health, providing protection to populations against VPDs and in some cases even leading to disease eradication.[39,43] There is an overwhelming need for a national immunization register in Canada. With a current lack in federal support for the management of

immunization programs in Canada, momentum is still required to cultivate and implement such a register. At present, it is imperative for BOH to assess immunization compliance in their jurisdiction to monitor vaccine uptake, and identify populations that are at high risk for contracting VPDs.

1.2.2. Epidemiology of Adverse Maternal Pregnancy Outcomes

Two adverse maternal pregnancy outcomes were studied in this thesis; gestational diabetes mellitus (GDM) and gestational hypertension (GH).

Gestational Diabetes Mellitus (GDM)

Diabetes is characterized by abnormal insulin levels, leading to poor glycemic control.[44] It is classified in three forms; type I, type II, and gestational.[44] Gestational diabetes mellitus (GDM) is defined as the development of hyperglycemia during pregnancy, with the severity of glucose intolerance being variable among women.[44,45] In 2011, the PHAC reported the incidence of GDM to be approximately three to five percent of all Canadian pregnancies resulting in a live birth.[44] However, varying ranges for the incidence of GDM have been reported by studies.[46–48]

During pregnancy, women affected by GDM experience an increase in insulin resistance which can reach the level of resistance seen in non-pregnant women with type II diabetes.[49] Thus, early diagnosis of the disease carries importance for the effective management of maternal and fetal health.[47] The gold standard for diagnosis of GDM is a two-step approach; 50g glucose challenge test, and if appropriate, proceeded with a 75g oral glucose test.[50] Alternatively, a one-step 75g oral glucose tolerance test can be carried out.[50] The Canadian Diabetes Association (CDA) recommends that all pregnant women be screened for the development of GDM at 24 to 28 weeks gestation.[44,50] Moreover, if a woman presents multiple risk factors for the disease, the CDA recommends regular screening throughout pregnancy.[50] Several predisposing factors have

been found to be associated with the development of GDM which include a previous diagnosis of GDM, race, ethnicity, advanced maternal age, excessive weight gain during pregnancy, multiparity, and familial history of diabetes.[44–47,51–53]

Early initiation of treatment for GDM is imperative, as untreated GDM can lead to adverse maternal and fetal health complications.[45,47,50] It is recommended for women with GDM to be monitored closely throughout pregnancy to ensure a glucose level between 4.0mmol/L and 7.0mmol/L is maintained.[50] If glycemic targets are not met, insulin therapy is typically initiated.[50] An alternative treatment is nutritional counselling.[50]

Typically after pregnancy, glucose homeostasis is restored to pre-pregnancy levels for normoglycemic pregnant women.[54] However, for women with GDM, this is not always the case. A previous diagnosis of GDM has been reported to increase the risk of recurrent GDM in subsequent pregnancies.[45,51,55] A study conducted by Getahun et al. reported the risk of GDM in the second pregnancy among women with and without previous GDM to be 41.3% and 4.2% (OR: 13.2; 95% CI: 12.0-14.6), respectively.[51] Moreover, women with a history of GDM have an increased risk of developing type II diabetes post-pregnancy, and their offspring are more likely to develop type I diabetes.[44,49,54,56]

Gestational Hypertension (GH)

According to the Canadian Hypertensive Disorders of Pregnancy Working Group, hypertensive disorders in pregnancy are leading causes of maternal and perinatal morbidity.[57] Hypertension in pregnancy encompasses a spectrum of disorders: pre-existing hypertension, gestational hypertension (GH), and preeclampsia.[58] Among the disorders, GH is the most frequent cause of hypertension during pregnancy, with an estimated rate of 46.2 per 1,000 Canadian deliveries for the year 2010/2011.[59] GH is clinically defined as the new onset of

hypertension that develops at, or after 20 weeks gestation in the absence of proteinuria or new signs of end-organ dysfunction, in women known to be normotensive.[57,59,60] Women diagnosed with GH have a systolic blood pressure ≥140mmHg, and/or a diastolic blood pressure ≥90mmHg, based on the average of a minimum two measurements taken at least 15 minutes apart.[57] On average, it is estimated that most women suffering from GH will return to their previous normotensive state six days post-labour.[61]

During pregnancy, some women with GH will go on to develop preeclampsia.[60] Preeclampsia is defined as GH in the presence of maternal end-organ dysfunction, and/or proteinuria; a urinary protein measurement ≥0.3g per day in a 24 hour urine collection.[58,60,62] It has been reported that the rate of progression from GH to preeclampsia is dependent on gestational age at the time of GH diagnosis. It is approximated that the rate reaches 50% when GH develops prior to 30 weeks gestation.[60] Maternal surveillance is indicated in all women with GH to monitor the progression of their disorder for the duration of their pregnancy.[60]

Studies have reported on the association between GH and maternal and perinatal morbid conditions. A study conducted by Allen et al. found that women with GH were 1.5 times more likely to have a live birth that was small for gestational age (less than 10th percentile) compared to normotensive women (95% CI: 1.4-1.6).[63] GH has also been found to be associated with preterm delivery (<37 weeks gestation).[64,65] A meta-analysis conducted by van Ostwaard et al. examined the recurrence of hypertensive disorders in subsequent pregnancies. The study found the recurrence of hypertension in pregnancy to be 20.7% (95% CI: 20.4-20.9), with recurrence manifested as GH in 8.6% of the studies included in the analysis.[66]

As a result of ethicality, clinical trials are unable to be conducted to determine the level of blood pressure at which treatment should be initiated to prevent GH complications.[60] Thus,

health professionals utilize results obtained from observational studies, and practice patterns to manage the treatment of patients with GH.[60] The primary objective of treatment for GH is the prevention of potential cardiovascular and cerebrovascular complications, to assure the health and well-being of both mother and baby.[60] For women with a sustained systolic blood pressure of at least 180mmHg, and a sustained diastolic blood pressure of at least 110mmHg, antihypertensive therapy is recommended for management.[60] Bedrest has been an alternative method reported for the management of GH. A study conducted by Crowther et al. examined whether admission to hospital for bed rest is of value for the management of GH.[67] The study found that women on hospital bed rest were 0.4 times less likely to have the severity of their GH progress (95% CI: 0.26-0.83) compared to women with GH not on bed rest.[67]

1.2.3. Epidemiology of Vaccine Preventable Diseases (VPD)

Three vaccine preventable diseases (VPD) were examined in this thesis: measles, mumps, and rubella.

Measles

Measles is a highly contagious, communicable respiratory disease that is caused by the measles virus, a member of the family *Paramyzoviridae*, genus *Morbillivirus*.[68–70] The WHO clinically defines a measles case as a person presenting all of the following symptoms: fever, maculopapular rash, cough, and coryza (runny nose) or conjunctivitis (red eyes).[71] Whereas the WHO criteria for laboratory diagnoses is the presence of measles-specific IgM antibodies.[71]

Measles disease is acquired by vehicle transmission of respiratory droplets from an infected individual to the respiratory mucosa of a susceptible host.[70] The clinical presentation of disease commences with the presentation of fever, cough, coryza, conjunctivitis, and Koplik's spots (small white lesions in the mouth).[70] These symptoms will progress in severity over several

days prior to the onset of maculopapular rash.[70] The rash will first appear on the face, and then spread to the trunk and extremities, lasting five to ten days before waning.[70] Individuals with measles are infectious several days before and after the onset of rash, when virus concentrations in blood and body fluids are presumed to be highest.[70] Medical complications such as blindness, pneumonia, and encephalitis are estimated to affect approximately 10% of confirmed measles cases.[69,70]

Measles disease prevention can be achieved by either active or passive immunity. In Canada, live measles vaccine was licensed for use in 1963.[72] In 1983, the measles vaccine, in a cocktail with mumps and rubella, was introduced for routine, publicly funded immunization across the nation, resulting in a substantial reduction of measles incidence rates.[68] A further reduction in incidence rates was experienced when a two-dose measles-mumps-rubella vaccine schedule was implemented in the years 1996 and 1997.[68] Infants become immune to the disease by passively acquiring maternal antibodies during the antenatal period.[70] However, immunity is lost as maternal antibodies subside, making infants susceptible to acquiring the disease.[70]

Prior to the widespread immunization against measles, the virus was responsible for approximately 2.6 million deaths per year worldwide.[68] In 1998, measles elimination status was achieved in Canada, and has been maintained ever since.[73] Elimination is defined as the absence of endemic measles transmission in a defined geographic area for ≥12 months.[73] In 2014, the PHAC reported 22 confirmed measles cases in Ontario, with an incidence rate of 1.6 cases per 1,000,000 population.[68] Despite the interruption of endemic measles in Canada, endemic transmission persists in other regions of the world such as Western Pacific, Eastern Mediterranean, Africa, and Southeast Asia.[73] As a result, Canada is at risk for the importation of

the measles virus from travel to these areas, making it imperative to maintain high measles immunization coverage.[73]

Mumps

Mumps, commonly referred to as the childhood viral disease, is a contagious infectious disease that belongs to the family *Paramyzoviridae*, genus *Rubulavirus*.[74] It is characterized by swelling of the parotid gland, and is clinically defined by the WHO as an acute onset of unilateral or bilateral tender, swelling of the parotid or other salivary glands, lasting two or more days without another apparent cause.[71] Whereas, WHO laboratory diagnosis is defined as either the isolation of mumps from a specimen, a positive serologic test for mumps-specific IgM antbodies, or a significant rise in serum mumps IgG titre.[71]

Mumps is acquired in the nasal or upper respiratory tract mucosa by vehicle of droplet spread, direct contact, or contaminated fomites.[74,75] The incubation period is approximated to range between 15 to 24 days. Infected persons are most contagious one to two days prior to the onset of clinical symptoms and for several days thereafter.[74] Initial symptoms include fever, malaise, headache, earache, sore throat, and difficulty swallowing.[76] However, approximately one third of mumps infections present with no recognized symptoms.[74] Complications can arise from mumps such as orchitis (inflammation of the testes), meningitis, and encephalitis.[76] In rare cases, deafness can occur.[77]

In 1969, Canada approved the license for a live mumps vaccine.[77,78] In a cocktail with measles and rubella, routine publicly funded immunization for one-dose mumps was commenced in 1983 across the nation, and a two-dose schedule was introduced in the years 1996 and 1997.[68] With the introduction of the mumps vaccine, the incidence of mumps has declined over the years. Between 1924 and 1958, incidence rates in Canada ranged from 52 cases to 449 cases per

100,000 population.[79] No incidence data exists between the years 1959 and 1985 due to the exclusion of mumps from the Canadian notifiable disease list for this period.[79] More recently in 2009, 108 cases of mumps were reported in Ontario with an incidence rate of 0.8 cases per 100,000 population.[80]

Rubella

Rubella, also known as German measles, is a contagious respiratory disease that is acquired from the causative agent, rubella virus.[81,82] The disease is a member of the family *Togaviridae*, genus *Rubivirus*, and is characterized as self-limiting with a gradual onset of a rash and flu like symptoms such as cough, sore throat, and sneezing.[81] According to WHO diagnostics standards, rubella cannot be clinically diagnosed; a laboratory confirmation of a positive blood test for rubella-specific IgM is required.[71]

The incubation period for rubella is estimated to be between 7 to 14 days in duration.[83,84] Rubella is acquired by route of droplet spread or transplacental transmission of the virus from an infected mother to her fetus during pregnancy. Passive placental transmission can lead to congenital rubella syndrome which can potentially occur in infants whose mother was infected with rubella prior to conception or within 8 to 10 weeks gestation.[83] Common birth defects associated with the syndrome most often affect the heart, brain, ears, eyes, and cause serious developmental delays.[81]

In 1969, rubella vaccine was licensed for use in Canada.[85] Immunization for a routine publicly funded one-dose rubella vaccine was implemented in 1983, in combination with measles and mumps.[86] In 2003, the Pan-American Health Organization established a goal to eliminate rubella from the WHO region of the America's by 2010.[86] While attending a 2005 national vaccine preventable disease conference, Canadian public health experts adopted the

WHO goal to attain elimination status in Canada.[86] Elimination was defined as (1) the interruption of endemic transmission, and (2) failure to re-establish endemic transmission within 12 months following importation.[86] On April 29, 2015, the Pan-American Health Organization attained their goal, announcing the elimination of rubella from the WHO region of the America's.[87] This elimination succeeds only two other diseases that have been eliminated from the WHO region of the America's: smallpox in 1971, and poliomyelitis in 1994.[87]

Since the implementation of routine immunization of rubella vaccine in Canada, the incidence has maintained a steady decline, despite occurrences of outbreaks.[86] In 2009, a total of three rubella cases were reported in Ontario with an incidence rate less than 1.0 cases per 100,000 population.[80] Even with Canada's success in achieving low incidence of rubella, sporadic cases will continue to occur in the nation for as long as the disease exists elsewhere in the world.[86]

1.3. Thesis Rationale and Objectives

Children are launched on trajectories of health prior to birth during pre-conception, which lays the foundation for the continuum of health and well-being across the life course. It has been well documented in the literature that early life exposure to health risks and preventative medicine can affect how biological, cognitive, emotional, behavioural, and social capabilities develop throughout childhood. Two fundamental domains of health that are recognized by the OPHS include reproductive health, and VPDs.[2] However, there is a paucity of child health research surrounding these two domains of health for rural Southern Ontario populations. Thus, this thesis sought to investigate (1) the association of pre-pregnancy BMI with the risk of developing GDM and GH in a rural Southern Ontario community (Chapter 2); and (2) the levels of immunization compliance for measles, mumps, and rubella, among children that reside in the

city of Guelph (Chapter 3). The availability of child health registers in the province of Ontario affords the opportunity to address these aims. It is imperative to conduct such research to identify populations that are at risk for the development of poor child health outcomes, and to establish baselines that can aid in the promotion of individual and population health. The following objectives were established for this thesis:

1. Estimate the probability of developing GDM by incremental pre-pregnancy BMI values, identifying and controlling for confounding variables, with pre-pregnancy BMI and net change in BMI as exposures of interest (Chapter 2)
2. Estimate the probability of developing GH by incremental pre-pregnancy BMI values, identifying and controlling for confounding variables, with pre-pregnancy BMI and net change in BMI as exposures of interest (Chapter 2)
3. Calculate immunization compliance for measles, mumps, and rubella among seven year old pupils residing in the city of Guelph (Chapter 3)
4. Map immunization compliance of seven year old pupils by neighbourhood within the city of Guelph (Chapter 3)
5. Identify neighbourhoods most at risk for potential measles, mumps, and rubella outbreaks (Chapter 3)

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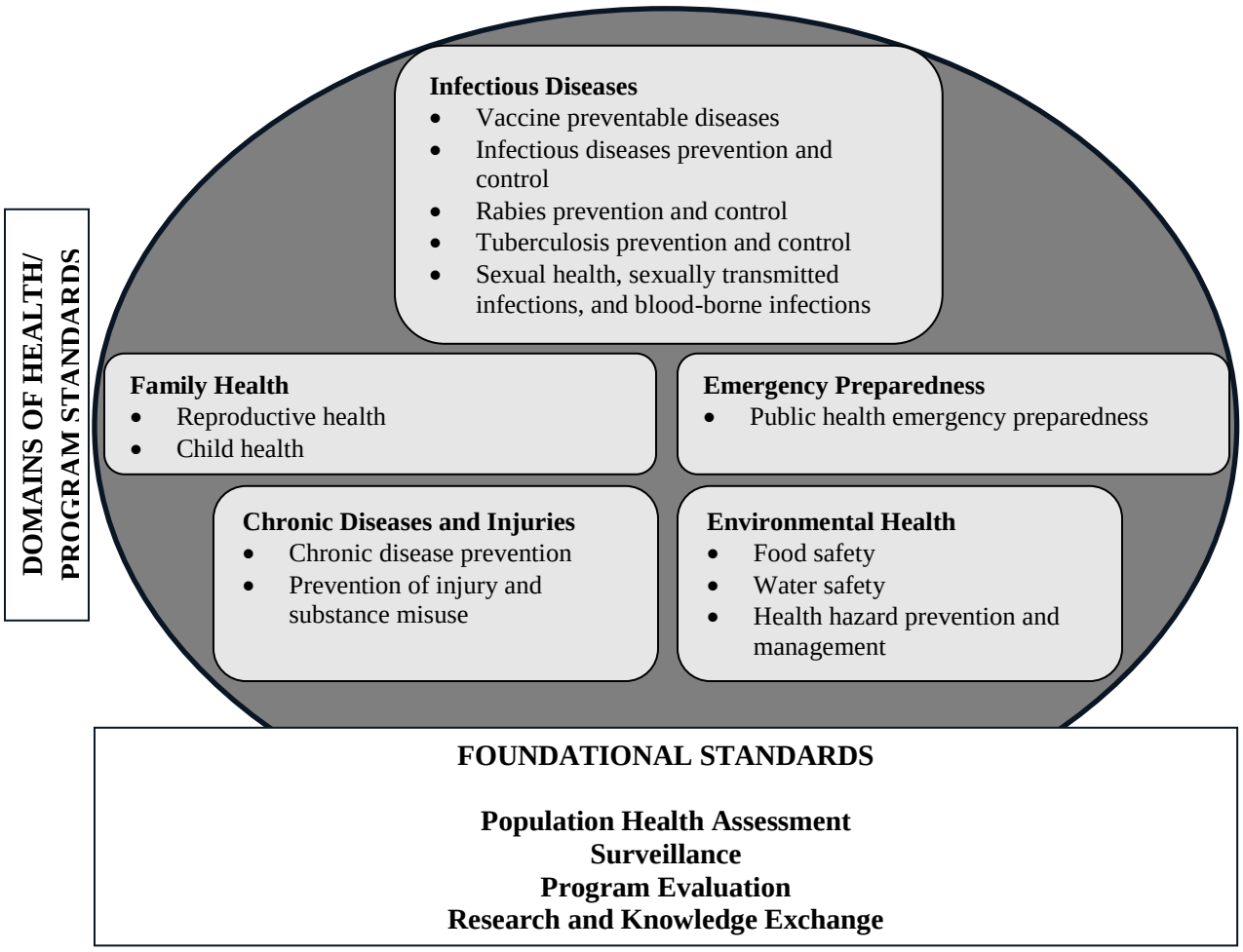
Figure 1.1. Ontario Public Health Standards (OPHS): Domains of health and foundational standards



Adopted from: Ministry of Health and Long-Term Care. *Ontario Public Health Standards 2008*. Toronto, ON: Queen's Printer for Ontario; 2014.

CHAPTER TWO

Establishing a Baseline: The risk of adverse maternal pregnancy outcomes in a rural Southern Ontario community

Prepared for: Paediatrics and Child Health – Canadian Paediatric Society

Abstract

Objective: To determine the association of pre-pregnancy body mass index (BMI) with the risk of developing gestational diabetes mellitus (GDM) and gestational hypertension (GH) in a rural Southern Ontario community.

Methods: This population based cohort study (n=788) was drawn from Ontario's Better Outcomes Registry and Network (BORN). Maternal and newborn antenatal, labour and perinatal data were extracted for all singleton pregnancies between January 1, 2010 and December 31, 2014 from a Level I rural Southern Ontario community hospital. Multivariable logistic regression models were built to assess potential confounders associated with the development of GDM and GH. The variables smoking during pregnancy, parity, and age were considered *a priori* as potential confounders for the GDM model. Whereas, smoking during pregnancy, parity, primigravida, diabetes, and age were considered *a priori* as potential confounders for the GH model. The variables pre-pregnancy BMI and net change in BMI were included in both models as exposures of interest.

Results: In our study group, the incidence risk of GDM was 4.8%, whereas the incidence risk of GH was 3.9%. For both GDM and GH, the incidence appeared to exponentially increase at a pre-pregnancy BMI of 27.5 kg/m^2 in comparison to the preceding pre-pregnancy BMI categories. After controlling for net change in BMI, pre-pregnancy BMI was significantly associated with

the incidence risk of both GDM and GH with adjusted odds ratio (OR) of 1.12 (95% CI, 1.05-1.20; p<0.001) and 1.21 (95% CI, 1.12-1.31; p<0.001), respectively. Net change in BMI and maternal age were also significantly associated with the incidence risk of GH with an adjusted OR of 1.26 (95% CI, 1.07-1.48; p=0.01) and 0.91 (95% CI, 0.84-0.99; p=0.04), respectively.

Conclusion: Pre-pregnancy BMI was significantly associated with the risk of developing both GDM and GH. A pre-pregnancy BMI of 27.5 kg/m^2 appeared to be a threshold for higher incidence of both diseases. These results can inform pre-conception counselling of healthy weight management for women of childbearing years.

Keywords: Body mass index (BMI), gestational diabetes mellitus (GDM), gestational hypertension (GH), pregnancy, and obesity.

Abbreviations

ANOVA: analysis of variance

BORN: Better Outcomes Registry and Network

BMI: body mass index

CDC: Centers for Disease Control and Prevention

CI: confidence interval

CIHI: Canadian Institute for Health Information

GDM: gestational diabetes mellitus

GH: gestational hypertension

HELLP: hemolysis, elevated liver enzymes, and low platelet count

IOM: Institute of Medicine

OR: odds ratio

PHAC: Public Health Agency of Canada

REB: Research Ethics Board

SOGC: Society of Obstetrics and Gynaecology of Canada

WHO: World Health Organization

2.1. Introduction

Obesity is a condition characterized by abnormal or excessive fat accumulation in adipose tissue and is measured clinically by body mass index (BMI).[1,2] BMI is the most widely integrated, albeit crude, measure of obesity at the population level,[1,3] and is measured by dividing an individual's weight in kilograms by height in meters squared.[3,4] The prevalence of obesity in Canadian women increased 16.8% between 2003 and 2013.[5] According to a 2006-2007 national survey, 21% of Canadian women enter pregnancy overweight, and 13.6% enter pregnancy obese.[6] A woman's BMI prior to pregnancy has a direct influence on her and her baby's health.[7] As the prevalence of obesity in Canadian women increases, it is anticipated that the incidence of adverse pregnancy outcomes will rise in parallel. Identifying populations that are at risk for adverse pregnancy outcomes, and promoting the importance of healthy pre-conception weight can contribute to the improvement of maternal and fetal health.

Maternal pre-pregnancy BMI is one of the most imperative modifiers that has a direct influence on maternal and infant health.[8] To improve maternal and child health outcomes, the Institute of Medicine (IOM) recommends women enter pregnancy within a normal BMI range, between 18.5 kg/m^2 and 24.9 kg/m^2.[8] Currently, one third of Canadian women are entering pregnancy with a BMI ≥25 kg/m^2, and <10% are entering pregnancy with a BMI <18.5 kg/m^2.[6,9] In comparison to women entering pregnancy within a normal BMI range (18.5 kg/m^2 to 24.9 kg/m^2), women with a BMI outside the normal range are at greater risk of poor maternal, fetal, and pregnancy outcomes.[10–17]

Two common diseases that have been linked with pre-pregnancy BMI are gestational diabetes mellitus (GDM), and gestational hypertension (GH).[12] GDM is denoted as the development of hyperglycemia during pregnancy.[18] A systematic review and meta-analysis

conducted by Bellamy et al. found that women with GDM are at an increased risk of developing type II diabetes compared to a normoglycaemic pregnancy (RR 7.43, 95% CI 4.79-11.51).[19] Moreover, children born to mothers with GDM have an increased risk of type I diabetes.[20] GH is characterized by an elevation of blood pressure at ≥20 weeks gestation, in a previously normotensive woman in the absence of proteinuria or new signs of end-organ dysfunction.[21,22] In comparison to normotensive pregnancies, women with GH have higher rates of pre-term birth (<37 weeks gestation)[23], and delivery of small for gestational age infants (<10th percentile).[24–26]

Good maternal and perinatal health begins prior to the conception of a baby.[7] Preconception care can benefit a woman's health across her lifespan and extend into pregnancy. It is imperative for women of childbearing age to be provided with the knowledge and support to maintain their health. The Society of Obstetrics and Gynaecology of Canada (SOGC) established clinical guidelines containing recommendations for the counselling and management of obesity in pregnancy.[2] One of the recommendations set forth is for health professionals to engage women in healthy lifestyle adaptation prior to conceiving. This can be accomplished by educating women about the potential adverse effects of being overweight or underweight on the health of a mother and baby.[27] However, there is a paucity of tools available to health professionals to inform preconception weight counselling.[28]

Preconception health, as defined by the Ontario Public Health Association, refers to the health of individuals during child bearing years.[29] The premise is to promote healthy fertility by focusing on individual health behaviours to increase readiness for pregnancy.[29] In Canada, no standardized framework exists either federally or provincially for guidelines in the area of preconception health.[29] The promotion of preconception health in Ontario is mandated under the

2008 Ontario Public Health Standards; however, implementation into clinical practice has been inconsistent.[30]

The purpose of this study was to determine the association of pre-pregnancy BMI with the risk of developing GDM and GH in a rural Southern Ontario community. Health care professionals can utilize the study results to identify populations most at risk, for whom targeted preconception weight counselling can be of benefit. Specifically, the objectives of the study were to: (1) estimate the probability of developing GDM by incremental pre-pregnancy BMI values, identifying and controlling for confounding variables, with pre-pregnancy BMI and net change in BMI as exposures of interest, and (2) estimate the probability of GH by incremental pre-pregnancy BMI values, identifying and controlling for confounding variables, with pre-pregnancy BMI and net change in BMI as exposures of interest.

2.2. Materials and Methods

2.2.1. Data Source

In the province of Ontario, data about each birth are able to be collected and entered into Ontario's Better Outcomes Registry and Network (BORN) Information System.[31] Established in 2009, BORN is Ontario's pregnancy, birth, and childhood registry and network that enables the collection and sharing of prenatal data, and is a prescribed registry under Ontario's Personal Health Information Protection Act.[31,32] The registry is active in every region of the province with data procured from many sources including hospitals.[32] The population for this cohort study was drawn from a Level I rural (an area lying outside population centres) Southern Ontario community hospital's BORN Information System. As a component of routine BORN data entry, pregnancy and birth records were manually entered into BORN by a designated perinatal nurse on-site at the hospital. Each pregnancy record was automatically assigned a unique identification

number upon entry into the registry. For the current study, maternal and newborn antenatal, labour, and perinatal data were extracted for all singleton pregnancies between January 1, 2010 and December 31, 2014. Prior to the transfer of these data to the University of Guelph researchers, a hospital analyst de-identified maternal demographic variables, and these variables were not assessable to the university researchers.

Ethics approval was obtained from the University of Guelph Research Ethics Board (REB), Certification of Ethical Acceptability of Research Involving Human Participants (#14DC008) and from the community hospital REB (#15-02).

2.2.2. Data Management

Maternal pre-pregnancy weight and height data were routinely obtained at the first antenatal visit. Pre-pregnancy weight was defined as a mother's self-reported weight closest to conception and no later than 12 weeks of gestation, transcribed in metric or imperial units.[33] Maternal end of pregnancy weight represents the self-reported weight closest to the end of pregnancy.[33] For the purpose of this study, maternal weight variables were converted to metric units (kilograms). Pre- and end of pregnancy maternal BMI was calculated for each record as weight in kilograms divided by height in metres squared. The net change in maternal BMI was calculated by subtracting pre-pregnancy BMI (kg/m^2) from end of pregnancy BMI (kg/m^2).

Pregnancy records were classified into one of several pre-pregnancy BMI categories. The categories were developed in accordance with the Canadian Guidelines for Body Weight Classification in Adults[3] which is aligned with the World Health Organization (WHO) International recommendation for BMI classification. The pre-pregnancy BMI categories were: underweight ($<18.5\ kg/m^2$), normal weight I ($18.5\ kg/m^2 \leq BMI < 23\ kg/m^2$), normal weight II ($23\ kg/m^2 \leq BMI < 25\ kg/m^2$), overweight I ($25\ kg/m^2 \leq BMI < 27.5\ kg/m^2$), overweight II (27.5

$kg/m^2 \leq BMI < 30\ kg/m^2$), obese class I ($30\ kg/m^2 \leq BMI < 35\ kg/m^2$) and obese class II ($35\ kg/m^2 \leq BMI < 40\ kg/m^2$).

Maternal smoking status during pregnancy was divided into two groups, yes or no. The discrete quantitative variables parity and gravida were categorized, with parity into three groups (<2, 2-3, ≥4), and gravida re-classified as primigravida (yes or no).

Data files were managed using Microsoft Excel 2010 Software (Microsoft. Microsoft Excel. Redmond, Washington), and data manipulation was performed using SAS 9.4 Software (SAS Institute, Inc., Cary, North Carolina). Maternal pre-pregnancy weight and height data were routinely obtained at the first antenatal visit.

2.2.3. Study Population

Due to the relatively low number of births at the community hospital per year, removal of some observations was necessary to maintain the anonymity of patients. Maternal ageswith a count ≤5 were excluded from the study. Pregnancy records with either a pre- or end of pregnancy weight <40.8 kg (90 lbs) were removed.

Hospitals designated as a Level I centre typically provide both Level I maternal and Level I newborn care to clients.[34] The designation of a hospital signifies the scope of services and treatments available, with Level I being the lowest tier of three levels.[34] The Level I hospital was equipped to provide care to normal singleton births at ≥34 weeks gestation or infants ≥1,800 grams, and had on-site caesarean section capability available.[34] If a mother or baby required a higher level of care, they would have been referred and/or transferred to a higher designated hospital.[35] Likewise, women with a pre-pregnancy BMI $\geq 40\ kg/m^2$ were referred and/or transferred to a higher designated hospital, and were therefore excluded from this study.

The outcomes of interest were the incidence risk of GDM and GH. Pregnancies complicated by pre-existing diabetes mellitus were excluded only for analyses of GDM, whereas pregnancies complicated by pre-existing hypertension were excluded only for analyses of GH. Pre-existing hypertensive conditions were inclusive to hypertension, eclampsia, preeclampsia and HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome. Pre-existing diabetes mellitus conditions included types I and II. The final study population was restricted to pregnancy records with available pre- and end of pregnancy maternal BMI.

2.2.4. Outcome Measures

GDM and GH outcomes are binary variables, classified either as positive for developing the disease or negative as not developing the disease during the recorded pregnancy. Disease status was physician diagnosed, and was representative of a woman's diseased state for the transcribed pregnancy.

2.2.5. Statistical Analysis

For each outcome of interest (incidence risk of GDM and GH, respectively), maternal descriptive and baseline characteristics were calculated and presented by pre-pregnancy BMI category as mean (±standard deviation) for continuous variables and frequency (percent) for categorical variables. For the outcome GDM, records with pre-existing diabetes mellitus were removed from analyses. Whereas for the outcome GH, records with pre-existing hypertension were removed from analyses. Maternal characteristics were then compared among all pre-pregnancy BMI categories; a chi-square test (χ^2) was used to assess the proportions of categorical maternal characteristics, whereas Fisher's exact test was used when at least one cell had an expected frequency of ≤ 5 for the chi-square test (χ^2).[36] Analysis of variance (ANOVA) was used

for continuous maternal characteristics to compare means.[36] Normality of continuous variables was assessed visually using a QQ-plot, as well as skewness and kurtosis.[37]

To estimate the probability of GDM and GH by pre-pregnancy BMI, separate multivariable logistic regression models for each outcome were built, adjusting for pre-pregnancy BMI and net change in BMI. The variables smoking during pregnancy, parity, and age were considered *a priori* as potential confounders for the GDM model. Whereas, smoking during pregnancy, parity, primigravida, diabetes, and age were considered *a priori* as potential confounders for the GH model. In both models, the variable pre-pregnancy BMI was included as the primary exposure of interest, and the variable net change in BMI was included as the secondary exposure of interest. The initial step was unconditional analysis of all covariates to screen for associations with the outcome using a liberal significance level of 20%.[36] For categorical covariates, a chi-square test (χ^2) was used while simple logistic regression was performed for continuous covariates. A potential confounding variable was retained for consideration in the multivariable model building process if significance was attained in the unconditional analysis ($p<0.2$).[36] The variables pre-pregnancy BMI and net change in BMI were forced into both models as the primary and secondary exposure of interest, respectively.

Linearity of continuous variables was then assessed by inclusion of quadratic terms in the unconditional simple logistic model. Quadratic terms were included with non-quadratic terms if significant at $\alpha<0.05$.[36] Linearity was also assessed graphically by plotting a lowess smoothed curve of the dichotomous outcome on the logit scale against the continuous independent variable on the logit scale.[36]

All pairwise correlations were examined among potential confounding variables that were significant at a level of 20% with the outcome using a Spearman Rank or Pearson

correlation analysis for categorical and continuous variables, respectively. A correlation coefficient greater than 0.8 ($|\rho|>0.8$) signified high collinearity among variables.[36] If the correlation coefficient of a pair of variables exceeded 0.8, the variable with the fewest missing observations and greatest biological plausibility was selected for inclusion in the multivariable model.[36]

Utilizing a backward elimination stepwise model building approach, the retained covariates were used to construct separate multivariable logistic regression models for each outcome; GDM, and GH. As exposures of interest, the variables pre-pregnancy BMI and net change in BMI were forced into each respective model regardless of their level of significance. All possible two-way interaction terms were generated between covariate pairs by adding the cross-product terms and were retained in the model if statistically significant ($\alpha<0.05$).[36] To achieve a parsimonious model, non-significant variables ($\alpha>0.05$) were removed from the multivariable model, one at a time. Removal commenced with the least significant variable until all covariates had a significance level of $\alpha<0.05$.[36] Removed variables were then assessed for confounding and retained in the model if they produced a >20% change in coefficients of one or more variable within the model.[36] Regardless of the level of significance, a variable was retained in the final model if it was a component of a significant interaction term.[36] A likelihood ratio test and Type 3 Analysis was completed to compare the fit of the full model to the fit of the reduced model. A significance level of $\alpha<0.05$ represented the full model fitting the data better than the reduced model.[36,38]

The fit of the final model for both GDM and GH were assessed by the Hosmer-Lemeshow goodness of fit test with a χ^2 *P*-value >0.05 signifying there being no found indication

that the model does not fit the data.[36] Potential outliers and points of interest were investigated by influence diagnostics.[36]

Utilizing the final GDM and GH model, predicted probability of each outcome was calculated by incremental pre-pregnancy BMI values that ranged from 16 kg/m^2 to 39 kg/m^2, respectively. The population average value for all other covariates in each final model was used in the calculation of predicted probability.

Statistical analysis was conducted using SAS 9.4 Software (SAS Institute, Inc., Cary, North Carolina), and STATA Intercooled Version 13.0 (StataCorp, 2007) was used for graphical assessment of linearity.

2.3. Results

2.3.1. Study Population

There were 1,950 pregnancies entered into BORN between January 1, 2010 and December 31, 2014 (Figure 2.1). After all exclusions, the final study denominator comprised 787 and 777 pregnancy records for the analyses of GDM and GH, respectively. From our base study population of 1,950 pregnancies, 1,115 (57.8%) had either missing weight or height data and were excluded.

2.3.2. Gestational Diabetes Mellitus (GDM) Outcome

GDM Maternal Descriptive and Baseline Characteristics

Table 2.1. presents the maternal descriptive and baseline characteristics of the study denominator by pre-pregnancy BMI categories for GDM; 1 record was removed from analyses for having a pre-existing diabetes mellitus condition. The majority of pregnancies (29.2%) were among the normal weight I BMI category ($18.5 \leq BMI < 23$), whereas the smallest proportion of pregnancies (2.3%) were among the underweight BMI category ($BMI < 18.5$). A significant

difference between BMI categories was observed in the incidence of GDM, age, parity, pre-pregnancy weight, post-pregnancy weight, gestational weight gain, and net change in BMI ($p<0.05$). There were no significant differences in smoking during pregnancy, primigravida, and maternal height by maternal pre-pregnancy BMI category ($p>0.05$).

The incidence risk of GDM was 4.8% in our study group. At a pre-pregnancy BMI of 27.5 kg/m^2, the incidence appeared to exponentially increase in comparison to the preceding pre-pregnancy BMI categories.

GDM Multivariable Logistic Regression Analysis

The factors age ($p=0.12$), pre-pregnancy BMI ($p<0.001$), and net change in BMI ($p=0.003$) were significantly associated with GDM in univariable analyses at $\alpha<0.20$ (Table 2.2.). The continuous variables age, pre-pregnancy BMI, and net change in BMI were normally distributed. All continuous variables had a linear relationship with GDM, thus satisfying the assumption of linearity. Collinearity was not a concern as rho $|\rho|<0.80$ for all pairwise correlations.

The variable for age was the least significant covariate in the full model with $p>0.05$ ($p=0.36$) and the removal of age produced a change in coefficients <20% for all retained covariates. The likelihood ratio test and Type 3 Analysis both concluded the presence of age in the model was not significantly associated with determining the status of GDM ($p=0.37$, respectively), and therefore age was removed from the model.

The final multivariable model is presented in Table 2.3. For every one unit increase in pre-pregnancy BMI (1 kg/m^2), the odds of developing GDM increased by 1.12 times (95% CI, 1.05-1.20; $p<0.001$). After controlling for pre-pregnancy BMI, net change in BMI was just beyond the cut point of significance ($p=0.07$); however, it was forced into the model as it was an

exposure of interest. Net change in BMI had a non-significant sparing effect for the development of GDM (OR, 0.86; 95% CI, 0.73-1.01). The Hosmer-Lemshow goodness of fit test found no indication that the model does not fit the data (p=0.33). Visual assessment of residuals identified one outlier pregnancy record. Removal of the record did not substantially change the interpretation of the model, and the record was retained.

Table 2.4. quantifies the adjusted predicted probability of GDM by pre-pregnancy BMI. Results are reported at the population average value for net change in BMI (5.08 kg/m^2). For a pre-pregnancy BMI between 16 kg/m^2 and 39 kg/m^2, the predicted probability ranged from 1.25% to 15.84%. Figure 2.2. depicts the positive relationship between increasing pre-pregnancy BMI and the predicted probability.

2.3.3. Gestational Hypertension (GH) Outcome

GH Maternal Descriptive and Baseline Characteristics

Table 2.5. presents the maternal descriptive and baseline characteristics of the study denominator by pre-pregnancy BMI categories for GH; 11 records were removed from analyses for having a pre-existing hypertensive condition. The majority of pregnancies (29.3%) were among the normal weight I BMI category ($18.5 \leq BMI < 23$), whereas the smallest proportion of pregnancies (2.3%) were among the underweight BMI category ($BMI < 18.5$). A significant difference between BMI categories was observed in the incidence of GH, age, parity, pre-pregnancy weight, post-pregnancy weight, gestational weight gain, and net change in BMI ($p<0.05$). There were no significant differences in smoking during pregnancy, primigravida, and maternal height by maternal pre-pregnancy BMI category ($p>0.05$).

The incidence risk of GH was 3.9% in our study group. At a pre-pregnancy BMI of 27.5 kg/m^2, the incidence appeared to exponentially increase in comparison to the preceding pre-pregnancy BMI categories.

GH Multivariable Logistic Regression Analysis

The factors primigravida ($p=0.02$), age ($p=0.07$), pre-pregnancy BMI ($p<0.001$), and net change in BMI ($p=0.14$) were significantly associated with GH in univariable analyses at $\alpha<0.20$ (Table 2.6.). The continuous variables age, pre-pregnancy BMI, and net change in BMI were normally distributed. All continuous variables had a linear relationship with GH, thus satisfying the assumption of linearity. Collinearity was not a concern as rho $|\rho|<0.80$ for all pairwise correlations.

The variable primigravida was the least significant covariate in the full model with $p>0.05$ ($p=0.09$) and the removal of primigravida produced a change in coefficients <20% for all retained covariates. The likelihood ratio test and Type 3 Analysis both concluded the presence of primigravida in the model was not significantly associated with determining the status of GH ($p=0.09$, respectively) and thus this variable was removed from the model.

The final multivariable model is presented in Table 2.7. For every one unit increase in pre-pregnancy BMI (1 kg/m^2), the odds of developing GH significantly increases 1.21 times (95% CI, 1.12-1.31; $p<0.001$). For each one unit increase in net change of BMI (1 kg/m^2), the odds of developing GH significantly increases 1.26 times (95% CI, 1.07-1.48; $p=0.01$). Maternal age has a significant sparing effect on the development of GH with the odds significantly decreasing 0.91 times for each one year increase in maternal age (95% CI, 0.84-0.99; $p=0.04$). The Hosmer-Lemeshow goodness of fit test found no indication that the model does not fit the data ($p=0.09$). Visual assessment of residuals identified two outlier pregnancy records. Removal

of the records did not substantially change the interpretation of the model, and the records were retained.

The adjusted predicted probabilities were calculated for GH (Table 2.4.). The population average value for age (28.88 years), and net change in BMI (5.06 kg/m^2) were used to calculate the results. Figure 2.3. depicts the positive relationship between increasing pre-pregnancy BMI and the predicted probability, which ranged from 0.36% to 24.45% for a pre-pregnancy BMI between 16 kg/m^2 and 39 kg/m^2.

2.4. Discussion

Maternal pre-pregnancy BMI was significantly associated with the risk of developing both GDM and GH. These results are consistent with previous literature. Torloni et al. published a systematic review and meta-analysis, quantifying the risk of GDM according to pre-pregnancy BMI. Seventy individual studies were included in the analysis which concluded the risk of GDM to be positively associated with pre-pregnancy BMI.[13] In a study examining pre-pregnancy BMI as an independent risk factor for the development of GH, authors reported that the risk of GH increased with maternal pre-pregnancy BMI.[15] The results of our study add breadth to the existing body of literature surrounding adverse maternal pregnancy outcomes, as it fills a void in studies conducted in rural Canadian populations.

The implications of our findings are that primary care physicians and obstetricians should be counselling patients of childbearing age to maintain a BMI less than 25.0 kg/m^2. In particular, women that are planning to conceive should be educated on the risks associated with having a high BMI. A woman's BMI status prior to pregnancy is a crucial factor that influences the health of the mother and her baby. If women receive education, they can be equipped to make informed decisions to lower their BMI before pregnancy. As the prevalence of obesity in Canadian women

continues to rise, doctors have the opportunity to make a critical difference in reducing the risk of adverse maternal health outcomes by incorporating preconception health into their routine practice.

The analysis examining factors associated with the development of GDM found that after controlling for pre-pregnancy BMI, net change in BMI appeared to have a non-significant sparing effect on the risk of GDM. The amount of weight a woman is recommended to gain during pregnancy is dependent on her weight prior to conception.[8] According to the widely accepted IOM 2009 guidelines on recommended weight gain during pregnancy, the lower a woman's pre-pregnancy weight, the more weight she is recommended to gain during gestation.[8] Thus, if a woman follows the IOM guidelines, a low pre-pregnancy BMI will produce a larger net change in BMI during pregnancy compared to a woman with a higher pre-pregnancy BMI. In our study population, women in the normal weight BMI categories (normal weight I (18.5 $kg/m^2 \leq BMI < 23\ kg/m^2$), and normal weight II ($23\ kg/m^2 \leq BMI < 25\ kg/m^2$)) produced the largest net change in BMI (refer to Table 2.1.). The resulting sparing effect is consistent with the IOM guidelines for normal weight individuals. Women should be encouraged to gain weight during pregnancy within these guidelines to reduce their odds of developing GDM.

Interestingly, maternal age was found to have a significant sparing effect on the development of GH after controlling for pre-pregnancy BMI and net change in BMI. In an analysis conducted by the Canadian Institute for Health Information (CIHI), the odds of developing GH were reported to be highest among pregnant women age 40 years and older.[39] As well, women giving birth at age 35 and older were reported to be more likely to have pre-existing hypertensive conditions.[39] In our population, maternal age ranged from 18 years to 39 years. Thus, our data did not include women that are most prone to developing GH.

In Ontario's 2012 Action Plan for Health Care, the government committed to establishing a multi-sectoral panel of content area and policy experts to inform the development of a strategy to improve child health, specifically obesity.[40] The government recognized that women's preconception health and weight, along with gestational weight gain, has a direct effect on the health and weight of their baby.[7,40] The Healthy Kids Panel was formed and provided the Ministry of Health and Long-Term Care a report of recommendations for action.

The panel recommended educating women of child bearing age about the impact of their health and weight on their own well-being and the well-being of their child.[7] The panel also recommended the development of guidelines and tools for the use by health professionals to deliver preconception health programs to reinforce the importance of women maintaining a healthy pre- and post-pregnancy weight.[7] The panel expressed that through experience with tobacco control initiatives, there is no "silver bullet", and a comprehensive evidence based strategy is required for preconception health interventions.[7,40] The estimated predicted probabilities can aid in the pre-conception counselling of healthy weight for women of childbearing years by informing them of their risk, and how their risk can change given a shift in pre-pregnancy BMI. Further studies are recommended to estimate the risk of developing other adverse maternal health outcomes by pre-pregnancy BMI in this population.

Results of the study must be interpreted in light of several limitations. The study was inclusive to one rural community hospital, limiting the generalizability of results. Data on height and weight were maternally self-reported. A Canadian study found that self-reported height tends to be overestimated, whereas self-reported weight tends to be underestimated[41]; however, the magnitude and accuracy of reporting is unknown in our data and we were unable to estimate the degree of possible misclassification.

In the literature, evidence suggests that maternal ethnicity confounds the relationship between BMI, and both GDM and GH.[42,43] Ethnicity data were not available in our dataset, thus we were unable to control for the potential confounding effects. A frequently reported risk factor for GDM is a family history of diabetes mellitus.[44,45] Likewise, our dataset did not contain data on maternal family history, and we were unable to control for this in our analyses. As well, literature suggests that a pregnancy complicated by GDM is at increased risk for the development of GDM in subsequent pregnancies.[46,47] Given our four year study period, it is possible that women present more than one pregnancy within the dataset. However, this was unable to be determined since maternal identifiers were not available to researchers.

Of the 1,950 pregnancy records in our study base, 1,115 (57%) had missing height or weight data and were excluded. The high percentage of missing data may be attributed to the short duration that the community hospital has been collecting and entering pregnancy records into BORN. The percent missing height or weight data was 100% in 2010, and progressively declined thereafter to 24% in 2014 (data not shown). With the progression of time, health professionals aim to have the collection and entry of pregnancy records become routine in clinical practice.

Analyses of adverse maternal health outcomes were restricted to the upper limit pre-pregnancy BMI of 39 kg/m^2 since the community hospital from which our data were obtained does not typically provide gynaecologic care to the ≥40 BMI cohort. A future study examining the risk of GDM and GH by pre-pregnancy BMI ≥40 kg/m^2 will allow for a more complete risk assessment of the source population across the spectrum of pre-pregnancy BMI categories.

2.5. Conclusion

This study examined the association between pre-pregnancy BMI and the risk of developing GDM and GH in a rural Southern Ontario community between January 1, 2010 and December 31, 2014. Pre-pregnancy BMI was significantly associated with the risk of developing both GDM and GH. The predicted probabilities of developing both conditions were calculated by incremental pre-pregnancy BMI values and these results can be utilized by health care professionals to aid in the pre-conception counselling of healthy weight management for women of childbearing years. Long-term, pre-conception counselling tools can help educate women to ensure they are informed on the benefits of entering pregnancy in the best health possible in order to decrease their risk of adverse pregnancy complications.

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2.7. Conflict of Interest

The authors declare no conflict of interest.

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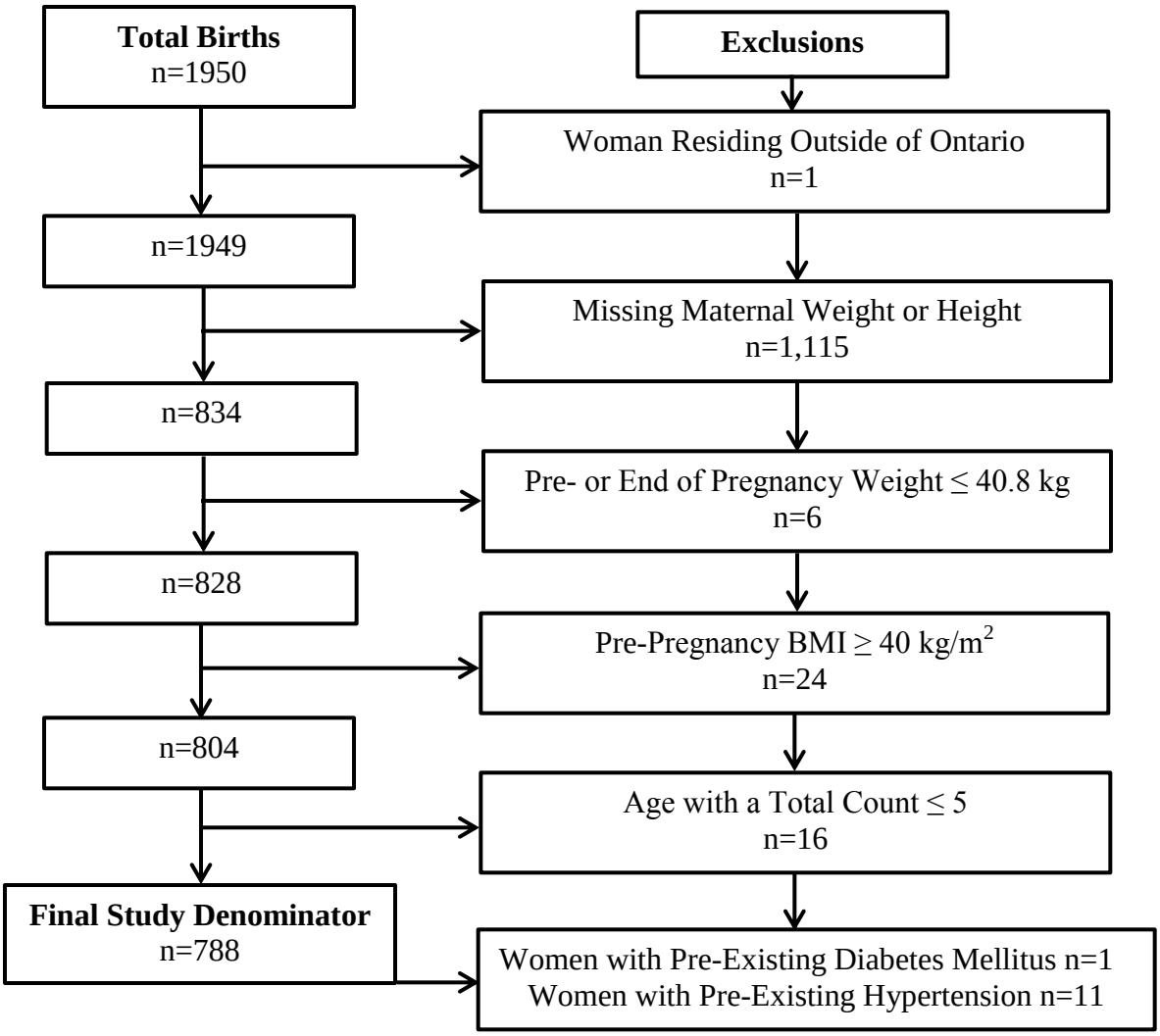


Figure 2.1. Flow diagram. Composition of study denominator for an evaluation of maternal pre-pregnancy BMI with the risk of developing gestational diabetes mellitus and gestational hypertension in a rural Southern Ontario community hospital.

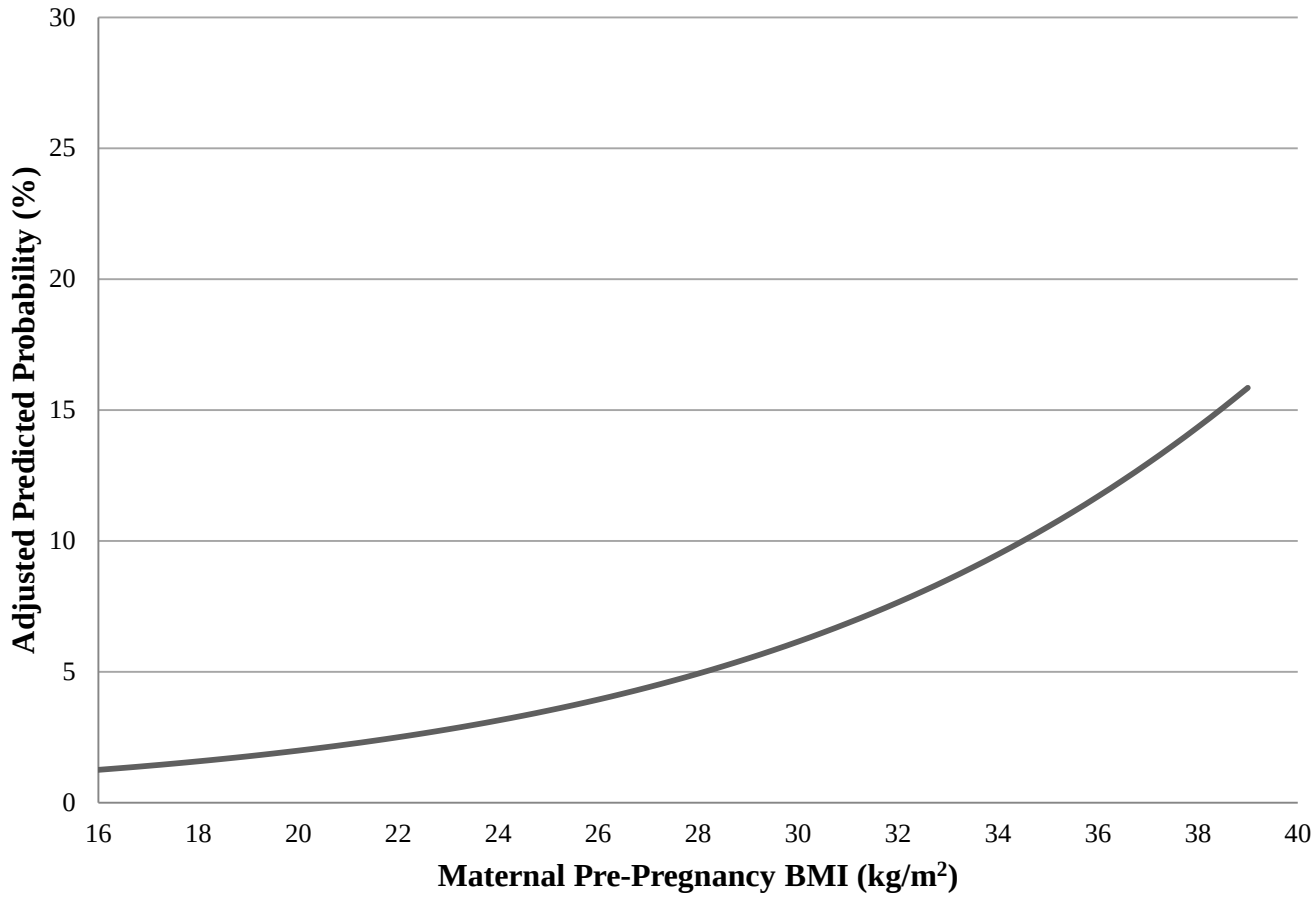


Figure 2.2. Adjusted predicted probability of gestational diabetes mellitus by maternal pre-pregnancy body mass index (BMI).

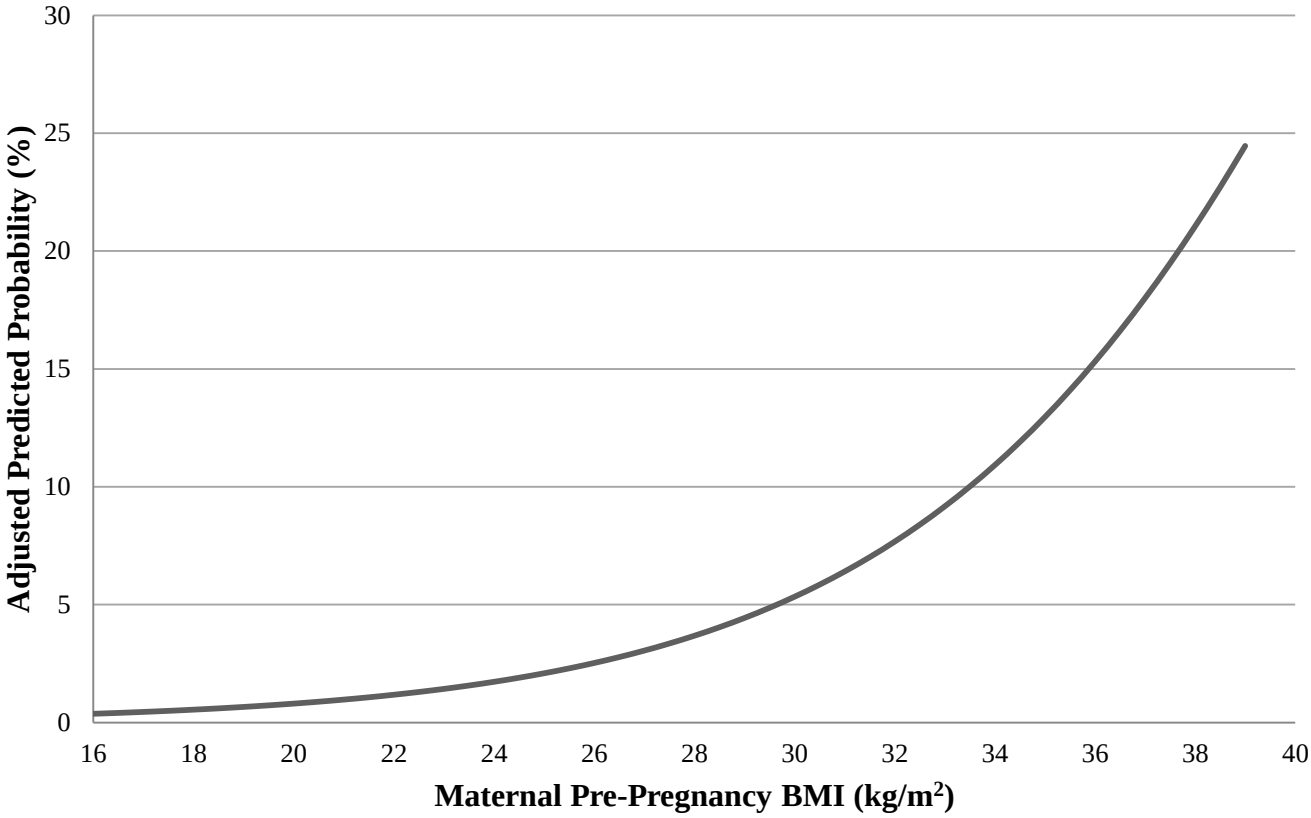


Figure 2.3. Adjusted predicted probability of gestational hypertension by maternal pre-pregnancy body mass index (BMI).

Table 2.1. Gestational Diabetes Mellitus: Maternal Descriptive and Baseline Characteristics by Pre-pregnancy Body Mass Index (BMI)

Maternal Characteristic	All	BMI Category (Kg/m^2) Underweight	Normal Weight I	Normal Weight II	Over Weight I	Over Weight II	Obese Class I	Obese Class II	*P**
	[n=787 (100)]	<18.5 [n=18 (2.3)]	18.5≤BMI<23 [n=230 (29.2)]	23≤BMI<25 [n=153 (19.4)]	25≤BMI<27.5 [n=135 (17.2)]	27.5≤BMI<30 [n=107 (13.6)]	30≤BMI<35 [n=101 (12.8)]	35≤BMI<40 [n=43 (5.5)]	
Age (years)[β]	28.9±4.6	28.4±3.5	28.0±4.8	28.8±4.2	28.6±4.4	29.8±5.0	30.1±4.0	29.8±4.5	0.002
Height (cm)	164.9.9±6.8	167.8±6.4	165.7±6.9	164.7±7.1	164.4±6.0	163.8±6.4	164.7±7.3	164.9±6.8	0.13
Smoking during Pregnancy									
No	722(91.7)	16(88.9)	210(91.3)	145(94.8)	121(89.6)	96(89.7)	95(94.1)	39(90.7)	0.64
Yes	65(8.3)	2(11.1)	20(8.7)	8(5.2)	14(10.4)	11(10.3)	6(5.9)	4(9.3)	
Parity									
<2	599(76.1)	8(44.4)	187(81.3)	112(73.2)	107(79.3)	77(72.0)	75(74.2)	33(76.7)	
2-3	139(17.7)	8(44.4)	31(13.5)	35(22.9)	17(12.6)	20(18.7)	21(20.8)	7(16.3)	0.02
≥4	49(6.2)	2(11.2)	12(5.2)	6(3.9)	11(8.1)	10(9.3)	5(5.0)	3(7.0)	
Primigravida									
No	524(66.6)	13(72.2)	144(62.6)	93(60.8)	96(71.1)	79(73.8)	68(67.3)	31(72.1)	0.20
Yes	263(33.4)	5(27.8)	86(37.4)	60(39.2)	39(28.9)	28(26.2)	33(32.7)	12(27.9)	
Pre-Pregnancy Weight (Kg)[∂ǂ]	70.1±14.0	50.1±3.4	57.8±5.7	65.1±6.0	71.2±5.2	77.1±6.1	86.9±8.8	101.2±8.9	<0.001
Post-Pregnancy Weight (Kg)[ωǂ]	83.8±13.9	64.0±5.1	72.9±8.1	79.9±7.7	84.9±8.3	90.3±8.7	98.8±10.3	110.0±11.1	<0.001
Gestational Weight Gain (Kg)[ɬǂ]	13.8±5.9	13.9±4.8	15.1±5.5	14.8±5.2	13.7±6.3	13.2±5.8	11.9±5.7	8.8±6.0	<0.001
Net Change in BMI (kg/m^2)[ρǂ]	5.1±2.2	5.0±1.8	5.5±2.0	5.5±2.0	5.1±2.3	4.9±2.2	4.4±2.2	3.2±2.2	<0.001
Gestational Diabetes Mellitus[ɬ]									
No	746(95.2)	17(94.4)	224(97.8)	151(98.7)	132(97.8)	95(88.8)	91(91.0)	36(85.7)	<0.001
Yes	38(4.8)	1(5.6)	5(2.2)	2(1.3)	3(2.2)	12(11.2)	9(9.0)	6(14.3)	

Data are (mean)±(standard deviation) or n(%) unless otherwise specified

BMI, body mass index; BMI = weight(kg)/[height(m^2)]

Record with pre-existing diabetes mellitus were removed from analyses (n=1)

Incidence risk gestational diabetes mellitus = 4.8%

*P values are a comparison among all pre-pregnancy BMI groups; chi-square test (χ^2) used to assess categorical maternal characteristics and ANOVA for continuous maternal characteristics

°Fishers exact test was used as at least one cell had an expected frequency of five or less

β Variable contains 15 missing observations

∂ Maternal weight closest to conception and no later than 12 weeks of gestation

ω Maternal weight closest to the end of pregnancy

ɬ Gestational weight gain = [end of pregnancy weight(kg)]-[pre-pregnancy weight(kg)]

ρ Net change in BMI = [end of pregnancy BMI(kg/m^2)]-[pre-pregnancy BMI(kg/m^2)]

ǂ Pre- and end of pregnancy weight was maternal self-reported (kg)

ɬ Variable contains 3 missing observations

Table 2.2. Maternal characteristics and their unconditional association with incidence risk of gestational diabetes mellitus in a rural Southern Ontario community hospital between January 1, 2010 and December 31, 2014.

Maternal Characteristic	OR	95% Confidence Interval		*P**
		Lower	Upper	
Smoking during Pregnancy ǂ ɬ	-	-	-	0.55
Parity ǂ	-	-	-	0.53
Age β	1.06	0.99	1.14	0.12 ω
Pre-Pregnancy BMI β ƨ	1.15	1.08	1.22	<0.001 ω
Net Change in BMI β ρ	0.79	0.67	0.92	0.003 ω

BMI, body mass index
* Significance measured at a liberal 80% confidence
ǂ Chi-square test (χ^2) was used to test significance of independent categorical variable
ɬ Interpreted Fisher's exact test
ɬ Diabetes status inclusive to pre-existing and gestational diabetes mellitus
β Simple logistic regression was used to test significance of continuous independent variable
ƨ Pre-pregnancy BMI = [pre-pregnancy weight(kg)/(pre-pregnancy height(m)^2)]
ρ Net change in BMI = [end of pregnancy BMI(kg/m^2)]-[pre-pregnancy BMI(kg/m^2)]
ω Statistically significant association ($p<0.20$) between the independent variable and gestational diabetes mellitus

Table 2.3. Adjusted odds ratios for the incidence risk of gestational diabetes mellitus in a rural Southern Ontario community hospital between January 1, 2010 and December 31, 2014.

Risk Factor	OR	95% Confidence Interval		*P**
		Lower	Upper	
Pre-Pregnancy BMI ƨ	1.12	1.05	1.20	<0.001 ω
Net Change in BMI ρ	0.86	0.73	1.01	0.07ǂ

Data are adjusted odds ratios
BMI, body mass index
* Significance measured at 95% confidence
ƨ Pre-pregnancy BMI = [pre-pregnancy weight(kg)/(pre-pregnancy height(m)^2)]
ρ Net change in BMI = [end of pregnancy BMI(kg/m^2)]-[pre-pregnancy BMI(kg/m^2)]
ω Statistically significant association ($p<0.05$) between the independent variable and gestational diabetes mellitus
ǂ Variable was retained as it was a secondary exposure of interest

Table 2.4. Adjusted predicted probabilities (%) of adverse maternal pregnancy outcomes by pre-pregnancy body mass index (BMI).

Pre-Pregnancy BMI (kg/m^2)	**Gestational Diabetes Mellitus[φŁ]**	**Gestational Hypertension[ω°]**
16	1.25 (0.005-0.029)	0.36 (0.001-0.011)
17	1.40 (0.006-0.030)	0.44 (0.001-0.012)
18	1.57 (0.007-0.032	0.54 (0.002-0.014)
19	1.77 (0.008-0.034)	0.66 (0.002-0.016)
20	1.98 (0.010-0.037)	0.80 (0.003-0.018)
21	2.22 (0.012-0.039)	0.97 (0.004-0.021)
22	2.49 (0.014-0.042)	1.17 (0.005-0.024)
23	2.80 (0.017-0.044)	1.42 (0.007-0.027)
24	3.13 (0.020-0.048)	1.72 (0.009-0.031)
25	3.51 (0.023-0.052)	2.08 (0.012-0.035)
26	3.93 (0.027-0.056)	2.52 (0.015-0.041)
27	4.40 (0.030-0.062)	3.04 (0.019-0.047)
28	4.92 (0.034-0.069)	3.67 (0.024-0.055)
29	5.50 (0.038-0.077)	4.43 (0.029-0.065)
30	6.14 (0.042-0.087)	5.33 (0.036-0.078)
31	6.86 (0.046-0.099)	6.40 (0.043-0.094)
32	7.65 (0.050-0.114)	7.67 (0.050-0.114)
33	8.52 (0.054-0.131)	9.16 (0.059-0.139)
34	9.48 (0.058-0.151)	10.91 (0.068-0.171)
35	10.53 (0.062-0.173)	12.95 (0.077-0.208)
36	11.69 (0.065-0.199)	15.30 (0.088-0.253)
37	12.96 (0.069-0.228)	18.00 (0.099-0.304)
38	14.34 (0.074-0.260)	21.04 (0.111-0.361)
39	15.84 (0.078-0.295)	24.45 (0.125-0.423)

Adjusted predicted probabilities are % (95% confidence interval)

ł Analysis was restricted to women without pre-existing diabetes mellitus

° Analysis was restricted to women without pre-existing hypertension

φ Predicted probabilities are reported at the population average value for net change in BMI (5.08 kg/m^2)

ω Predicted probabilities are reported at the population average values for covariates age(28.88 years), and net change in BMI (5.068 kg/m^2)

Table 2.5. Gestational Hypertension: Maternal Descriptive and Baseline Characteristics by Pre-pregnancy Body Mass Index (BMI)

Maternal Characteristic	All	BMI Category (Kg/m^2) Underweight	Normal Weight I	Normal Weight II	Over Weight I	Over Weight II	Obese Class I	Obese Class II	*P**
	[n=777 (100)]	<18.5 [n=18 (2.3)]	18.5≤BMI<23 [n=228 (29.3)]	23≤BMI<25 [n=150 (19.3)]	25≤BMI<27.5 [n=134 (17.3)]	27.5≤BMI<30 [n=105 (13.5)]	30≤BMI<35 [n=98 (12.6)]	35≤BMI<40 [n=44 (5.7)]	
Age (years)[β]	28.9±4.5	28.4±3.5	28.1±3.5	28.7±4.2	28.7±4.4	29.7±5.0	30.2±4.0	29.9±4.4	0.002
Height (cm)	164.9.9±6.8	167.8±6.4	165.7±6.9	164.8±7.1	164.4±6.1	164.1±6.3	164.5±7.4	164.7±6.8	0.16
Smoking during Pregnancy									
No	713(91.8)	16(88.9)	208(91.2)	142(94.7)	120(89.6)	95(90.5)	92(93.9)	40(90.9)	0.72
Yes	64(8.2)	2(11.1)	20(8.8)	8(5.3)	14(10.4)	10(9.5)	6(6.1)	4(9.1)	
Parity									
<2	591(76.1)	8(44.4)	185(81.1)	109(72.7)	106(79.1)	77(73.3)	72(73.5)	34(77.3)	
2-3	137(17.6)	8(44.4)	31(13.6)	35(23.3)	17(12.7)	28(17.1)	21(21.4)	7(15.9)	0.02
≥4	49(6.3)	2(11.2)	12(5.3)	6(4.0)	11(8.2)	10(9.5)	5(5.1)	3(6.8)	
Primigravida									
No	520(66.9)	13(72.2)	144(63.2)	92(61.3)	95(70.9)	77(73.3)	67(68.4)	32(72.7)	0.28
Yes	257(33.1)	5(27.8)	84(36.8)	58(38.7)	39(29.1)	28(26.7)	31(31.6)	12(27.3)	
Pre-Pregnancy Weight (Kg) [ƨ‡]	70.1±14.0	50.1±3.4	57.8±5.8	65.2±6.0	71.1±5.3	77.3±5.9	86.7±8.8	101.0±8.8	<0.001
Post-Pregnancy Weight (Kg) [ω‡]	83.8±13.8	64.0±5.1	72.9±8.1	80.0±7.8	84.8±8.2	90.5±8.6	98.8±10.3	109.8±11.1	<0.001
Gestational Weight Gain (Kg)[ɬ‡]	13.7±5.9	13.9±4.8	15.1±5.5	14.8±5.2	13.6±6.2	13.2±5.8	11.8±5.7	8.8±6.0	<0.001
Net Change in BMI (kg/m^2)[ρ‡]	5.1±2.2	5.0±1.8	5.5±2.0	5.5±2.0	5.0±2.3	4.9±2.2	4.4±2.2	3.2±2.1	<0.001
Gestational Hypertension									
No	747(96.1)	18(100)	224(98.2)	146(97.3)	132(98.5)	98(93.3)	93(94.9)	36(81.8)	<0.001°
Yes	30(3.9)	0	4(1.8)	4(2.7)	2(1.5)	7(6.7)	5(5.1)	8(18.2)	

Data are (mean)±(standard deviation) or n(%) unless otherwise specified

BMI, body mass index; BMI = weight(kg)/[height(m)^2]

Records with pre-existing hypertension were removed from analyses (n=11)

Incidence risk gestation hypertension = 3.9%

*P values are a comparison among all pre-pregnancy BMI groups; chi-square test (χ^2) used to assess categorical maternal characteristics and ANOVA for continuous maternal characteristics

°Fishers exact test was used as at least one cell had an expected frequency of five or less

β Variable contains 15 missing observations

ƨ Maternal weight closest to conception and no later than 12 weeks of gestation

ω Maternal weight closest to the end of pregnancy

ɬ Gestational weight gain = [end of pregnancy weight(kg)]-[pre-pregnancy weight(kg)]

ρ Net change in BMI = [end of pregnancy BMI(kg/m^2)]-[pre-pregnancy BMI(kg/m^2)]

‡ Pre- and end of pregnancy weight was maternal self-reported (kg)

Table 2.6. Maternal characteristics and their unconditional association with incidence risk of gestational hypertension in a rural Southern Ontario community hospital between January 1, 2010 and December 31, 2014.

Maternal Characteristic	OR	OR 95% Confidence Interval Lower	Upper	*P**
Smoking during Pregnancy ǂ ǂ	-	-	-	1.00
Parity ǂ	-	-	-	0.38
Primigravida	-	-	-	0.02 ω
Diabetes ɬ ǂ	-	-	-	1.00
Age β	0.93	0.85	1.01	0.07 ω
Pre-Pregnancy BMI β ƨ	1.17	1.09	1.25	<0.001 ω
Net Change in BMI β ρ	1.23	0.96	1.32	0.14 ω

BMI, body mass index
* Significance measured at a liberal 80% confidence
ǂ Chi-square test (χ^2) was used to test significance of independent categorical variable
ǂ Interpreted Fisher's exact test
ɬ Diabetes status inclusive to pre-existing and gestational diabetes mellitus
β Simple logistic regression was used to test significance of continuous independent variable
ƨ Pre-pregnancy BMI = [pre-pregnancy weight(kg)/(pre-pregnancy height(m)^2)]
ρ Net change in BMI = [end of pregnancy BMI(kg/m^2)]-[pre-pregnancy BMI(kg/m^2)]
ω Statistically significant association ($p<0.20$) between the independent variable and gestational hypertension

Table 2.7. Adjusted odds ratios for the incidence risk of gestational hypertension in a rural Southern Ontario community hospital between January 1, 2010 and December 31, 2014.

Risk Factor	OR	95% Confidence Interval		*P**
		Lower	Upper	
Maternal Age	0.91	0.84	0.99	0.04 ω
Pre-Pregnancy BMI ƨ	1.21	1.12	1.31	<0.001 ω
Net Change in BMI ρ	1.26	1.07	1.48	0.01 ω

Data are adjusted odds ratios
BMI, body mass index
* Significance measured at 95% confidence
ƨ Pre-pregnancy BMI = [pre-pregnancy weight(kg)/(pre-pregnancy height$(m)^2$)]
ρ Net change in BMI = [end of pregnancy BMI(kg/m^2)]-[pre-pregnancy BMI(kg/m^2)]
ω Statistically significant association ($p<0.05$) between the independent variable and gestational hypertension

Appendix 2.1.

University of Guelph Research Ethics Approval

UNIVERSITY of GUELPH

RESEARCH ETHICS BOARDS

Certification of Ethical Acceptability of Research Involving Human Participants

APPROVAL PERIOD:	December 24, 2014
EXPIRY DATE:	December 24, 2015
REB:	NPES
REB NUMBER:	14DC008
TYPE OF REVIEW:	Delegated Type 1
PRINCIPAL INVESTIGATOR:	Papadopoulos, Andrew (apapadop@uoguelph.ca)
DEPARTMENT:	Population Medicine
SPONSOR(S):	N/A
TITLE OF PROJECT:	BORN: Establishing a Baseline

The members of the University of Guelph Research Ethics Board have examined the protocol which describes the participation of the human participants in the above-named research project and considers the procedures, as described by the applicant, to conform to the University's ethical standards and the Tri-Council Policy Statement, 2nd Edition.

The REB requires that researchers:

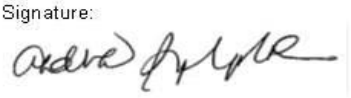
- Adhere to the protocol as last reviewed and **approved** by the REB.
- Receive approval from the REB for any **modifications** before they can be implemented.
- Report any **change in the source of funding.**
- Report **unexpected events or incidental findings** to the REB as soon as possible with an indication of how these events affect, in the view of the Principal Investigator, the safety of the participants, and the continuation of the protocol.
- Are responsible for **ascertaining and complying with all applicable legal and regulatory requirements** with respect to consent and the protection of privacy of participants in the jurisdiction of the research project.

The Principal Investigator must:

- Ensure that the ethical guidelines and approvals of facilities or institutions involved in the research are obtained and filed with the REB prior to the initiation of any research protocols.
- Submit a **Status Report** to the REB upon completion of the project. If the research is a multi-year project, a status report must be submitted annually prior to the expiry date. Failure to submit an annual status report will lead to your study being suspended and potentially terminated.

The approval for this protocol terminates on the **EXPIRY DATE**, or the term of your appointment or employment at the University of Guelph whichever comes first.

Signature: Date: December 24, 2014



A. Papdopoulos
Chair, Research Ethic Board-NPES

Page 1 of 1

CHAPTER THREE

Immunization Compliance for the Vaccine Preventable Diseases Measles, Mumps and Rubella among Children Seven Years of Age in the City of Guelph, Ontario, Canada

Prepared for: Paediatrics and Child Health – Canadian Paediatric Society

Abstract

Objective: Childhood vaccinations guard pupils and the community against vaccine preventable diseases (VPD). We examined immunization compliance for measles, mumps, and rubella, among children seven years of age (2006 birth year) residing in the city of Guelph.

Methods: Data were obtained from Wellington-Dufferin-Guelph Public Health's (WDGPH) Immunization Records Information System (IRIS), for records that were entered into IRIS as of June 30th, 2014, and were inclusive to seven year old pupils that were active in IRIS and resided in the city of Guelph. The proportions of pupils compliant to measles, mumps, and rubella vaccine requirements were calculated for both the National Advisory Committee on Immunization (NACI), and Immunization of School Pupils Act (ISPA) immunization standards. These proportions were then compared to the national coverage targets for the recommended minimum number of vaccination doses to be achieved and maintained by a child's seventh birthday. Chi-square (χ^2) tests determined if there were differences in the proportion of overall compliance to each of the NACI, and ISPA immunization standards between (1) the 19 city of Guelph neighbourhoods, and (2) the city of Guelph priority neighbourhoods (n=4) and non-priority neighbourhoods (n=15).

Results: National vaccine coverage targets were not met for measles, mumps or rubella. Priority neighbourhoods (neighbourhoods with the highest 20% of overall ranking for eight social

determinants of health indicators; a higher rank represents worsened social determinants of health.) were less likely (77.7%) to be overall compliant to NACI immunization standards compared to non-priority neighbourhoods (82.9%) (p=0.04).

Conclusion: Seven year old pupils in the city of Guelph are inadequately protected against measles, mumps and rubella. Public health initiatives aimed at educating the public about vaccines should be heightened, targeting neighbourhoods most at risk for potential measles, mumps, and rubella outbreaks in the city of Guelph.

Keywords: childhood immunization, measles, mumps, rubella, and vaccine compliance

Abbreviations

BOH: board of health

FSA: forward selection area code

GIS: geographic information system

IRIS: Immunization Records Information System

ISPA: Immunization of School Pupils Act

MMR: measles, mumps, and rubella (German measles)

MMRV: measles, mumps, rubella (German measles), and varicella

NACI: National Advisory Committee on Immunization

VPD: vaccine preventable disease

REB: research ethics board

WDGPH: Wellington-Dufferin-Guelph Public Health

3.1. Introduction

In preventive medicine, there are few measures of such value, cost-effectiveness, and ease of implementation that can match the success of routine immunizations against infectious diseases.[1] Routine immunization programs are implemented across Canada for the administration of childhood vaccinations.[2] The programs are meant to protect pupils and the community against vaccine preventable diseases (VPD).[3] Investing in child health through vaccination is an upstream approach; when a high proportion of a population is vaccinated, a threshold is met, providing protection to susceptible individuals by establishing herd immunity.[3,4] In 2013, Ontario's Public Health Leadership Council presented their strategic goal to improve the prevention and control of infectious diseases by increasing the uptake of vaccines to protect individual and population health.[5] The Council recognized immunization as a key component to Ontario's public health system.[5] Monitoring immunization compliance and identifying under- and unimmunized populations that are at high risk for contracting VPDs can significantly improve public health.

Recommendations for the use of vaccines in Canada are governed by The National Advisory Committee on Immunization (NACI). The committee is comprised of specialists in the fields of pediatrics, infectious diseases, immunology, medical microbiology, internal medicine, and public health.[6] NACI recommendations are published in the Canadian Immunization Guide; a guide summarizing the criteria required to achieve immunity for diseases with active vaccines in Canada.[6,7] NACI recommendations are the national standards utilized to estimate immunization coverage.[2,7] Under NACI, at least 2 doses of measles and mumps-containing vaccine, and at least 1 dose of rubella-containing vaccine are required to achieve compliance for children seven years or age.[8–10]

Ontario is one of three Canadian provinces, along with New Brunswick and Manitoba, with legislative immunization policies for mandatory school-entry vaccines.[11] The Ontario Immunization of School Pupils Act (ISPA) ensures Ontario pupils are adequately immunized to increase protection and guard against the following six designated diseases: measles, mumps, rubella, poliomyelitis, tetanus, and diphtheria.[12–15] Until June 30, 2014, the ISPA required proof of immunization for at least one dose of mumps and rubella-containing vaccine, two doses of measles-containing vaccine, and three doses of tetanus, diphtheria and poliomyelitis vaccine.[3,13] To align with NACI guidelines, effective July 1, 2014, the ISPA changed the mumps dose requirement to two.[16] Pupils who are not adequately immunized may be suspended from school under the direction of their jurisdictional board of health (BOH). The suspension is rescinded when proof of adequate immunization, or proof of initiation and intention to continue immunization is presented.[3,13]

There is an exemption clause in the ISPA, allowing parents and guardians to absolve their children from vaccinations on the basis of religious/conscience belief or medical reasoning.[3] To be exempt by religious/conscience belief, a notarized list of vaccines that the parent or guardian objects to, must be provided.[3] Physicians and nurses are authorized to grant exemption on medical grounds, and are required to provide the reasoning and duration that the exemption is in effect.[3]

In Ontario, seven year old school pupils for the 2012-2013 school year were below the required coverage needed to achieve herd immunity for both measles and mumps.[13,17–20] Measles coverage was estimated to be 88.3%, and mumps coverage 87.9%, whereas the coverage required to achieve herd immunity is greater than or equal to 95% and 88%-92%, respectively.[17–19] In 2006, a mumps outbreak among college students was reported in the United States, in which

the population had a very high 2-dose coverage (90%), suggesting the estimate of herd immunity thresholds may be low and that coverage must be as high as possible.[21] Low immunization coverage can lead to outbreaks or resurgence of diseases.[3] Outbreaks continue to occur in Canada, and efforts to improve measles and mumps coverage in Ontario should be made to best protect the population and prevent transmission.[13]

In Ontario, immunizations against measles, mumps, and rubella are administered only through trivalent measles-mumps-rubella (MMR) vaccine, and quadrivalent measles-mumps-rubella-varicella (MMRV) vaccine.[2,8–10,13] The first dose is administered using MMR vaccine, no earlier than at one year of age.[8–10] The second dose is administered using either MMR or MMRV vaccine, a minimum 28 days after the first dose was received.[8–10] NACI has currently not specified a predilection for using either vaccine.[22] If the first dose is given prior to one year of age, and/or the second dose within 28 days of the first, then the vaccination is deemed invalid and must be repeated in order to reduce the risk of vaccine failure.[8–10] In accordance with ISPA, BOH's within Ontario are responsible for the surveillance of immunization coverage for children under the age of 18 years.[14]

The purpose of this study was to establish levels of immunization compliance for measles, mumps, and rubella, among children seven years of age (2006 birth year) that reside in the city of Guelph. Specifically, the objectives of this study were to: (1) calculate immunization compliance for measles, mumps, and rubella among seven year old pupils residing in the city of Guelph; (2) map immunization compliance of seven year old pupils by neighbourhood within the city of Guelph; and, (3) identify neighbourhoods most at risk for potential measles, mumps, and rubella outbreaks, for whom public health initiatives should be targeted.

3.2. Materials and Methods

3.2.1. Data Source

Childhood immunization data in the province of Ontario are routinely collected and entered into a decentralized provincial database known as the Immunization Records Information System (IRIS).[3,23,24] IRIS was developed in 1992 by the Ontario Ministry of Health and Long-Term Care for Ontario's 36 boards of health (BOH) to maintain the immunization records of all school pupils attending a school within their health unit.[3,13,23] Under the ISPA, parents and guardians are responsible for the immunization status of their children and are obligated to report their immunization records to their local BOH.[3,12,23] At the commencement of each school year, BOH request a student enrollment list accompanied by student demographic information from publicly funded boards of education and private schools located within their geographic boundary.[3] This information is then uploaded into IRIS either electronically or manually by a data clerk. The Immunization Management Protocol recommends that the upload be completed at least once per year to update IRIS.[3] Once uploaded into IRIS, each school pupil is automatically assigned a unique identification number.

At the time of school enrollment, pupil vaccination records are collected and retrospectively entered into IRIS. Data clerks manually enter records as they are received via telephone, fax or online reporting.[3] Following the entry of vaccination records into IRIS, a review process is commenced as per local BOH practice. Immunization questionnaires are generated from IRIS which identifies children that are not compliant with ISPA standards and describes the immunization dose(s) for which the child is overdue.[3] The BOH will then request missing/incomplete immunization records and a notice will be sent to the parent/guardian stating the pupil is eligible for suspension until records or valid exemptions are received.[3]

The population for the cohort used in this study was drawn from WDGPH's IRIS. Demographic and immunization data were extracted for all pupils with a school enrollment record in IRIS by a WDGPH data analyst. Ethics approval was obtained from the University of Guelph Research Ethics Board (REB), Certification of Ethical Acceptability of Research Involving Human Participants (#14NV019) and from WDGPH's REB.

3.2.2. Study Denominator

The study denominator was inclusive to seven year old pupils that were active in IRIS and resided in the city of Guelph. Seven year old pupils were defined as children born between January 1, 2006 and December 31, 2006, representing the 2006 birth cohort. For the purpose of this study, only active immunization records were retained, defined as pupil's school-level classified as "elementary" in IRIS.

The city of Guelph has six designated forward selection area codes (FSA), represented by the first three characters of a postal code.[25] Pupils were identified as residing in the city of Guelph if both their city and FSA were transcribed as Guelph. Discrepancies in FSA codes not matching the city of Guelph, and vice versa, were queried via Canada Post and amended when correct addresses were available. The resulting records were then mapped using WDGPH geographic information system (GIS) for the city of Guelph. Addresses situated outside the city of Guelph's geographic boundary were excluded.

The city of Guelph consists of 23 neighbourhoods, of which 19 are used by WDGPH for data analyses and reporting purposes. Of the four neighbourhoods excluded from data analyses and reporting, three are classified as non-residential, meaning premises are primarily occupied by commercial rather than residential properties. The last excluded neighbourhood, referred to as "University", is occupied by the University of Guelph campus and the inhabitants are a non-

representative sample of the population for the city of Guelph. A variable was created corresponding to the neighbourhood in which the pupils resided. Pupils residing in non-residential neighbourhoods were suppressed into the closest adjoining neighbourhood, whereas those residing in the University neighbourhood were excluded.

Data files were managed on-site at WDGPH using Microsoft Excel and Microsoft Access 2013 Software (Microsoft. Microsoft Office Professional Plus. Redmond, Washington).

3.2.3. Immunization Exemptions

A variable was created to identify pupils with valid immunization exemptions for measles, mumps and rubella vaccines.

3.2.4. Data Anonymity

To maintain confidentiality and data security, pupil date of birth was de-identified on-site at WDGPH prior to the transfer of data to University of Guelph researchers. First, a variable was created to calculate the age in days of each pupil as of June 30, 2014; the date data were extracted from IRIS. Another variable was created to calculate pupil age in days for each recorded date a vaccine was administered. All demographic variables were deleted from the dataset and were not made available offsite from WDGPH to University of Guelph researchers.

3.2.5. Immunization Records

Data files were managed using Microsoft Excel 2010 Software (Microsoft. Microsoft Excel. Redmond, Washington) and data manipulation was performed using SAS 9.4 Software (SAS Institute, Inc., Cary, North Carolina). Measles, mumps, and rubella immunizations were entered into IRIS either as a combination vaccine (MMR, MMRV) or single vaccine component. The following data characterizations were completed for the measles, mumps, and rubella vaccines to identify the sum of valid immunization doses for each pupil.

Measles

A variable was created, identifying immunization records that were measles vaccines. All measles vaccine records were then retained. Inappropriate vaccination for pupils less than one year of age at the time of measles vaccine administration were removed as the timing of administration rendered the dose invalid.[9,26] To correct for data entry error, duplicate records were deleted for vaccinations entered more than once into IRIS for the same dose.

The resulting measles vaccination records were ranked across observations for each pupil by ascending administration date. A rank of 1 signified the first valid measles vaccine a pupil received. In order for the second measles vaccination to be considered valid, a minimum of 27 days must have elapsed from the time the first measles vaccine was administered.[9,26] Utilizing pupil age at the time of a valid first measles vaccination, pupil age in days was calculated for the 28th day thereafter. This computation was repeated for subsequent vaccine rankings for each pupil. Records of invalid second measles vaccine doses (administered less than 28 days after the first dose) were deleted. A variable was then constructed, calculating the sum of valid measles vaccinations each pupil received. Records indicating the highest vaccine count for pupils were retained for statistical analyses.

Mumps and Rubella

The data characterization methods outlined above for measles were replicated for both mumps and rubella.

3.2.6. Immunization Compliance

Exclusion of Immunization Exemptions

The NACI and ISPA immunization standards that were in effect for the year 2014 were used to determine pupil immunization compliance status. The 2014 standards were utilized for

our study as they correspond to the standards in effect at the date of data extraction from IRIS. Two variables were created in SAS; one for NACI immunization standards and another for ISPA immunizations standards, indicating the immunization compliance status of pupils for measles, mumps and rubella for each respective standard. Both variables excluded pupils with valid immunization exemptions for measles, mumps and rubella. Pupils were coded as compliant to NACI immunization standards if they had received at least two valid doses of measles and mumps, and at least one valid dose of rubella-containing vaccine[8–10]; else pupils were coded as non-compliant. Whereas, pupils were coded as compliant to ISPA immunization standards if they had received at least 2 valid doses of measles, and at least 1 valid dose of mumps and rubella-containing vaccine[3]; else pupils were coded as non-compliant.

Inclusion of Immunization Exemptions

Two variables were created, identifying pupil compliance status to NACI and ISPA immunizations standards, including pupil records with valid immunization exemptions for measles, mumps or rubella. Pupils with valid immunization exemptions were coded as non-compliant to both NACI and ISPA immunization standards.

3.2.7. Statistical Analysis

The level of significance used for the study was $\alpha<0.05$.

Exclusion of Pupils with Immunization Exemptions

The following statistical analyses excluded pupils with valid immunization exemptions.

Measles, mumps, and rubella-containing vaccines were analyzed by dose. Dose for each respective vaccine was classified into the following four categories: less than one valid dose, equal to one valid dose, equal to two valid doses, and greater than two valid doses. The

proportion of pupils having received each respective vaccine dose was calculated, with the number of non-excluded pupils as the denominator.

The proportions of pupils compliant to measles, mumps, and rubella vaccine requirements were calculated for both the NACI and ISPA immunization standards. The Canadian national immunization targets were used to determine whether or not these proportions met the targets to be achieved and maintained by a pupil's seventh birthday.[27,28] The proportion of pupils attaining compliance to all three vaccine requirements (overall compliance), was then calculated for both the NACI and ISPA immunization standards. If the immunization requirements for all three vaccines were not met for either standard, pupils were deemed non-compliant to the respective standard.

A separate chi-square (χ^2) test was applied to determine if there was a difference in the proportion of overall compliance to both NACI and ISPA immunization standards between the 19 city of Guelph neighbourhoods, respectively. The resulting proportions of overall compliance by city of Guelph neighbourhoods were then geo-mapped using ArcMap 10.3 Software (ArcGIS, Esri, Redlands, California).

City of Guelph neighbourhoods were then classified into two categories; priority neighbourhoods as defined by a system of rankings to eight social determinants of health indicators by WDGPH (n=4; Onward Willow, Two Rivers, Brant, and West Willow Woods),[29] and non-priority neighbourhoods (n=15). Priority neighbourhoods were identified as the highest 20% of overall rank for the eight social determinants of health indicators; a higher rank represents worsened social determinants of health.[29] Refer to Appendix 3.1. for additional information regarding the identification of priority neighbourhoods. To determine if there was a difference in the proportion of overall compliance to both NACI and ISPA immunization

standards between the priority neighbourhoods and non-priority neighbourhoods, a χ^2 test was applied for each standard.

Inclusion of Pupils with Immunization Exemptions

Including pupils with valid immunization exemptions for measles, mumps, and rubella vaccinations, χ^2 tests were applied to determine if there was a difference in the proportion of overall compliance to both NACI and ISPA immunization standards between the priority neighbourhoods and non-priority neighbourhoods in the city of Guelph. This allowed for the comparison of results to those obtained from the analysis excluding immunization exemptions.

Pupil immunization exemptions were analyzed via a χ^2 test to determine if there was a difference in the proportion of exemptions between the 19 city of Guelph neighbourhoods. The proportions of immunization exemptions by city of Guelph neighbourhoods were geo-mapped using ArcMap 10.3 Software.

3.3. Results

A total of 1,535,115 vaccination records were drawn from WDGPH IRIS on June 30, 2014, representing 148,780 pupils. From this, 4,446 pupils were born in the 2006 birth cohort, of which 4,094 pupils were active in IRIS with a school-level classification of "elementary". Inactive pupil status is attributed to either a pupil relocating to a residence outside the city of Guelph, or to a pupil being home schooled. We then excluded 2,676 pupils; 2,674 pupils residing outside of the city of Guelph geographic boundaries, and two pupils residing in the University neighbourhood. The final cohort consisted of 1,418 pupils that were seven years of age, active in IRIS, and resided in the city of Guelph.

Of the final cohort (n=1,418), 31 pupils possessed valid immunization exemptions for measles, mumps, and rubella vaccinations. All 31 pupils were exempt for all three vaccinations.

Researchers were unable to determine the specific reason for exemptions from immunization with the data available.

For the 1,418 pupils that comprised our final cohort, a total of 81 individual immunization records were excluded due to invalid measles vaccination for pupils as they were less than one year of age at the time of first vaccine administration. Likewise, there were 57 invalid mumps immunization records that were excluded. One measles vaccine dose was entered more than once into IRIS for one pupil. The duplicate records for this dose were excluded. There were two records of invalid second measles, mumps, and rubella vaccine doses, administered within the 28-day window, which were excluded.

3.3.1. Exclusion of Immunization Exemptions

The denominator (n=1,387) for the following analysis excludes pupils with valid immunization exemptions (n=31).

Figure 3.1. illustrates the proportion of pupils that received valid measles, mumps and rubella-containing vaccinations by maximum number of acquired dose(s). The ranking of proportions from highest to lowest were the same amongst the three vaccinations. The dose classification with the highest proportion of pupil vaccine acquirement was two doses; 79.0% measles, 79.1% mumps, and 79.1% rubella-containing vaccine. This was followed by the dose classification of one dose, zero doses, and lastly greater than two doses.

Pupil vaccination compliance among measles, mumps, and rubella are displayed in Table 3.1. for both NACI and ISPA immunization standards. For NACI immunization standards, the highest vaccine compliance was rubella at 92.5%. Compliance for measles and mumps followed at 82.1% and 81.8%, respectively. For ISPA immunization standards, compliance for rubella and

mumps vaccination was highest at 92.5%, respectively, followed by measles (82.1%). National vaccine coverage targets were not met for measles, mumps or rubella.

Figure 3.2. presents the proportion of pupils attaining immunization compliance with all three vaccine requirements (overall compliance) separately for NACI as well as ISPA immunization standards. Pupils had a higher proportion of overall compliance to ISPA immunization standards (82.1%) for measles, mumps and rubella-containing vaccines compared to the proportion of overall compliance to NACI immunization standards (81.8%).

The proportion of overall immunization compliance to NACI immunization standards ranged from 71.3% to 97.6% and was significantly different between the city of Guelph's 19 neighbourhoods (p=0.03) (Figure 3.3.). The three neighbourhoods with the highest proportion of overall immunization compliance were Kortright Hills (97.6%), Hales Barton (92.3%) and St. Georges Parkway (90.6%). Whereas the three neighbourhoods with the lowest proportion of overall immunization compliance were Downtown-Sunny Acres (74.3%), Hanlon Creek (74.3%), and Onward Willow (71.3%).

A significant difference was also observed in the proportion of overall immunization compliance to ISPA immunization standards between the city of Guelph's 19 neighbourhoods (p=0.03). The overall compliance proportions by neighbourhood were the same as those achieved for NACI immunization standards with the exception of two neighbourhoods: Hanlon Creek (75.7%) and West Willow Woods (83.5%). The three neighbourhoods with the highest proportion of overall immunization compliance were Kortright Hills (97.6%), Hales Barton (92.3%), and St. Georges Parkway (90.6%). The three neighbourhoods with the lowest proportion of overall compliance were Dover Cliff (75.0%), Downtown-Sunny Acres (74.3%), and Onward Willow (71.3%).

There was a significant difference in overall immunization compliance to NACI standards between the city of Guelph's priority neighbourhoods and non-priority neighbourhoods (p=0.04). The priority neighbourhoods were less likely (77.7%) to be overall compliant to NACI immunization standards compared to non-priority neighbourhoods (82.9%). However, there was no significant difference (p=0.10) in overall immunization compliance to ISPA immunization standards between the city of Guelph's priority neighbourhoods (78.7%) and non-priority neighbourhoods (83.0%).

3.3.2. Inclusion of Immunization Exemptions

The denominator (n=1,418) for the following analysis includes pupils with valid immunization exemptions (n=31).

Figure 3.4. depicts the proportion of pupils with valid immunization exemptions by the city of Guelph's 19 neighbourhoods. The proportions ranged from 0% to 5.9%. Seven neighbourhoods had an immunization exemption proportion of 0%. The three neighbourhoods with the greatest proportion of immunization exemptions were St. Georges Parkway (5.9%), Clairfields (5.6%), and Old University (5.5%). The frequency of immunization exemptions (n=31) were too sparse to assess if there was a significant difference in proportion between the city of Guelph's 19 neighbourhoods.

There was no significant difference (p=0.17) in overall immunization compliance to NACI standards between the city of Guelph's priority neighbourhoods (77.1%) and non-priority neighbourhoods (80.8%). As well, there was no significant difference (p=0.31) in overall immunization compliance to ISPA immunization standards between city of Guelph's priority neighbourhoods (78.2%) and non-priority neighbourhood (80.9%).

3.4. Discussion

Immunization compliance is an important indicator of individual and population health as it measures the susceptibility of a population to VPDs, and can also be used as a surrogate measure to evaluate health services, systems, and interventions.[2] The present study is the first to establish levels of immunization compliance to both national and ISPA immunization standards for measles, mumps, and rubella, among children seven years of age (2006 birth year) that reside in the city of Guelph.

In Canada, the first dose of MMR vaccine is to be administered no earlier than 12 months of age.[8–10] However, in the presence of a measles, mumps, or rubella outbreak, or if an infant is to be travelling abroad, a dose of MMR can be given as early as six months of age.[9,30] This may offer some explanation as to why our cohort had 81 invalid measles and 57 invalid mumps records that were excluded from our analysis on the premise of being invalid (administered prior to 12 months of age). A study that assessed immunogenicity of measles vaccine in infants younger than 12 months of age found that humoral immunity was deficient (seroconversion rate=67%) in infants vaccinated for measles at six months of age.[31] The researchers concluded that developmental maturation of immune response to measles may occur within the first year from birth.[31] For children that receive an MMR vaccine prior to 12 months of age, it is critical to educate parents and guardians on the importance of re-vaccinating their children at 12 months to ensure adequate protection against measles, mumps, and rubella.

The proportion of pupils in our cohort with greater than or equal to two valid doses of measles-containing vaccine (82.1%) was larger than the proportion of pupils with two or more valid doses of each mumps and rubella-containing vaccine (both equal to 81.8%). The higher proportion estimated for valid measles-containing vaccine may be attributed to the vaccine

availability as a single antigen in countries outside of Canada, whereas mumps and rubella vaccinations are not offered in many countries outside of Canada.[2,8,10] In support of this observation, in 2006, 21.2% of Guelph residents were immigrants.[29] There is currently no standardized catch-up vaccine program for immigrant Canadian children upon arrival.[32] Health care professionals need to be aware of these gaps in immunization and ensure they optimize opportunities to update vaccinations in newly arrived immigrants.

Among vaccine compliance for measles, mumps, and rubella, the only difference in compliance between NACI and ISPA immunization standards was for mumps. These results echo the differentiating factor between NACI and ISPA immunization standards; at least two doses of mumps are required for NACI standards compared to only one dose for ISPA standards.[3,8–10,13] To prevent pupils from being suspended from school due to inadequate vaccination, pupils need only meet the ISPA standards for immunization compliance. A study investigating a Canadian mumps outbreak that occurred between September 2009 and June 2010, reported that in the general population, the effectiveness of one dose mumps-containing vaccine ranged from 49.2% to 81.6%, whereas the effectiveness of two doses ranged from 66.3% to 88.0%.[33] This observation is important, as it suggests that some pupils may be unprotected and susceptible to mumps, and are only vaccinating when informed by the BOH for ISPA standards. Greater outreach is required by public health to ensure residents know the requirements for NACI standards, and vaccine efficacy. Furthermore, this highlights the importance of increasing vaccine compliance for mumps to better protect pupils and the general population against the disease.

Of importance, if immunization compliance is too low, it results in failure to achieve herd immunity, leaving the population at an increased risk of an outbreak.[3] To achieve herd immunity,

immunization compliance of at least 95% is required for measles,[17,18] 88% to 92% for mumps,[19] and 83% to 85% for rubella.[20] Immunization compliance according to both NACI and ISPA standards in our study cohort was well below that required to achieve herd immunity for all three vaccines. This indicates a need for increased awareness regarding the benefits of immunization, which would be more effective by identifying and targeting efforts towards neighbourhoods that have the lowest overall immunization compliance in the city of Guelph.

WDGPH has reported that, despite the many community strengths in the city of Guelph, some neighbourhoods experience challenges and are struggling.[29] Using a ranking system of eight social determinants of health indicators, WDGPH identified Brant, Onward Willow, Two Rivers, and West Willow Woods as priority neighbourhoods in the city of Guelph.[29] The lower overall compliance for measles, mumps, and rubella vaccination in the four priority neighbourhoods may be related to parental and guardian educational attainment. Educational attainment is low for all four priority neighbourhoods.[29] Brant has the lowest educational attainment of all neighbourhoods in the city with 25.9% of adults and youth without a high school education.[29] In 2014, a group of researchers investigated parent's knowledge about immunization using a pre-test post-test study design. The study concluded that there was a significant difference in parental knowledge by educational level; as educational attainment increased, parental immunization knowledge increased.[34] Thus, implementation of an immunization education program could benefit priority neighbourhoods in the city of Guelph, and may lead to increased vaccine compliance.

In 1796, Dr. Edward Jenner inoculated an 8-year old boy with cowpox, in what would become the first vaccination in history and would ultimately lead to the eradication of smallpox.[35] Despite the fact that vaccines have been around for hundreds of years and many

VPDs have been identified and described as early as thousands of years ago, outbreaks of VPDs are still a major societal concern in modern times. In recent years, there have been many false controversies surrounding the MMR vaccine. In 1998, a British medical journal published a study that claimed to link the MMR vaccine to autism.[35] The study was discredited and retracted in 2010.[35] Education and communication is critical to disprove myths surrounding immunization, and to improve the public's awareness and uptake of vaccines, in reducing proportions of under-vaccination.[35] Public health initiatives aimed at increasing vaccination compliance are unlikely to change the attitudes of those who are opposed to immunization due to religious beliefs; however, they can help those who are concerned or hesitant about immunization to make informed decisions.[14] Interventions need to be implemented to educate parents that vaccinating their children for measles, mumps, and rubella will protect against VDPs, benefitting children and the community at large.

There are several limitations in the present study that warrant discussion. It is possible that some of the pupils described as being non-compliant to measles, mumps, and rubella vaccinations were appropriately immunized. Parents/guardians may not have supplied the BOH with documentation of their children's vaccination, or documentation may have been provided, however not yet entered into IRIS at the time data extraction was completed. For new immigrants to Canada, immunization history is only considered valid if written documentation with exact dates of vaccine administration are presented.[3] For these instances, if pupils are appropriately immunized however deemed non-compliant to measles, mumps, and rubella vaccination, this can lead to misclassification of vaccine compliance status.

The extent to which home-schooled pupils are represented in our denominator is variable. In Ontario, home-schooled children are not required to provide immunization records to their

local BOH.[3] Some boards of education may voluntarily submit demographic information to BOH's for children that are home-schooled; however, this is not consistently practiced. If their demographic information is submitted to the BOH, these children are included in the BOH annual review of vaccination compliance to ISPA standards.[3]As this population does not attend a school, local BOH for these children are unable to suspend those whom are inadequately immunized, weakening their leverage to attain ISPA vaccine compliance.

Pupils are exempt from immunization if they possess one of the following types of immunization exemptions that pertain to pupils: (1) statement of medical exemption, or (2) statement of conscience or religious belief.[3] Researchers were unable to differentiate the codes that were entered into IRIS to classify the type of immunization exemption a pupil holds. Due to this, we were unable to discriminate between the types of exemptions in our study. Future research examining the differences in types of immunization exemption would benefit vaccine surveillance in determining if the types of exemptions temporally change. As well, targeting educational messages for vaccine compliance to neighbourhoods with immunization exemptions could help inform these populations about the benefits of immunization.

3.5. Conclusion

Measles, mumps, and rubella vaccine compliance in the city of Guelph among pupils seven years of age was below the national coverage targets for the recommended minimum number of vaccination doses to be achieved and maintained by a child's seventh birthday. As well, immunization compliance was below what is required to achieve herd immunity for all three vaccines. Despite universal access to health care in Canada, the population of seven year old pupils in the city of Guelph are inadequately protected against measles, mumps and rubella. This makes the overall population more susceptible to acquire these diseases, and more

vulnerable to an outbreak. Moreover, there was a significant difference in overall immunization compliance; the city of Guelph's four priority neighbourhoods were less likely to be compliant to NACI standards compared to non-priority neighbourhoods. Public health initiatives aimed at educating the public about vaccines should be heightened, targeting neighbourhoods most at risk for potential measles, mumps, and rubella outbreaks in the city of Guelph; and neighbourhoods with a high proportion of exemptions. This can help disprove myths surrounding immunization, and improve the public's awareness and uptake of vaccines.

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3.7. Conflict of Interest

The authors declare no conflict of interest.

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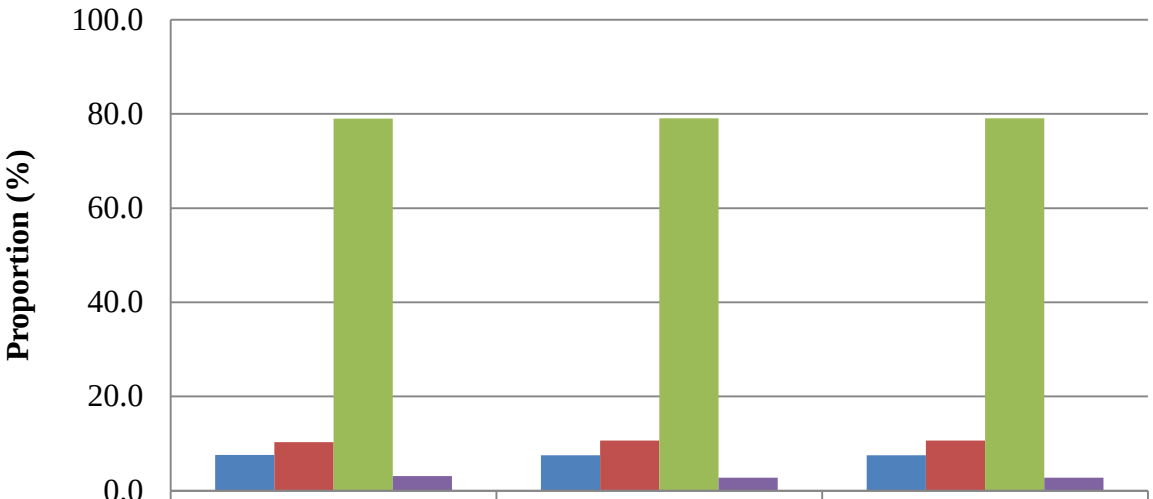
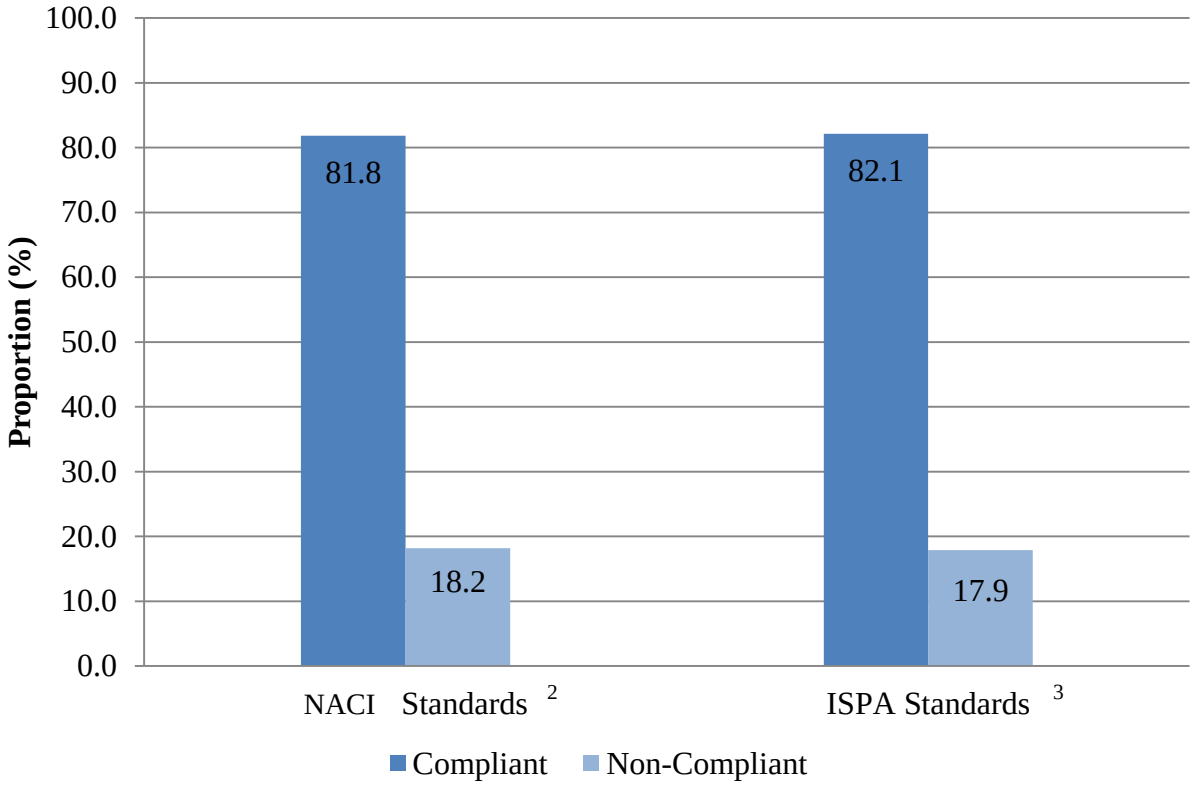
Figure 3.1. The proportion of valid measles, mumps and rubella-containing vaccine dose(s) received by 7-year-old pupils that were born in the 2006 birth cohort and reside in the city of Guelph, ON, Canada (n=1,387).



	Measles	Mumps	Rubella
0 Doses	7.6	7.5	7.5
1 Dose	10.3	10.7	10.7
2 Doses	79.0	79.1	79.1
>2 Doses	3.1	2.7	2.7

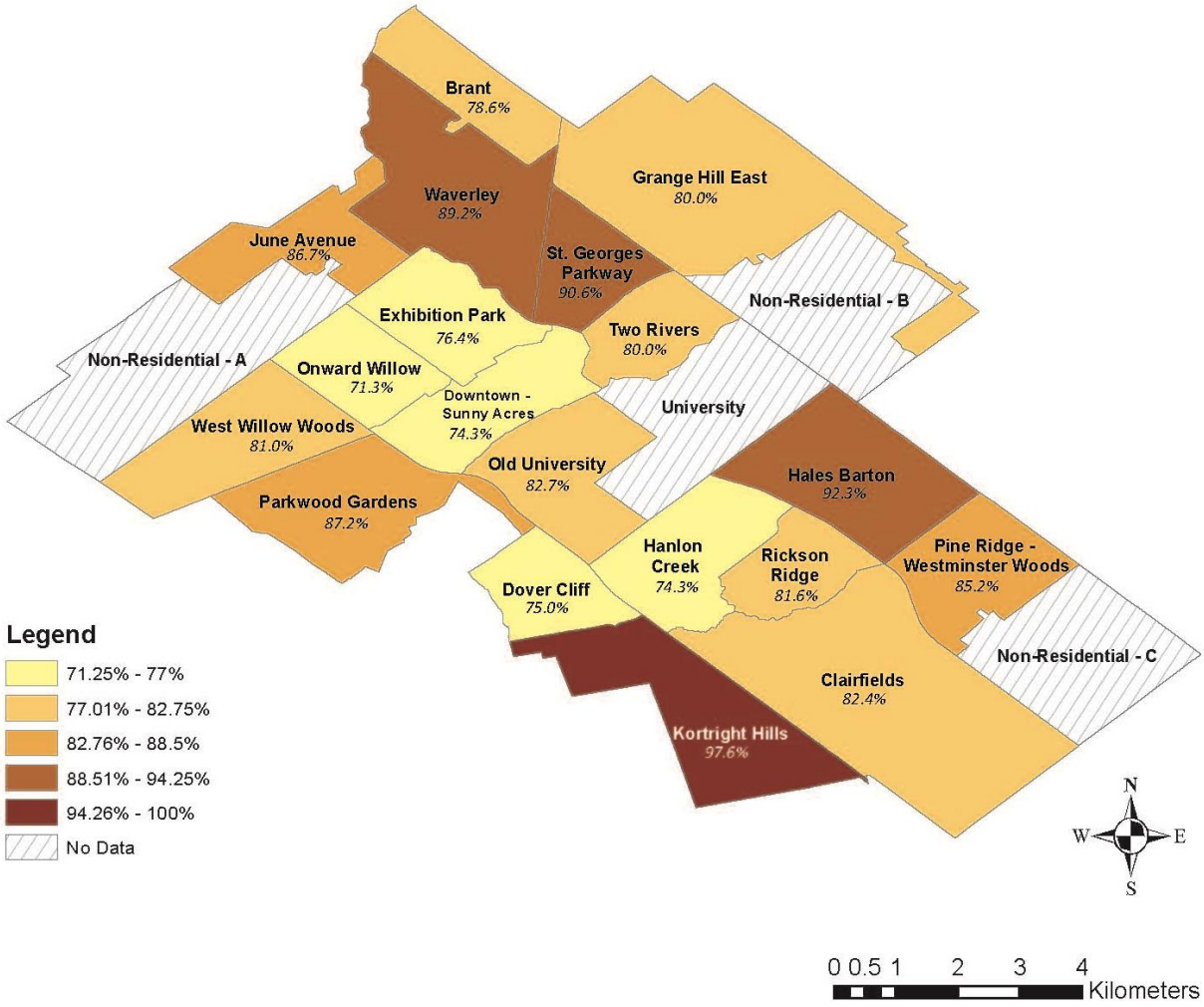
1. Data excludes pupils with a valid immunization exemption for measles, mumps and rubella vaccines (n=31)
2. Results are representative of immunization records that were entered into IRIS as of June, 30, 2014

Figure 3.2. Overall immunization compliance for National Advisory Committee on Immunization (NACI) and Immunization of School Pupils Act (ISPA) immunization standards in the city of Guelph, among pupils seven years of age for the 2006 birth cohort.[1]



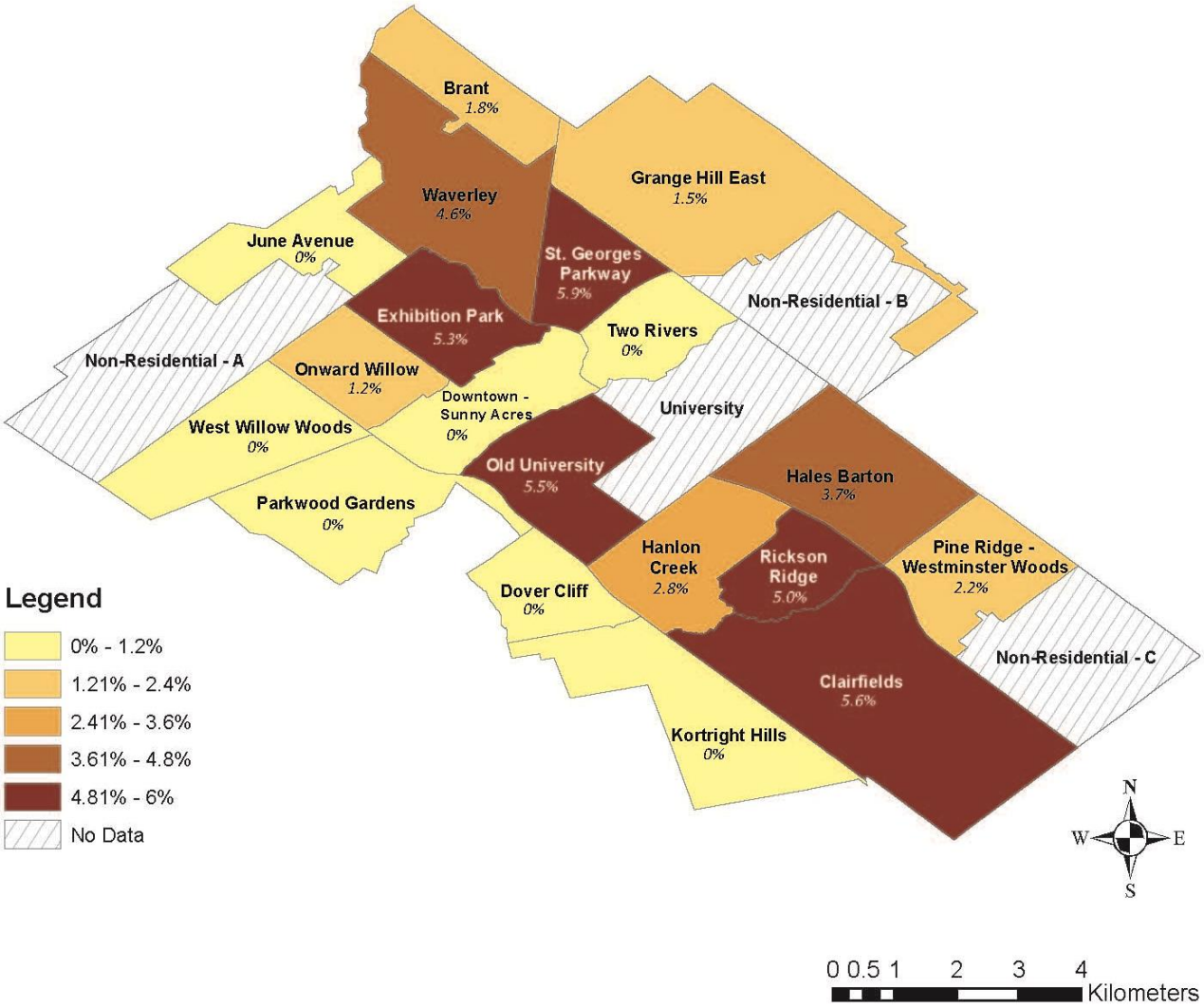
1. Data excludes pupils with a valid immunization exemption for measles, mumps and rubella vaccines (n=31)
2. Compliance for 2 doses of measles and mumps-containing vaccines and at least 1 dose of rubella-containing vaccine as per the recommendations of the National Advisory Committee on Immunization (NACI) and the Canadian Immunization Guide
3. Compliance for 2 doses of measles-containing vaccines and at least 1 mumps and rubella-containing vaccines as per the Immunization of School Pupils Act (ISPA)

Figure 3.3. Choropleth map of the proportion of pupils aged 7-years-old compliant to the recommendations of the National Advisory Committee on Immunization (NACI) and the Canadian Immunization Guide for at least two doses of measles and mumps-containing vaccines and at least one dose of rubella-containing vaccine in the city of Guelph by neighbourhood for the 2006 birth cohort.



1. Data excludes pupils with a valid immunization exemption for measles, mumps and rubella vaccines (n=31)

Figure 3.4. Choropleth map of the proportion of immunization exemptions among pupils aged 7-years-old by neighbourhood in the city of Guelph for the measles, mumps, and rubella vaccine vaccinations designated under the Immunization of School Pupils Act (ISPA) for the 2006 birth



cohort. ǂ

ǂ Exemptions are inclusive to medical or religious/conscientious objection

Table 3.1. Measles, mumps and rubella vaccine compliance in the city of Guelph among pupils seven years of age, 2006 birth cohort.

Vaccine-Preventable Disease	**NACI Standards[1] (%)**	**ISPA Standards[2] (%)**	**Canadian National Coverage Target[3] (%)**
Measles	82.1	82.1	99.0[4]
Mumps	81.8	92.5	99.0[4]
Rubella	92.5	92.5	97.0[5]

1. Vaccine compliance for 2 doses of measles and mumps-containing vaccines and at least 1 dose of rubella-containing vaccine as per the recommendations of the National Advisory Committee on Immunization (NACI) and the Canadian Immunization Guide
2. Compliance for 2 doses of measles-containing vaccines and at least 1 mumps and rubella-containing vaccine as per the Immunization of School Pupils Act (ISPA)
3. The national target for the recommended minimum number of vaccination doses to be achieved and maintained by the seventh birthday of children
4. Public Health Agency of Canada. *Canadian National Report on Immunization , 2006*. Ottawa, ON: Her Majesty the Queen in right of Canada, represented by the Minister of Health; 2006. http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/06pdf/32s3_e.pdf
5. Final Report on Outcomes from the National Consensus Conference for Vaccine-Preventable Diseases in Canada, June 12-14, 2005-Quebec City, Quebec. Can Comm Dis Report. 2008;34 Suppl 2:1-56

Appendix 3.1.

Eight Social Determinants of Health Indicators Utilized by Wellington-Dufferin-Guelph Public Health to Rank City of Guelph Neighbourhoods, and to Identify Priority Neighbourhoods[1]

Social Determinant of Health Characteristic	Social Determinant of Health Indicator
Income	1. Percentage of children aged 6 years and under in private households with low income 2. Unemployment rates for individuals in the labour force aged 25 years and older 3. Percentage of persons in private households with low income after tax
Education Level	4. Percentage of population with aged 25 to 64 years without high school education
Social and Community Support	5. Percentage of families that were lone parent families
Housing	6. Housing affordability; the proportion of households that spent ≥30% of income on housing costs
Immigration	7. Percentage of population who were recent immigrants
Early Childhood Development	8. Percentage of senior kindergarten children who were vulnerability on 2 or more domains of the Early Developmental Index (EDI)

1. Neighbourhoods in the highest twentieth percentile of overall ranking for the eight social determinant of health indicators were identified as priority (n=4)

Table adopted from: Wellington-Dufferin-Guelph Public Health (2013). Addressing Social Determinants of Health in Wellington-Dufferin-Guelph: A public health perspective on local health, policy and program needs. Guelph, Ontario.

Appendix 3.2.

University of Guelph Research Ethics Approval

UNIVERSITY of GUELPH

RESEARCH ETHICS BOARDS

Certification of Ethical Acceptability of Research Involving Human Participants

APPROVAL PERIOD:	December 9, 2014
EXPIRY DATE:	December 9, 2015
REB:	NPES
REB NUMBER:	14NV019
TYPE OF REVIEW:	Delegated Type 1
PRINCIPAL INVESTIGATOR:	Papadopoulos, Andrew (apapadop@uoguelph.ca)
DEPARTMENT:	Population Medicine
SPONSOR(S):	N/A
TITLE OF PROJECT:	Childhood immunizations: an analysis of the inequalities in immunization rates and the association between socioeconomic status and immunization coverage

The members of the University of Guelph Research Ethics Board have examined the protocol which describes the participation of the human participants in the above-named research project and considers the procedures, as described by the applicant, to conform to the University's ethical standards and the Tri-Council Policy Statement, 2nd Edition.

The REB requires that researchers:

- Adhere to the protocol as last reviewed and **approved** by the REB.
- Receive approval from the REB for any **modifications** before they can be implemented.
- Report any **change in the source of funding.**
- Report **unexpected events or incidental findings** to the REB as soon as possible with an indication of how these events affect, in the view of the Principal Investigator, the safety of the participants, and the continuation of the protocol.
- Are responsible for **ascertaining and complying with all applicable legal and regulatory requirements** with respect to consent and the protection of privacy of participants in the jurisdiction of the research project.

The Principal Investigator must:

- Ensure that the ethical guidelines and approvals of facilities or institutions involved in the research are obtained and filed with the REB prior to the initiation of any research protocols.
- Submit a **Status Report** to the REB upon completion of the project. If the research is a multi-year project, a status report must be submitted annually prior to the expiry date. Failure to submit an annual status report will lead to your study being suspended and potentially terminated.

The approval for this protocol terminates on the **EXPIRY DATE**, or the term of your appointment or employment at the University of Guelph whichever comes first.

Signature: Date: December 9, 2014

A. Papdopoulos
Chair, Research Ethic Board-NPES

Page **1** of **1**

Appendix 3.3.

The proportion of pupils aged 7-years-old compliant to the recommendations of the National Advisory Committee on Immunization (NACI) and the Canadian Immunization Guide for at least two doses of measles and mumps-containing vaccines and at least one dose of rubella-containing vaccine in the city of Guelph by neighbourhood for the 2006 birth cohort

City of Guelph Neighbourhood	Overall NACI Immunization Compliance by Neighbourhood (%)
Kortright Hills	97.6
Hales Barton	92.3
St. Georges Parkway	90.6
Waverley	89.2
Parkwood Gardens	87.2
June Avenue	86.7
Pine Ridge - Westminster Woods	85.2
Old University	82.7
Clairfields	82.4
Rickson Ridge	81.6
West Willow Woods	81.0
Two Rivers	80.0
Grange Hill East	79.6
Brant	78.6
Exhibition Park	76.4
Dover Cliff	75.0
Downtown - Sunny Acres	74.3
Hanlon Creek	74.3
Onward Willow	71.3

Data excludes pupils with a valid immunization exemption for measles, mumps and rubella vaccines (n=31)

APPENDIX 3.4.

The proportion of pupils aged 7-years-old compliant to the Immunization of School Pupils Act (ISPA) immunization standards for at least two doses of measles, and at least one dose of mumps and rubella-containing vaccine in the city of Guelph by neighbourhood for the 2006 birth cohort

City of Guelph Neighbourhood	Overall ISPA Immunization Compliance by Neighbourhood (%)
Kortright Hills	97.6
Hales Barton	92.3
St. Georges Parkway	90.6
Waverley	89.2
Parkwood Gardens	87.2
June Avenue	86.7
Pine Ridge - Westminster Woods	85.2
West Willow Woods	83.5
Old University	82.7
Clairfields	82.4
Rickson Ridge	81.6
Two Rivers	80.0
Grange Hill East	79.6
Brant	78.6
Exhibition Park	76.4
Hanlon Creek	75.7
Dover Cliff	75.0
Downtown - Sunny Acres	74.3
Onward Willow	71.3

Data excludes pupils with a valid immunization exemption for measles, mumps and rubella vaccines (n=31)

Appendix 3.5.

August 2011 Ontario Publicly Funded Immunization Schedule

Publicly Funded Immunization Schedules for Ontario – August 2011

Publicly funded vaccines may be provided only to eligible persons and must be free of charge.

SCHEDULE 1. Routine Schedule for Children Beginning Immunization in Early Infancy (Starting at 2 months of age)

Age at vaccination: Completed months and years	DTaP-IPV[1]-Hib[2]	Pneu-C-13[3]	Rot-1[4]	Men-C-C[5]	MMR[6]	Var[7]	MMRV[8]	Men-C-ACYW[9]	HB[10]	HPV-4[11]	Tdap[12]	Inf[13]
2 months old	■ ■	■	■									
4 months old	■ ■	■	■									
6 months old	■ ■											
12 months old		■†		■	■							
15 months old						■						
18 months old	■ ■											
4-6 years old	■*						■‡					
Grade 7 students								■§	■§			
Grade 8 females										■§		
14-16 years old (10 years after 4-6 year old booster)											■¶	
Every year (in autumn)												■**

*DTaP-IPV preferably given at 4 years of age; administer to children <6 years old, see Schedule 3. †For Pneu-C-13 high risk schedule, see Table 3. ‡MMRV preferably given at 4 years of age. §Administered through school-based program. ¶See Schedule 4 for adult Td immunization. **Previously unimmunized children <9 years receive 2 doses of Inf 4 weeks apart.

Notes:

High risk: For high risk eligibility criteria, please see page 3.

Catch-up: for catch-up schedules, please refer to Schedules 2 and 3.

Interruption of a vaccine series does not require restarting the series, regardless of the length of time elapsed since the last dose.

Up to date immunization records or valid exemptions are required for attendance at school *(Immunization of School Pupils Act)* and licensed daycare centres *(Day Nurseries Act)* in Ontario.

Vaccine Administration:

Never mix and administer different vaccines together in the same syringe unless indicated in the product monograph.

Route of administration:
Intramuscular (IM): DTaP-IPV-Hib, DTaP-IPV, Tdap, Td, HA, HB, HPV-4, Men-C-C, Men-C-ACYW, Inf, and Pneu-C-13.
Subcutaneous (SC): MMR, Var, MMRV, and IPV (if given as a separate antigen).
IM or SC: Pneu-P-23
Oral (PO): Rot-1

Site: For site of administration go to:
http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/D/vacc_admin.pdf

Needle Length: The appropriate size and length of needle for vaccine administration should be based on the age and size of the individual. For IM injections:
- infants <6 months use 7/8 inch (2.2 cm) needle
- children ≥6 months use 1 inch (2.5 cm) needle
- adolescents and adults use 1 inch to 1 ½ inch (2.5cm to 3.8 cm) needle

1. Diphtheria, Tetanus and Acellular Pertussis vaccine – Inactivated Poliovirus Vaccine, (DTaP-IPV)

Routine: The 4-6 year (5th) or school entry dose of DTaP-IPV in Schedules 1 and 2 is not necessary if the 4th dose was given after the 4th birthday. For the infant/primary series, the series should start no earlier than 6 weeks of age. DTaP-IPV (Quadracel®) should ***not*** be given to children >6 years of age.

Catch-up: Tdap plus IPV should be given separately to children who missed their 4-6 year booster dose of DTaP-IPV.

2. *Haemophilus influenzae* type b Vaccine (Hib)

DTaP-IPV-Hib (Pediacel®) or monovalent Hib. Hib vaccine is not routinely recommended for children ≥5 years of age.

3. Pneumococcal Conjugate 13-valent Vaccine (Pneu-C-13)

Routine: 3-dose schedule at 2, 4 months with a booster dose at 12 months of age for all low risk children <2 years of age.

Catch-up: Unimmunized children <5 years of age remain eligible for Pneu-C-13. See Schedule 2.

One time catch-up for 2011 only: The following children who have completed a primary series of Pneu-C-10 and/or Pneu-C-7 are eligible to receive an additional single dose of Pneu-C-13:
- low risk children <3 years old;
- high risk children <5 years old;
- Aboriginal children <5 years old; or
- children attending group day care <5 years old.

4. Rotavirus ORAL Vaccine (Rot-1)

Routine: 2-dose schedule at 2 and 4 months. 2 doses at least 4 weeks apart should be completed by 24 weeks of age. Although the vaccine manufacturer has indicated that the first dose may be administered as early as 6 weeks and as late as 20 weeks of age, NACI recommends that the first dose be administered between 6 weeks and <15 weeks of age as the safety of providing the first dose of rotavirus vaccine in older infants is not known.

5. Meningococcal Conjugate C Vaccine (Men-C-C)

Routine: Children aged 1 year old should receive a single dose.

Catch-up: Unimmunized persons remain eligible for a single dose of Men-C-C if they were:
- 1 year of age on or after Sept. 2004; or
- born between 1986 and 1996.

6. Measles, Mumps, Rubella Vaccine (MMR)

The 1st dose of MMR should be given **on or after the 1st birthday**. The 2nd dose of MMR vaccine should be given as MMRV at 4-6 years of age.

MMR is a live virus vaccine. MMR and varicella vaccine must be given on the same day or at least 28 days apart.

Adults born prior to 1970 are assumed to have naturally acquired immunity to measles and mumps. Adults born in 1970 or later without evidence of immunity to measles or mumps should receive 1 dose of MMR.

A 2nd dose of MMR is recommended for young adults (18-25 years), post secondary students, persons who received killed measles vaccine (1967-1970), health care workers and those who plan to travel internationally.

All women of reproductive age should have at least 1 documented dose of rubella vaccine **or** serologic evidence of immunity.

7. Varicella Vaccine (Var)

Routine: Children 15 months of age should receive the 1st dose. The 2nd dose should be given as MMRV at 4-6 years of age.

Catch-up: Children born on or after Jan. 1, 2000 **and who are at least 1 year of age** are eligible for 2 doses of varicella vaccine.

Varicella is a live virus vaccine. Varicella and MMR vaccine must be given on the same day or at least 28 days apart.

8. Measles, Mumps, Rubella, Varicella Vaccine (MMRV)

Routine: 1 dose of MMR at 12 months, 1 dose of Var at 15 months and 1 dose of MMRV at 4-6 years of age (preferably prior to school entry).

Catch-up: Children 7-11 years of age who have not received any doses of MMR or varicella may receive 2 doses of MMRV.

MMRV is a live virus vaccine. MMRV and varicella must be given 3 months apart and MMRV and MMR must be given 6 weeks apart.

9. Meningococcal Conjugate ACYW-135 Vaccine (Men-C-ACYW)

Routine: Students in grade 7 are eligible to receive a single dose of Men-C-ACYW.

Catch-up: Since 2009, students who were eligible in grade 7 and have not yet received the vaccine; remain eligible for a single dose of Men-C-ACYW.

10. Hepatitis B Vaccine (HB)

Routine: 2-dose schedule for grade 7 students, given 4-6 months apart depending on the product used.

Catch-up: Any Grade 7 student who missed 1 or both doses of HB is eligible to complete the series by the end of Grade 8.

11. Human Papillomavirus Vaccine (HPV-4)

Routine: All female Grade 8 students receive 3 doses given at 0, 2 and 6 months.

One time catch-up for 2010/2011 school year only: Female students who received at least 1 dose of HPV-4 in their Grade 8 year or before the 1st day of grade 9 may complete the series in Grade 9.

12. Diphtheria, Tetanus and Acellular Pertussis Vaccine (Tdap)/Inactivated Poliovirus Vaccine (IPV)

Routine: A **single** dose of Tdap is recommended for all adolescents between the ages of 14-16 years old (with eligibility until 18 years of age) and 10 years after the 4-6 year old booster.

Catch-up: Unimmunized children/adolescents beginning their primary series at 7 years of age or older should receive 3 doses of Tdap plus IPV (3 separate injections). The 14-16 year old booster dose should be given at least 5 years after the third dose.

13. Seasonal Influenza Vaccine (Inf)

All individuals aged 6 months and older who live, work or attend school in Ontario are eligible to receive seasonal influenza vaccine.

Previously unimmunized children 6 months to <9 years of age require 2 doses of trivalent inactivated influenza vaccine (TIV), given 4 weeks apart. Children <9 years of age who have received 1 or more doses of TIV in preceding seasons are recommended to receive 1 dose per season thereafter.

Vaccine Antigen Abbreviations: DTaP = diphtheria, tetanus, acellular pertussis; **IPV** = inactivated poliovirus; **Hib** = haemophilus influenzae type b; **Pneu-C-13** = pneumococcal conjugate-13 valent; **Rot-1** = rotavirus ORAL; **MMR** = measles, mumps, rubella; **MMRV** = measles, mumps, rubella, varicella; **Men-C-C** = meningococcal conjugate C; **Men-C-ACYW** = meningococcal conjugate ACYW-135; **Var** = varicella zoster; **HA** = hepatitis A; **HB** = hepatitis B; **Tdap** = tetanus, diphtheria, acellular pertussis ; **Td** = tetanus, diphtheria; **Inf** = seasonal influenza; **HPV-4** = human papillomavirus quadrivalent; **Pneu-P-23** = pneumococcal polysaccharide-23 valent

Ontario

CHAPTER FOUR

Summary Discussion, Limitations, Future Directions, and Conclusion

4.1. Summary Discussion

This thesis was an exploration of child health in the province of Ontario through the study of reproductive health and vaccine preventable diseases (VPDs). The objective was to identify populations most at risk for adverse maternal pregnancy outcomes, and potential VPD outbreaks. More specifically, this thesis sought to investigate (1) the association of pre-pregnancy body mass index (BMI) with the risk of developing gestational diabetes mellitus (GDM) and gestational hypertension (GH) in a rural Southern Ontario community; and (2) the levels of immunization compliance for measles, mumps, and rubella among children seven years of age that reside in the city of Guelph. These objectives were accomplished by establishing baseline levels of maternal pre-pregnancy BMI, and childhood immunization compliance through the conduct of two independent studies. Study data were obtained from two provincial child health registers, Ontario's Better Outcomes Registry and Network (BORN) (Chapter 2), and the Immunization Records Information System (IRIS) (Chapter 3).

In chapter two, multivariable logistic regression models allowed for the assessment of potential confounders associated with the risk of developing GDM and GH, respectively. The variables pre-pregnancy BMI and net change in BMI were included in both models as exposures of interest. The predicted probability of developing both GDM and GH were calculated by incremental pre-pregnancy BMI values. Within our study group, the incidence risk of GDM was 4.8%, whereas the incidence risk of GH was 3.9%. For both GDM and GH, a pre-pregnancy BMI of 27.5 kg/m^2 appeared to be a threshold beyond which there was an exponential increase

of disease incidence in comparison to the preceding pre-pregnancy BMI categories. Moreover, it was found that pre-pregnancy BMI was associated with the risk of developing both GDM and GH with adjusted odds ratio (OR) of 1.12 (95% CI, 1.05-1.20; $p<0.001$) and 1.21 (95% CI, 1.12-1.31; $p<0.001$), respectively.

These study results are consistent with previous literature. Torloni et al. published a systematic review and meta-analysis, quantifying the risk of GDM according to pre-pregnancy BMI. Seventy individual studies were included in the analysis which concluded the risk of GDM to be positively associated with pre-pregnancy BMI.[1] Similarly, a study that examined pre-pregnancy BMI as an independent risk factor for the development of GH reported the risk of GH to be positively associated with maternal pre-pregnancy BMI.[2]

In chapter three, the proportions of pupils compliant to measles, mumps, and rubella vaccine requirements were calculated for both the National Advisory Committee on Immunization (NACI) and Immunization of School Pupils Act (ISPA) immunization standards. These proportions were then compared to the Canadian national immunization targets for the recommended minimum number of vaccination doses to be achieved and maintained by a child's seventh birthday. Chi-square (χ^2) tests determined if there were differences in the proportion of overall compliance to each of the NACI, and ISPA immunization standards between the 19 city of Guelph neighbourhoods. Results indicate that national vaccine coverage targets were not met for measles, mumps or rubella. Furthermore, a significant difference was found in overall immunization compliance to NACI immunization standards between the city of Guelph's priority neighbourhoods (highest 20% of overall ranking for eight social determinants of health indicators; a higher rank represents worsened social determinants of health)[3] and non-priority

neighbourhoods (p=0.04). The priority neighbourhoods were less likely (77.7%) to be overall compliant to NACI immunization standards compared to non-priority neighbourhoods (82.9%).

Both of these studies are the first to examine adverse maternal pregnancy health outcomes, and childhood immunization compliance for VPDs within these Southern Ontario communities. It is imperative to conduct such research in these populations to establish baselines for the risk of developing adverse health outcomes which can aid in the promotion of individual and population health.

4.2. Limitations and Future Directions

The results presented in this thesis should be interpreted in light of several limitations. As a result of these limitations, directions for potential future research arose.

4.2.1. Chapter Two Limitations and Future Directions

From our study base population, 57 percent (n=1,115) of pregnancy records were missing either height or weight data. As a result, BMI values were unable to be calculated for these records, and they were excluded from analyses. The community hospital from which the data were obtained has been collecting and entering pregnancy records into BORN since 2010. The high proportion of missing data may be attributed to the short duration that the register has been in practice. Since 2010, the percentage of missing height and weight data in our study population has successively declined annually. Hospital personnel aim to have the collection and entry of pregnancy records become more routine in practice which can lead to enhanced data procurement and quality.

Moreover, data on height and weight were maternally self-reported. A study conducted by Elgar et al. examined the validity of self-reported clinical data variables. The researchers found that self-reported height tends to be overestimated, whereas self-reported weight tends to

be underestimated.[4] The magnitude and accuracy of potential over- and under-reporting of height and weight is unknown in our data, and we are unable to estimate the degree of possible misclassification of BMI categories used in our analyses.

Studies examining the association between pre-pregnancy BMI and adverse maternal pregnancy outcomes have reported ethnicity to confound the relationship between BMI, and both GDM and GH.[5,6] Data on maternal ethnicity were not available within our dataset. We were therefore unable to control for potential confounding of ethnicity in the analyses. Moreover, studies suggest that index pregnancies complicated by GDM are at increased risk of developing GDM in subsequent pregnancies.[7,8] It is possible that there were women with multiple pregnancies represented within our dataset, however maternal identifiers were not provided to researchers. This prevented us from identifying subsequent pregnancy records in our study, which would have an elevated risk for developing GDM.

Our study established baseline levels for which women of childbearing age are at increased risk for the development of GDM and GH. The finding of a pre-pregnancy BMI of 27.5 kg/m^2 appearing to be a threshold for increased risk of both GDM and GH has the potential to change the mode of clinical practice for women of childbearing age. Being aware of this threshold, health professionals can identify priority populations for whom programs should be targeted to better educate and aid in the pre-conception counselling of healthy weight management for women of childbearing years. Future study is warranted in a larger and more diverse cohort to increase the power of our observation and strengthen our findings.

It would also be of interest to conduct follow-up studies on women that developed GDM in our cohort, as well as their offspring. Research suggests that women with GDM are more likely to develop type II diabetes post-pregnancy compared to normoglycaemic women. Bellamy

et al. conducted a systematic review and meta-analysis, concluding that women having developed GDM are 7.43 times more likely to develop type II diabetes compared to normoglycaemic women (RR 7.43, 95% CI 4.79-11.51).[9] Furthermore, women with GDM may predispose their offspring to an increased risk of developing early-onset type I diabetes mellitus.[10] A longitudinal study examining the relationship between GDM and early-onset type I diabetes mellitus in rural Southern Ontario communities would provide evidence for the long-term potential effects GDM imposes on both mother and baby.

4.2.2. Chapter Three Study Limitations and Future Directions

The extent to which home-schooled pupils were represented in our study population is variable. Ontarian home-schooled children are not required to report their immunization records to local boards of health (BOH).[8] For children to be eligible to attend school in Ontario, they are required under the ISPA to meet minimum immunization standards, or else face suspension.[9] For children that are home-schooled, BOH's do not have leverage in issuing suspensions to those that are inadequately vaccinated. Hence, the cohort of children that are home-schooled potentially does not receive equal levels of vaccine advocacy as the cohort that is not home-schooled.

Another limitation to the study was the unknown proportion of immigrants within our denominator. Vaccination records for new immigrants to Canada are only considered valid when written documentation with exact dates of vaccine administration is presented to BOH.[11] It is possible for an individual to be appropriately immunized upon entry to Canada. However, due to incomplete documentation they may be deemed non-compliant, and would be required to re-vaccinate in order to have a complete immunization record. If re-vaccination does not occur, the individual would be deemed non-compliant, which can lead to misclassification of their status

for immunization compliance. Within our study, we were unable to determine if misclassification was present, and if so, the extent to which it occurred.

It would be interesting to longitudinally investigate mumps ISPA compliance in our study population. With the change in ISPA requirements for mumps-dosage, from one to two doses effective July 1, 2014, it is imperative to examine if children are adequately vaccinated to meet the new ISPA standards for mumps, as well as the rate of uptake once the new standard went into effect. Additionally, a future study examining immunization compliance to other VPDs would provide additional baseline compliance levels in order to better promote vaccine uptake in under-vaccinated populations.

4.3. Conclusion

Early life exposure to health risks and preventative medicine affect the health trajectory on which children are launched at the start of life. Clinical and population health assessment is critical, as early childhood experiences have an immediate and long lasting impact upon one's health. The research conducted in this thesis established baselines for populations most at risk for the development of adverse pregnancy outcomes and potential VPDs in communities for which groups most at risk were previously not identified. Enhancing efforts to improve child health in the province of Ontario can have a long-lasting impact on individual and population well-being. These results lay the foundation to develop health programs and interventions to target priority populations, for whom heightened health promotion initiatives can be of great benefit.

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