Evaluating the individual- & population-level effects of the Quebec rotavirus vaccination program

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Abstract

Rotavirus was the leading cause of pediatric emergency department visits and hospitalizations for acute gastroenteritis in Canada and other high-income countries during the pre-vaccine era. In consideration of the burden of rotavirus gastroenteritis, the Province of Quebec implemented a routine childhood rotavirus vaccination program in November 2011. Under this program, Quebec residents are eligible to receive monovalent rotavirus vaccine at no cost, with the vaccine routinely administered at 2 and 4 months of age. Evaluation of the program's success is essential given its scope and financial costs, and may dually provide insight into the significance of differing program design choices among rotavirus vaccine programs globally. The aim of my doctoral research was to advance scientific knowledge regarding rotavirus vaccine programs and epidemiologic methods related to vaccine program assessment via the evaluation of the Quebec monovalent rotavirus vaccine program. This thesis is based upon three manuscripts.

1. Effectiveness of monovalent rotavirus vaccine in a high-income, predominant-use setting

The first objective of this thesis was to evaluate the vaccine effectiveness, or direct effect, of the monovalent rotavirus vaccine to prevent emergency department visits and hospitalizations among children 8 weeks to 35 months of age. Prior to this work, there was little research examining the effectiveness of the monovalent rotavirus vaccine in a high-income setting, where it was predominantly used over pentavalent rotavirus vaccine. We implemented a test-negative case-control study design among eligible children seeking emergency care for acute gastroenteritis who were enrolled in active rotavirus surveillance at three Quebec hospitals. We estimated that the adjusted ≥1-dose monovalent vaccine effectiveness was 92.5% (95% CI: 69.3%, 98.2%). We concluded that monovalent rotavirus vaccine was highly effective to prevent emergency department visits and hospitalizations due to rotavirus infection, and found that our estimates were similar to those from high-income settings with concurrent monovalent and pentavalent rotavirus vaccine use.

2. **Two birds with one stone: estimating population vaccination coverage from a test-negative vaccine effectiveness case-control study**

The second objective of this thesis was to evaluate the uptake of rotavirus vaccination in the Quebec population. Since Quebec did not have an immunization registry at the time the

rotavirus vaccine program was implemented, we demonstrated how rotavirus vaccine coverage for the population may be estimated using coverage data from control subjects in a test-negative vaccine effectiveness case-control study, which we implemented to estimate rotavirus vaccine effectiveness in objective 1. We discussed our underlying assumptions to generalize rotavirus vaccine coverage estimates to a broader population, validated our estimates with comparison to estimates from the Quebec immunization survey, and used simulations to explore the effect of diagnostic accuracy to discern control subjects on coverage estimates. We estimated that rotavirus ≥1-dose coverage was 86.8% (95% CI: 82.7%, 90.0%) among participants eligible for vaccination under the Quebec rotavirus vaccine program, and concluded that controls from a test-negative vaccine effectiveness case-control study may be a valuable resource for vaccine coverage information, when reasonable assumptions can be made to generalize coverage estimates.

3. Estimation of the overall effect of a rotavirus vaccine program attributable to a per-unit change in rotavirus vaccine coverage in the population

The third and final objective of this thesis was to evaluate the impact, or overall effect, of the Quebec rotavirus vaccine program to prevent all-cause acute gastroenteritis hospitalizations among a random sample of approximately 25% of children 8 to 35 months of age residing in the Montreal census metropolitan area, using a time series study design. In accordance with standard practice, we estimated the overall effect of the vaccine program as a rate ratio comparing adjusted rates of our outcome in the post- versus pre-vaccine periods. Additionally, we demonstrated how the overall effect may be characterized as the effect associated with a 10% increase in rotavirus vaccine coverage in the population by using continuous rotavirus vaccine coverage as our exposure variable, derived from the application of the study design highlighted in objective 2. We estimated that the vaccine program was associated with a mean 29.3% (95% CI: 16.5%, 40.1%) relative decline in adjusted weekly rates of all-cause acute gastroenteritis hospitalizations in the post- versus pre-vaccine period, or that a 10% increase in rotavirus ≥1-dose vaccine coverage was associated with a 6.8% (95% CI: 3.9%, 9.5%) relative decline in adjusted weekly rates. We also discussed the utility of measuring the overall effect associated with a per-unit change in vaccine coverage, and concluded that researchers may consider estimating this measure, in addition to standard measures, to promote the generalizability of their estimates to other coverage levels and settings.

Collectively, the results from this thesis research demonstrated the relative success of the Quebec monovalent rotavirus vaccine program, with (i) greater than 90% effectiveness of monovalent rotavirus vaccine to prevent emergency department visits and hospitalizations due to rotavirus gastroenteritis, (ii) achievement of more than 85% ≥1-dose rotavirus vaccine coverage among the population eligible for vaccination under the new program, and (iii) a near 30% average relative decline in adjusted weekly rates of all-cause acute gastroenteritis hospitalizations since the implementation of the program among children 8 to 35 months of age. This research also makes two important methodological contributions to the field of vaccine program evaluation with its suggestion of an alternative design to estimate vaccine coverage in the population, and an additional measure to estimate the overall effect of a vaccine program. While this research highlights the initial success of the Quebec rotavirus vaccine program, ongoing research is necessary to evaluate its continued achievements.

Résumé

Le rotavirus était la principale cause des gastro - entérites aigües se soldant par des visites aux urgences pédiatriques et des hospitalisations au Canada ainsi que dans d'autres pays développés au cours de l'ère pré-vaccinale. Compte tenu du fardeau des gastro-entérites à rotavirus, la province de Québec a mis en place un programme de vaccination de routine contre le rotavirus chez les enfants en novembre 2011. Dans le cadre de ce programme, les résidents du Québec sont admissibles à recevoir un vaccin monovalent contre le rotavirus sans frais, le vaccin étant administré de routine à 2 et 4 mois d'âge. L'évaluation du succès du programme est essentielle compte tenu de sa portée et de ses coûts financiers et peut donner un aperçu de l'importance des différents choix de conception de programme parmi les programmes de vaccin contre le rotavirus à l'échelle mondiale. L'objectif de ma recherche doctorale était de faire avancer les connaissances scientifiques et les méthodes épidémiologiques au sujet des programmes de vaccination, en évaluant le programme de vaccination par le vaccin monovalent contre le rotavirus au Québec. Cette thèse repose sur trois manuscrits.

1. Effectiveness of monovalent rotavirus vaccine in a high-income, predominant-use setting

Le premier objectif de cette thèse était d'évaluer l'efficacité du vaccin ou l'effet direct du vaccin monovalent contre le rotavirus afin de prévenir les visites aux urgences et les hospitalisations des enfants âgés de 8 semaines à 35 mois. Il existait auparavant peu de recherches sur l'efficacité du vaccin monovalent contre le rotavirus en pays développés où son utilisation prédominait par rapport au vaccin pentavalent contre le rotavirus. Nous avons mis en place une étude cas-témoin test-négatif au sein d'une cohorte d'enfants admissibles qui se présentaient aux urgences pour une gastro-entérite aigüe et qui avaient été enrôlés dans une surveillance active des infections à rotavirus, dans trois hôpitaux québécois. Nous avons estimé que l'efficacité ajustée du vaccin monovalent ≥ 1 dose était de 92,5% (95% CI: 69,3%, 98,2%). Nous avons conclu que le vaccin monovalent contre le rotavirus était très efficace pour prévenir les visites aux urgences et les hospitalisations en raison d'une infection à rotavirus et avons constaté que nos estimations étaient semblables à celles provenant de pays développés où il y avait une utilisation simultanée des vaccin monovalent et pentavalent contre le rotavirus.

2. Two birds with one stone: estimating population vaccination coverage from a test-negative vaccine effectiveness case-control study

Le deuxième objectif de cette thèse était d'évaluer la couverture vaccinale contre le rotavirus dans la population québécoise. Étant donné que le Québec n'avait pas de registre de vaccination au moment où le programme de vaccination contre le rotavirus a été implanté, nous avons démontré comment la couverture vaccinale contre le rotavirus pouvait être estimée en utilisant les données de couverture des sujets témoins dans une étude cas-témoin test-négatif d'efficacité du vaccin, tel que décrit dans l'objectif 1. Nous avons discuté de nos hypothèses sous-jacentes nous permettant de généraliser les estimations de la couverture vaccinale contre le rotavirus à une population plus large, validé nos estimations par comparaison aux estimations de l'enquête sur la couverture vaccinale du Québec et utilisé des simulations pour explorer l'effet de la précision diagnostique à détecter les témoins sur les estimations de couverture. Nous avons estimé que la couverture ≥1-dose du vaccin rotavirus était de 86,8% (95% CI: 82,7%, 90,0%) parmi les participants admissibles à la vaccination dans le cadre du programme au Québec et avons conclu que les témoins d'une étude cas-témoin test-négatif d'efficacité du vaccin pouvait être une ressource précieuse pour l'information sur la couverture vaccinale, lorsque des hypothèses de base peuvent être émise pour généraliser les estimations de couverture.

3. Estimation of the overall effect of a rotavirus vaccine program attributable to a per-unit change in rotavirus vaccine coverage in the population

Le troisième et dernier objectif de cette thèse était d'évaluer l'impact, ou l'effet global, du programme de vaccination contre le rotavirus au Québec à prévenir les hospitalisations secondaire à une gastro-entérite aiguë, toutes causes confondues, parmi un échantillon aléatoire d'environ 25% des enfants de 8 à 35 mois résidant dans la région métropolitaine de recensement de Montréal, en utilisant un devis de séries chronologiques. Conformément à la pratique standard, nous avons estimé l'effet global du programme de vaccination en utilisant un ratio de taux, comparant les taux ajustés de notre issue des périodes post versus pré-vaccinales. En outre, nous avons démontré comment l'effet global pouvait être caractérisé en tant qu'effet associé à une augmentation de 10% de la couverture vaccinale dans la population en utilisant la couverture vaccinale comme variable continue, puisque notre variable d'exposition pouvait être dérivée du devis de l'étude décrite dans l'objectif 2. Nous avons estimé que le programme de vaccination était associé à une baisse relative moyenne de 29,3% (95% CI: 16,5%, 40,1%) des taux hebdomadaires ajustés de toutes les

hospitalisations pour gastro-entérites aigües dans la période post versus pré-vaccin ou qu'une augmentation de 10% de la couverture vaccinale contre le rotavirus ≥ 1 dose était associée à une baisse relative de 6,8% (95% CI: 3,9%, 9,5%) des taux hebdomadaires ajustés. Nous avons également discuté de l'utilité de la mesure de l'effet global associé à un changement d'une unité de la couverture vaccinale et conclu que les chercheurs peuvent envisager utiliser cette mesure, en plus des mesures standard, pour promouvoir la généralisation de leurs estimations à d'autres milieux et niveaux de couverture.

Collectivement, les résultats de cette thèse ont démontré le succès relatif du programme de vaccination contre le rotavirus au Québec, avec (i) une efficacité supérieure à 90% du vaccin monovalent contre le rotavirus à prévenir les visites aux urgences et les hospitalisations causées par les gastro-entérites à rotavirus, (ii) plus de 85% de couverture vaccinale ≥ 1 dose parmi la population éligible dans le cadre du nouveau programme et (iii) un déclin relatif moyen de près de 30% des taux hebdomadaires ajustés d'hospitalisations dues aux gastro-entérites aigües toutes causes depuis la mise en œuvre du programme chez les enfants de 8 à 35 mois. Cette recherche fait également deux contributions méthodologiques importantes dans le domaine de l'évaluation du programme de vaccination avec la proposition d'un devis alternatif pour estimer la couverture vaccinale dans la population et une mesure supplémentaire pour estimer l'effet global d'un programme de vaccination. Bien que cette recherche souligne le succès initial du programme vaccinal contre le rotavirus au Québec, une recherche est nécessaire pour évaluer ses résultats continus.

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Prior to my doctorate, I worked as a vaccine-preventable diseases epidemiologist at the New York City Department of Health and Mental Hygiene. I would like to gratefully acknowledge my supervisors during that time, Dr. Christopher Zimmerman and Dr. Jennifer Rosen, who encouraged me to pursue my doctorate, and thank them both for their support throughout the years.

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Contribution of Authors

Manuscript 1: Doll, M.K., D.L. Buckeridge, K.T. Morrison, A. Gagneur, B. Tapiero, H. Charest, C. Quach. Effectiveness of monovalent rotavirus vaccine in a high-income, predominant-use setting. *Vaccine* 2015; 33(51): 7307-7314.

I researched and designed the analytical methods for this study, with methodological input from Dr. Buckeridge, Dr. Morrison, and Dr. Quach, and substantive input from Dr. Quach. I cleaned study data, conducted all analyses, interpreted results, and drafted the original manuscript. Dr. Quach conceived of the active surveillance protocol and developed the tools for data collection, and in conjunction with Dr. Gagneur and Dr. Tapiero, implemented active surveillance and data collection at 3 hospital sites. Dr. Charest directed the laboratory testing of study specimens. All authors provided critical feedback on the manuscript.

Manuscript 2: Doll, M.K., K.T. Morrison, D.L. Buckeridge, C. Quach. Two birds with one stone: estimating population vaccination coverage from a test-negative vaccine effectiveness case-control study. *Clinical Infectious Diseases,* 2016; 63(8): 1080-1086.

I conceived of the study premise, objectives, and developed the study protocol, with methodological input from Dr. Buckeridge, Dr. Morrison, and Dr. Quach, and substantive input from Dr. Buckeridge and Dr. Quach. I cleaned study data, conducted all study analyses, interpreted study results, and drafted the study manuscript. Dr. Quach conceived of the active surveillance protocol, and was the principal investigator in the execution of active surveillance at 3 hospitals. All authors provided critical feedback on the manuscript.

Manuscript 3: Doll, M.K., C. Quach, D.L. Buckeridge. Estimation of the overall effect of a rotavirus vaccine program attributable to a per-unit change in rotavirus vaccine coverage in the population. Currently under consideration at the *American Journal of Epidemiology*.

I conceived of the study premise, objectives, and developed the study protocol, with methodological and substantive input from Dr. Buckeridge and Dr. Quach. I conducted all study analyses, interpreted study results, and drafted the study manuscript. Dr. Buckeridge conceived of the original design of the population health record (PopHR) cohort, and is the principal investigator for all research using the cohort. All authors provided critical feedback on the manuscript.

Statement of Originality

This thesis research is based upon original scholarship executed in three manuscripts, which each contribute new knowledge to inform the success of the Quebec rotavirus vaccination program, and advance either the scientific understanding of rotavirus vaccination programs or methods to evaluate vaccine programs, generally. In manuscript 1 (Chapter 3), I evaluated the effectiveness of monovalent rotavirus vaccine to protect against rotavirus hospitalizations and emergency department visits. To our knowledge, this was the first evaluation of monovalent vaccine effectiveness in Quebec, and the second evaluation of the vaccine in a high-income setting where the vaccine is predominantly used over other vaccines. Further, in manuscript 2, I demonstrated a new method to derive rotavirus vaccine coverage in the general population by using data from a test-negative case-control rotavirus vaccine effectiveness study, and estimated rotavirus vaccine coverage among children eligible for the new program in the Quebec population, documenting the program's relative success. Finally, in manuscript 3, I characterized the effect of the Quebec rotavirus vaccine program using time series methods that had not previously been used to evaluate the Quebec rotavirus vaccine program, and characterized the overall effect (i) attributable to the program as a whole, and (ii) attributable to a per-unit increase in vaccine coverage. To our knowledge, the overall effect attributable to a per-unit increase in vaccine coverage has never been used to estimate the effect of a rotavirus vaccine program before, and represents a new measure that can be applied to evaluate other vaccine programs and settings.

While I gratefully acknowledge the outstanding guidance that I have received from my co-supervisors and co-authors on methodological and substantive aspects of this thesis, I declare that the manuscripts presented in this thesis represent my own original work.

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Abbreviations and Acronyms

AGE: acute gastroenteritis

AIC: Akaike information criterion

CHU: centre hospitalier universitaire

CI: confidence interval

EIA: enzyme immunoassay

INSPQ: Institut National de Santé Publique du Québec

IP: incidence proportion

IRB: institutional review board

NACI: National Advisory Committee on Immunization

OR: odds ratio

PD: prevalence difference

RR: relative rate or risk

RV1: Rotarix® monovalent rotavirus vaccine

RV5: RotaTeq® pentavalent rotavirus vaccine

RT-PCR: real-time reverse-transcriptase polymerase chain reactions

VE: vaccine effectiveness

Chapter 1: Introduction

1.1 Background

Rotavirus was the major cause of pediatric acute gastroenteritis (AGE) among Canadian children during the pre-vaccine era.[1-7] In Quebec, approximately 50 to 74 per 10,000 children under 5 years of age were hospitalized for rotavirus AGE annually, and 117 to 152 per 10,000 children under 5 years of age required emergency department care.[7] Given the high prevalence of severe disease, rotavirus infection was costly and burdensome. Canadians spent an estimated $125 million per birth cohort on rotavirus-related medical expenses by the time the cohort reached 5 years of age.[8]

Currently, two rotavirus vaccines, Rotarix® (RV1, monovalent) and RotaTeq® (RV5, pentavalent), are licensed for use in Canada.[9,10] In November 2011, the Province of Quebec implemented a routine childhood rotavirus vaccination program with the decision to exclusively fund RV1 vaccine. To date, there has been little evaluation of the RV1 program, which is essential to justify the program's scope and financial costs. Evaluation of the program can also provide insight into the significance of differing rotavirus vaccine program design choices, such as the decision to use RV1 and/or RV5 vaccine, and provide an opportunity to innovate upon existing methods of vaccine program evaluation.

Three key indicators frequently used to inform the success of vaccination in a jurisdiction that are also foci of this thesis research, are measurement of: (i) the direct effect of vaccination, or vaccine effectiveness, (ii) vaccine coverage, and (iii) the overall effect of a vaccination program. While measurement of vaccine coverage addresses the population-level success of the *implementation* of a vaccine program, evaluation of the direct and overall effects of vaccination examine the downstream consequences of vaccination on a disease outcome, either at the level of the individual exposed to a vaccine (*i.e.* direct effect), or the population exposed to a vaccination program (*i.e.* overall effect).[11-14] The latter measure not only encompasses direct effects of vaccination among people that have received vaccine, but also indirect effects among both vaccinated and unvaccinated populations, arising from vaccine-related changes in the prevalence of a disease in the population.[11-14] Together, evaluation of these three measures will form a comprehensive assessment of RV1 vaccination in Quebec, both among individuals receiving the RV1 vaccine, and the Quebec population exposed to the RV1 vaccination program.

1.2 Research Objectives

The overall goal of my doctoral thesis was to advance scientific knowledge regarding rotavirus vaccine programs and epidemiologic methods related to vaccine program assessment, through the evaluation of the Quebec RV1 rotavirus vaccine program. The three specific aims of this thesis were:

1. To examine the vaccine effectiveness, or direct effect, of the RV1 vaccine to prevent pediatric emergency department visits and hospitalizations in Quebec (**Manuscript 1**).
2. To estimate rotavirus vaccination coverage among the Quebec population eligible for vaccination, and innovate upon existing methods of vaccine coverage assessment (**Manuscript 2**).
3. To evaluate the population impact, or overall effect, of the Quebec rotavirus vaccine program to prevent pediatric all-cause AGE hospitalizations, and characterize the effect attributable to the program as a whole, according to standard practice, and the effect attributable to a per-unit change in vaccine coverage, a newly proposed measure that may help to promote the generalizability of overall effect estimates (**Manuscript 3**).

1.3 Organization of Thesis

This manuscript-based thesis is organized into six chapters. In Chapter 2, I discuss the current state of the literature as relevant to the thesis goal and specific aims outlined here in Chapter 1. Chapters 3-5 form the core of the thesis, with each chapter representing a manuscript written to address one of the thesis specific aims. Specifically, in Chapter 3, I evaluate the effectiveness of RV1 vaccine using data from an active surveillance study at 3 hospitals in Quebec; I use the same dataset to assess rotavirus vaccine coverage among the population eligible for vaccination under the new program in Chapter 4; and in Chapter 5, I characterize the overall effect of the Quebec RV1 vaccination program in the population among a sample of the Montreal pediatric population, using vaccine coverage data derived from the study design highlighted in Chapter 4. This thesis concludes in Chapter 6, where I summarize key results of the thesis as well as its limitations and overall conclusions, and highlight areas for future research.

Chapter 2: Literature review

2.1 Rotavirus clinical features, epidemiology, and surveillance in the pre-vaccine era

Rotavirus is a highly contagious viral illness that spreads from infected to susceptible persons by fecal-oral transmission via contact with contaminated hands, surfaces, food, or water.[15] Once transmitted, the incubation period is 1-2 days.[16] Although infection may be asymptomatic, the classic clinical presentation includes mild to severe AGE, with non-pathognomonic, generalized symptoms of diarrhea, fever, vomiting, and abdominal pain; infected individuals are most infectious when experiencing AGE symptoms.[16]

Rotavirus virions contain two proteins in their outer capsid that can be genotyped to delineate the virion's "G" and "P" genotypes, that when combined together form the binary classification system for a rotavirus strain.[17] There are many rotavirus strains that can infect humans, but approximately 90% of infections in North America during the pre-vaccine era were caused by 3 strains: G1P[8], G2P[4], and G3P[8], with strain G1P[8] typically comprising more than 70% of the rotavirus diarrheal burden.[17] In temperate climates, rotavirus produces annual epidemics with peak disease occurring in winter-spring time periods.[18-20] Multiple strains of rotavirus can circulate simultaneously during a season, and predominant strains may fluctuate annually.[17]

By 5 years of age, nearly all children had experienced at least one rotavirus infection.[15] Although repeated infection can occur, the first infection is usually the most severe.[15] Among young children residing in Canada, rotavirus was the leading cause of severe AGE,[5] and during the annual 6- to 7-month peak of a rotavirus season, rotavirus infection represented approximately 40-56% of all-cause AGE hospitalizations and emergency department visits.[6,21,22] Between 1 in 45 and 1 in 106 Canadian children were hospitalized due to rotavirus infection by 5 years of age, with many more seeking emergency care.[2,3] Specifically in Quebec, an estimated 50 to 74 per 10,000 children under 5 years of age were hospitalized for rotavirus AGE annually, including hospitalizations in short stay units, while 117 to 152 per 10,000 children under 5 years of age required emergency department care.[7] Given the high prevalence of severe disease, rotavirus infection was costly and burdensome. Canadians spent approximately $125 million per birth cohort on rotavirus-related medical expenses by the time the cohort reached 5 years of age.[8]

Since rotavirus diagnosis does not affect the clinical management of patients with rotavirus AGE, diagnostic testing for rotavirus is not routinely performed in healthcare settings.[23] Calculation of the absolute burden of rotavirus illness is thus not possible without significant investment in active surveillance, an approach to monitoring rotavirus disease by prospectively recruiting and testing AGE patients for rotavirus. In contrast, passive surveillance, or monitoring disease trends using existing, administrative healthcare datasets, is a more sustainable approach to monitoring the burden of rotavirus over time, since it relies upon data from routine care. Healthcare utilization data for all-cause AGE is frequently used as a proxy for rotavirus AGE to examine trends in disease over time among pediatric patients.[7,24-28]

2.2 Rotavirus vaccines

Two oral, live attenuated rotavirus vaccines are currently available for use among infants in Canada.[9,10] Licensed in 2006, Merck's RV5 vaccine is recommended for routine use as 3 doses administered to children at 2, 4, and 6 months of age, and contains 5 rotavirus genotypes: P[8], G1, G2, G3, G4.[9] In 2008, GlaxoSmithKline's RV1 vaccine was licensed, and recommended for routine use as 2 doses with administration to children at 2 and 4 months of age; RV1 contains only 1 rotavirus strain: G1P[8].[10]

In separate, prelicensure trials of RV5 or RV1 efficacy in high-income settings, both vaccines were found to be highly efficacious to prevent severe rotavirus AGE among pediatric patients.[29,30] RV5 efficacy was estimated as 93.8% (95% CI: 90.8%, 95.9%) to prevent hospitalizations and emergency department visits due to rotavirus AGE among children up to 3 years of age,[30] while efficacy of RV1 was estimated as 90.4% (95% CI: 85.1%, 94.1%) to prevent severe rotavirus AGE, as determined by symptom scores, and 96.0% (95% CI: 83.8%, 99.5%) to prevent rotavirus AGE hospitalizations among children up to 2 years of age.[29] Both vaccines were also found to provide significant protection against rotavirus strains not included in their respective formulation; strain-specific estimates, however, were largely imprecise making it difficult to rule out differences in strain-specific RV1 or RV5 vaccine efficacy.[29,30]

2.3 Quebec rotavirus vaccination program

Although rotavirus vaccine has been available in Canada since 2006, publicly funded provincial and territorial healthcare systems did not initially pay for vaccination. The Province of Quebec opted to add routine childhood rotavirus vaccination to the provincial vaccination

formulary on November 1, 2011, but made the decision to exclusively fund RV1 vaccine, in consideration of its cost-effectiveness to prevent severe pediatric rotavirus AGE. Under the program, Quebec residents are eligible to receive RV1 vaccine at no cost, with routine administration at 2 and 4 months of age, and series completion by 8 months of age.[31] At the time of program implementation, it was recommended that the rotavirus series be initiated before 15 weeks of age;[32] this recommendation was later revised to allow series initiation up to 20 weeks of age.[31] To date, there has been little evaluation of the effect of RV1 vaccination on the burden of pediatric rotavirus AGE in Quebec.[33,34]

2.4 Vaccine program evaluation

The evaluation of a vaccine program using real-world, post-implementation data is essential to justify its financial costs and scope. Three key indicators frequently used to inform the success of vaccination that are also foci of the present research are evaluation of: (i) vaccine coverage, (ii) the direct effect of vaccination, or vaccine effectiveness, and (iii) the overall effect of vaccination. While measurement of vaccine coverage can inform the success of the implementation of a vaccine program, the direct and overall effects of vaccination examine the consequences of vaccination on a downstream, disease outcome.

2.4.1 Vaccine coverage

Assessment of vaccine coverage among a program's target population is often the principal indicator to evaluate the success of a new vaccine program.[35-37] Vaccine coverage can inform issues related to program delivery and/or public acceptance of a new vaccine,[38,39] and stratified estimates among population subgroups can also identify inequities in vaccine coverage.[37,40,41] Vaccine coverage is estimated by dividing the number that received a vaccine or vaccine series in a specified population (numerator), by the total number of individuals in the same population (denominator);[37] this proportion is multiplied by 100 to express vaccine coverage as the percentage of the population that has received a vaccine or vaccine series.

Population surveys are often considered the "gold standard" approach to produce valid and precise vaccine coverage estimates in many jurisdictions, including the Province of Quebec.[36-38,42-44] Survey methods are implemented to recruit a representative sample of the population of interest,[36,43,45,46] and key population subgroups can be oversampled to ensure estimate precision.[46] Advantages of survey methods are that the underlying population need not be explicitly defined in

a jurisdiction, since the population surveyed is used as the coverage denominator,[44] and that a standardized protocol can be used to derive comparable estimates of coverage over time, even across a large population.[42] A disadvantage of immunization surveys, however, is that they are potentially costly to implement, as they require significant human resources to design, recruit, enroll and interview participants, and verify their immunizations.[36,44,46] Further, survey administrators face challenges to recruit a representative sample of the population, particularly with the rise of new technology,[43,47] such as cellular phones and caller identification. Though some population-based surveys have adapted survey protocols to address changes in technology by expanding recruitment procedures to include random-digit dialing of cellular phones,[47] or additional attempts to contact eligible participants via mail,[43] challenges to recruit representative populations in a jurisdiction still remain.

An alternative method to ascertain vaccine coverage is to use administrative data to derive coverage estimates, such as a population-based registry of immunization records or a health insurance database.[36,41,42,44,45] Advantages of using administrative data are reduced costs, ease of implementation, and the ability to rapidly examine the uptake of vaccine in a population after the implementation of a new vaccine program.[44] Yet, the validity of coverage estimates derived from these databases depend upon the accuracy and reliability of the administrative system to record the relevant immunizations administered to the population of interest, and enumerate the population denominator, regardless of an individual's immunization status.[36,42,44] Additionally, administrative methods are not appropriate to measure vaccine coverage across a large population where the quality of administrative data varies by geographic region or subpopulation.[42]

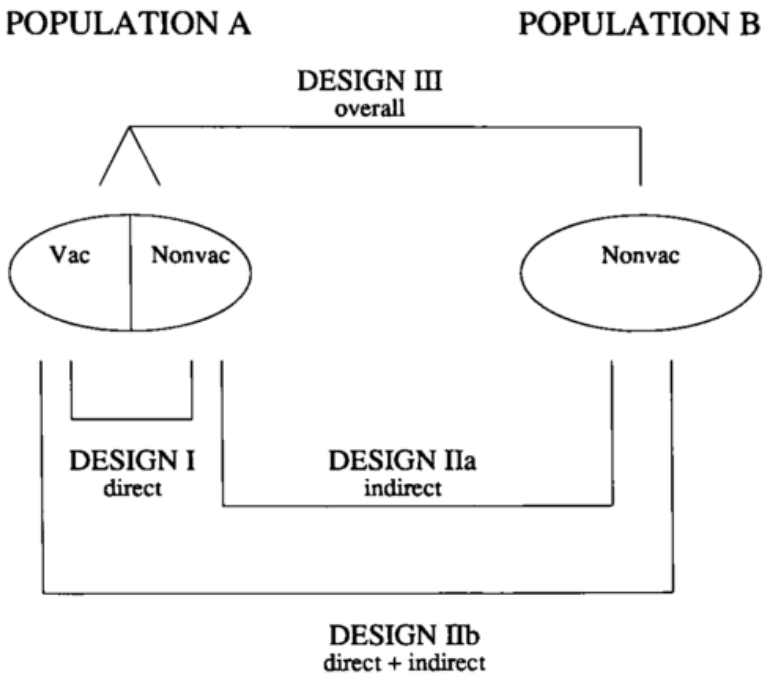
Given differential biases and limitations of survey versus administrative methods, recent research has investigated the effect of combining methods and/or datasets to derive vaccine coverage, based upon the premise that combined data can improve the accuracy of coverage estimates.[41,42,45] Alternatively, researchers have compared estimates from survey and/or administrative systems as a means of validating alternate methods of deriving vaccine coverage estimates in a population.[44,45]

2.4.2 Measurement of the effects of vaccination

Due to the infectious nature and transmissibility of communicable diseases, any public health intervention, such as vaccination, which targets a communicable disease has the potential to exert influence on the disease outcome via two different pathways, acting either: (i) *directly*,

where persons exposed have a different risk of infection than unexposed persons due to receipt of the intervention, and/or (ii) *indirectly*, where the presence of the exposure within a jurisdiction can affect the transmission and prevalence of the disease in the population, which, in turn, can subsequently affect the disease incidence at a later timepoint in the general population (comprised of both exposed and unexposed individuals).[11-14] In their seminal paper, *"Study designs for dependent happenings"*, Halloran and Struchiner (1991) explain this phenomenon and introduce 4 study designs to measure the 4 different effects that can arise from a public health intervention that targets a communicable disease.[14] These 4 study designs are presented here in **Figure 2-1** from Halloran and Struchiner's 1991 paper,[14] and describe measurement of the direct, indirect, total, and overall effects of vaccination. Subsequent discussion of these effects will only focus upon the direct and overall effects of vaccination, since these are foci in the present thesis research.

Figure 2-1. Halloran and Struchiner (1991) study designs to measure vaccination effects.[46]



2.4.3 Direct effect of vaccination

The direct effect of vaccination compares the risk or rate of a disease outcome among vaccinated persons relative to unvaccinated persons.[11-14] In order to isolate the direct effect, vaccinated and unvaccinated persons must be from a population with the same vaccination strategy, thus, cancelling out any observed indirect effects of vaccination.[11-14] When the

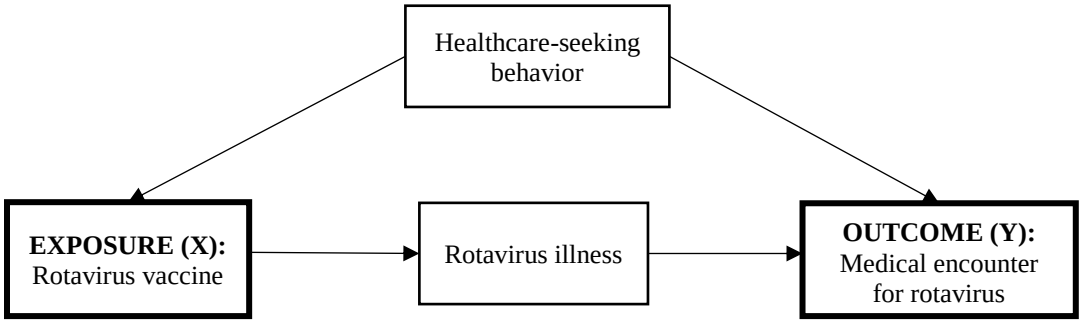
comparison is performed using "real-world" data, the percentage reduction in the relative risk or rate (RR) of the disease outcome is referred to as vaccine effectiveness, estimated as (1 - RR of a disease outcome) * 100.[48-50] The term is often confused with vaccine efficacy,[48,51] which in contrast to vaccine effectiveness, measures the same percentage reduction using data from a setting in which "ideal" conditions for vaccination were implemented, such as vaccine administration to recipients with a robust immune system, with adherence to the recommended vaccination schedule, and proper procedures for vaccine storage, handling, and dosage.[48-50] Whereas vaccine efficacy is typically estimated via a per-protocol analysis of data from vaccine prelicensure phase III studies, *i.e.* randomized controlled trials, vaccine effectiveness is measured in post-licensure, phase IV studies.[49-51] Since randomized controlled trials are no longer ethical following the licensure of an effective vaccine, vaccine effectiveness is typically assessed using observational data from cohort or case-control study designs.[50-52]

Cohort studies can be expensive to estimate vaccine effectiveness, particularly when administrative data is not readily available to track and follow a cohort member's vaccination status, potential confounders, and/or data on a disease outcome over time.[51] As a result, case-control study designs are frequently used to evaluate vaccine effectiveness, since they enable researchers to oversample cases of disease, and thus, estimate vaccine effectiveness with greater efficiency requiring fewer total study participants.[51] In case-control studies, the odds of vaccination are compared between the cases and controls to estimate the odds ratio (OR) of interest.[13,53-56] When certain design features are implemented, such as sampling study controls in a manner proportional to the amount of person-time contributed in a cohort study, the OR will approximate the RR,[13,55,57,58] and can be substituted in place of the RR in the vaccine effectiveness formula.[53,54,59]

One of the biggest challenges of a case-control study is recruitment of study controls who represent the source population of the cases. This presents a challenge especially for vaccine effectiveness studies, where cases of vaccine-preventable disease are frequently ascertained and diagnosed at a healthcare encounter, and people that seek healthcare may also have a different propensity to be vaccinated than other individuals in a population.[53-55] As a result, healthcare-seeking behavior is an important confounder in studies of vaccine effectiveness (**Figure 2-2**).[53-55] To address confounding by healthcare-seeking behavior, several types of case-control studies have been developed to estimate vaccine effectiveness, including the test-negative, case-case, and

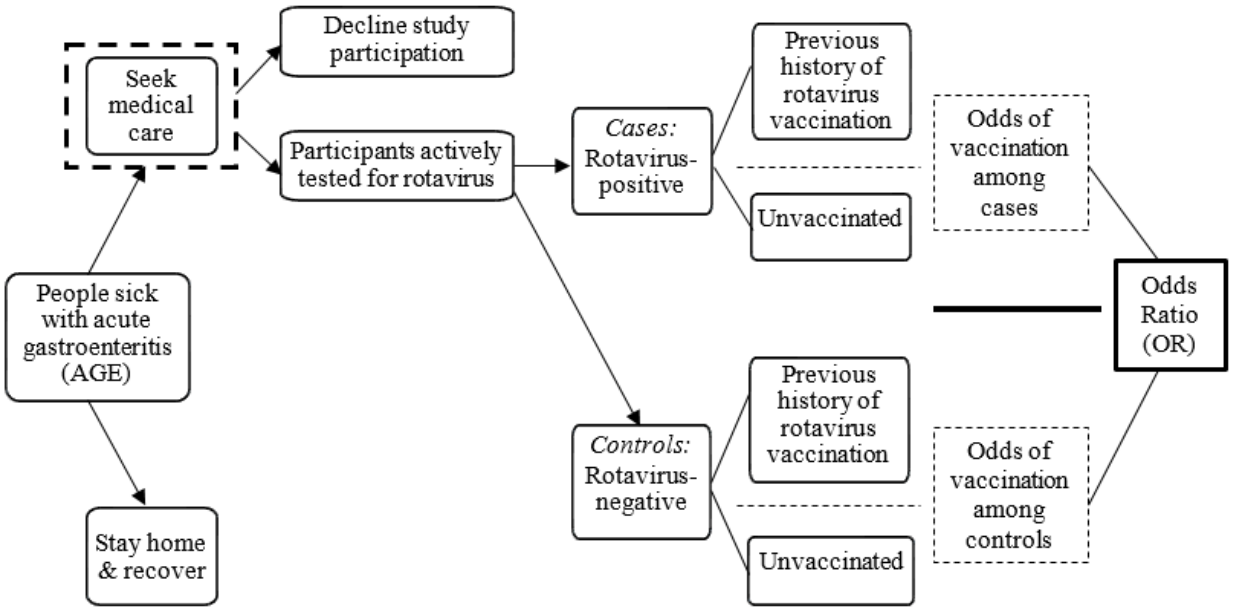
indirect cohort case-control designs.[50,54,55] The motivation for each of these alternative case-control study designs is to sample controls from the same source population of the cases, with the same healthcare-seeking behavior.[50,54,55] The test-negative design is used in this thesis research to estimate RV1 vaccine effectiveness, and is explained in greater detail below.

Figure 2-2. Directed acyclic graph examining the role of healthcare-seeking behavior in rotavirus vaccine effectiveness studies.



The test-negative design was originally developed to examine seasonal influenza vaccine effectiveness,[55,56] but has been increasingly used to estimate rotavirus vaccine effectiveness.[60-65] In this design, only patients that are actively seeking medical care for a "syndrome" of clinical symptoms are recruited for study participation.[53,55,56] Upon enrollment, all study participants are tested for the disease outcome of interest; patients that test positive for the disease are enrolled as study cases, whereas patients that test negative for the disease are enrolled as study controls.[53,55,56] As with other case-control designs, the odds of vaccination for the disease are compared between the cases and controls to estimate the OR of interest, which is used to calculate vaccine effectiveness.[53-56] **Figure 2-3** (below) is a schematic representation of the test-negative design, implemented to estimate rotavirus vaccine effectiveness.

Figure 2-3. Schematic representation of recruitment and execution of the test-negative case-control study design to estimate rotavirus vaccine effectiveness.



Since study participation in a test-negative study is conditional upon seeking medical care, the design is often preferred among researchers because it reduces confounding bias by healthcare-seeking behavior, and is easy to implement.[53-56] Active diagnostic testing of participants for rotavirus additionally reduces confounding bias arising from differential ascertainment of rotavirus cases due to healthcare testing practices.[54,56] Inclusion of only healthcare-seekers, however, assumes that vaccine effectiveness does not differ by healthcare-seeking behavior.[53,54,56] Additionally, in using rotavirus-negative patients as controls, the design further assumes that rotavirus vaccination does not affect the incidence or rate of non-rotavirus AGE among healthcare seekers.[54,55,66]

There have been several studies that examine the validity of the test-negative design to estimate vaccine effectiveness.[53-56,66-68] These studies have concluded that the test-negative design can be used to produce valid and reliable estimates of vaccine effectiveness, but have also illuminated several design aspects that should be considered to reduce potential biases in vaccine effectiveness estimates derived via the test-negative design.[53-56,66-68] In particular, simulations have revealed that the diagnostic accuracy of the test used to ascertain the disease status of participants should be high, especially with regard to specificity, which has a greater effect on vaccine effectiveness estimates than sensitivity.[54,55,66,67] Additionally, other research has shown that the

disease of interest must be circulating during the time period when controls are recruited, since recruiting subjects outside a period of circulation is equivalent to sampling persons in a cohort study that are not at risk of a disease, akin to immortal time bias in a cohort study.[54] Further, since time can be associated with the risk of the outcome as well as the uptake of the vaccine in a population, adjustment for time is also necessary to reduce bias in vaccine effectiveness estimates.[54]

2.4.4 Overall effect of vaccination

The overall effect of vaccination measures the rate or risk of disease in a population where a vaccine program exists, relative to the rate or risk of disease in a population without such a vaccine program.[11-14] The effect is comprised of both direct and indirect effects of vaccination, and represents an average of the observed effects among vaccinated and unvaccinated individuals, weighted by their respective proportion in the population (*i.e.* as determined by vaccine coverage).[11,13,14,50] The overall effect of vaccination is frequently referred to as the assessment of the "impact" of a vaccination program, and where the effect is characterized as the percentage relative decrease in the RR, or (1 – RR) * 100, the measure may also be referred to as vaccine program effectiveness.[50,69]

Often, the overall effect of a vaccine program is estimated using an ecological, observational study design comparing rates of disease in a post-vaccine program period with rates of disease for the same population during a pre-vaccine program period.[13] Because rates of an infectious disease may vary naturally over time in a population, time series methods that can model underlying secular and/or seasonal disease trends are ideally suited to estimate the overall effect of vaccination, and several years of data from pre- and post-vaccine program periods should be included to capture natural variation between seasons.[13,69,70]

Development of a statistical model to characterize an infectious disease time series, however, is not without challenges. Time series of communicable diseases can exhibit strong autocorrelation, and while the presence of residual autocorrelation in other applications typically only biases standard errors, residual autocorrelation in communicable disease time series can also lead to biased effect measures.[69,71] Further, it may not be possible to explain natural patterns in a communicable disease time series using solely exogenous explanatory variables, which do not account for the dynamic relationship between susceptible-infected-recovered persons in a population.[71] Additionally, controlling for patterns of communicable disease seasonality can be

difficult, while inadequate adjustment may bias overall effect estimates.[72] Fortunately, there have been several developments in time series regression in the field of environmental epidemiology that can be applied to communicable disease time series.[71,73,74] For example, Brumback et al. (2000) suggested the use of transitional regression methods, which include an autoregressive term in generalized linear models to remove strong residual autocorrelation.[71,73] Further, Lopman et al. (2009) addressed the dynamic relationship between susceptible-infected-recovered persons in time series models that examined the effect of weather on norovirus disease by including a model covariate to account for the number of persons recovered and presumed immune to norovirus, based upon the number previously experiencing the norovirus outcome.[71,74] Researchers have also included model covariates such as time strata, Fourier terms, or flexible spline functions to successfully adjust for time series seasonality.[72]

Once estimated, the overall effect of vaccination must be considered in the context of population vaccine coverage, since vaccine uptake influences the magnitude of the overall effect.[70] As a result, the current practice in evaluation studies is to report the level of vaccine coverage observed in the population, in addition to estimates of the overall effect.[24,25,27,28,75] Yet, these methods do not readily enable comparisons of the overall effect between similar jurisdictions with differing vaccine programs and discrepant coverage. For example, most systematic reviews and/or meta-analyses (SR/MA) that compare overall effects between vaccine programs report jurisdictional vaccine coverage in their narrative or a results table;[76-80] however, when multiple estimates are compared, it is difficult for readers to track and synthesize this information. While other SR/MA account for differences in vaccine coverage by stratifying overall effect estimates by coverage,[81,82] coverage strata tended to be overly broad (*i.e.* coverage <50% vs. ≥50%, or low/moderate/high coverage) and are thus, potentially insufficient to adjust for differences in program effects due to vaccine coverage alone.[81,82] Further, while meta-analyses of the overall effect can directly adjust for vaccine coverage as a covariate in statistical models,[83] the overall effect estimates from primary studies may not reflect a post-program period with uniform vaccine coverage, particularly for new vaccine programs, such as rotavirus, where coverage can change rapidly in the population following program implementation;[24,25,27,28,75] thus, direct adjustment for vaccine coverage in pooled analyses may not be possible or accurate. These scenarios illustrate that current methods can be insufficient to enable meaningful comparisons of the overall effect of vaccination between jurisdictions. Yet, where comparisons of the overall effect do successfully

account for differences due to vaccine coverage, researchers may gain important insights into the consequences of differing vaccine program design choices on population health outcomes, and policy-makers may use this knowledge to improve vaccination programs.

2.5 Evaluation of rotavirus vaccination in Quebec and other high-income countries

Since the licensure of RV5 and RV1 vaccines in many countries throughout the world, there has been much research regarding the effects of rotavirus vaccination.[24-28,33,60-64,84-117] One finding from these studies is that the effects of rotavirus vaccination differ by country income level, with greater RV1 and RV5 vaccine effectiveness observed in high-income settings compared with middle- and low-income settings.[115-117] This difference is presumably due to differences in rotavirus epidemiology, circulating strains, and characteristics of the vaccine-eligible population.[115,116] The following sections examine the current state of knowledge with regard to the evaluation of the Quebec RV1 program, and describe findings of the direct and overall effects of rotavirus vaccination from other high-income settings, since these are most relevant to the Quebec program.

2.5.1 Rotavirus vaccine coverage in Quebec

Since 2006, provincial immunization surveys from the Institut National de Santé Publique du Québec (INSPQ) have been the "gold standard" approach for evaluating population-level vaccine coverage in the Province of Quebec.[43] Although these surveys do not provide time series data to evaluate the uptake of a new vaccine over calendar time, INSPQ surveys do provide biennial coverage estimates by vaccine among a population-representative sample of children at 1 and 2 years of age.[43] In 2014, or nearly 3 years after the implementation of the rotavirus vaccination, the INSPQ provincial coverage survey reported high, ≥2-dose rotavirus coverage of 85.9% among children 15 months of age, and 78.2% among children 24 months of age.[43] These data demonstrate the rapid, relative success of the Quebec program, with high initial vaccine uptake and sustained coverage during the first 3 years following program implementation. In comparison, 3 years after the United States (U.S.) implemented a rotavirus vaccination program, the average rotavirus ≥1-dose coverage was 72% among sentinel locations, ranging from 48% to 86%.[118]

Currently, there are no administrative datasets in Quebec that can be used to examine vaccine coverage at the provincial level. Vaccine administration information is not captured in healthcare administrative billing data among Quebec provincial insurance recipients. Although Quebec recently introduced a province-wide population immunization registry in June 2014, the roll-out of the registry is gradual and it is not expected to cover all regions of Quebec until December 2018.[118,119]

2.5.2 Direct effects of rotavirus vaccination

Given differences in formulations and dosing, comparison of the direct effect, or vaccine effectiveness, of RV1 and RV5 is of considerable interest.[60-62,64,84-87] Results from post-licensure evaluations in high-income jurisdictions with concurrent RV1 and RV5 use reveal high, indistinguishable effectiveness of each vaccine of >70% to prevent rotavirus hospitalizations and emergency department visits.[60-62,64,84-87] RV5 vaccine effectiveness was similar in several high-income locales with exclusive RV5 use, either prior to RV1 licensure, or in a jurisdiction with its exclusive reimbursement.[63,88-93]

Little research exists, however, that examines the effectiveness of RV1 in a high-income, non-outbreak setting where RV1 vaccine is predominantly used over RV5 vaccine.[120] To our knowledge, RV1 vaccine effectiveness in a high-income, non-outbreak setting where RV1 is predominantly used was only assessed in Belgium, prior to this thesis.[120] In Belgium, RV1 vaccine effectiveness was estimated as 90% to prevent hospitalization.[120] Additional research to examine RV1 vaccine effectiveness in this setting is important, since simultaneous uptake of RV5 vaccine in the population can impact rotavirus transmission dynamics and strain circulation, factors which may also influence RV1 vaccine effectiveness.[13]

A recent systematic review was performed to further investigate strain-specific effectiveness of RV1 and RV5 in high-income settings.[117] Although its authors did not detect significant differences by strain for either RV1 or RV5 vaccine, in general, confidence intervals for strain-specific vaccine effectiveness were wide, particularly for RV1, and only a small number of studies (*i.e.* n=1 or n=2) were retrieved to address RV1 effectiveness by rotavirus strain.[117] Because even small differences in strain-specific vaccine effectiveness can introduce strain-specific selection pressures and change the prevalence of circulating rotavirus strains in a region following the uptake of a rotavirus vaccine,[117,121,122] additional evaluation of RV1 effectiveness in high-income settings where it is predominantly used is necessary to ensure that RV1 vaccine is

similarly effective compared with concurrent-use settings. Additionally, researchers should also monitor circulating rotavirus strains in the post-vaccine period to ensure that strain replacement does not occur. [117,121,122]

2.5.3 Overall effects of rotavirus vaccination

In general, evaluations of RV5 and/or RV1 vaccination programs in high-income countries have found large and sustained reductions in pediatric all-cause and rotavirus-specific AGE healthcare utilization, including hospitalizations and emergency department visits.[24-28,33,93-114] Relatively few of these studies, however, have used time series methods to adjust for seasonal and secular trends to estimate reductions in disease to estimate reductions in hospitalizations.[24,26,28,106-108] Failure to account for annual rotavirus secular variation may bias estimated reductions in rotavirus incidence, with the direction and magnitude of the bias depending on the representativeness of rotavirus transmission in the seasons used for comparison.[123]

Specifically, only two, recently published manuscripts have examined the effect of a RV1-only vaccination program on weekly all-cause AGE hospitalizations via time series analysis in high-income jurisdictions.[24,28] Among children less than 1 year of age in England, a relative reduction of 26% (95% CI: 16%, 35%) in weekly all-cause AGE hospitalizations was observed in the first year following the implementation of the vaccination program relative to the pre-vaccine period, with 93% RV1 2-dose vaccine coverage observed among children of this age group.[24] In the Province of Ontario, a 20% (95% CI: 1%, 35%) relative reduction in weekly all-cause AGE hospitalizations was estimated in the 1.5 years post-implementation of the vaccine program relative to the pre-vaccine period among children less than 1 year of age, with RV1 2-dose coverage among this age group of 87%.[28] While these studies provide early data to document the relative success of RV1-only vaccination programs, both analyze less than 1.5 years of data from a post-vaccine period,[24,28] which may be insufficient to accurately characterize average reductions in the post-vaccine period, particularly given the natural seasonal variation in rotavirus AGE in the pre-vaccine era.[70]

Time series analyses from RV5-only or RV5 and RV1 concurrent programs found similar declines in all-cause AGE hospitalizations.[106,107] In Finland, a 24.2% (95% CI: 12.8%, 34.1%) relative reduction in weekly cause-unspecified AGE hospitalizations was observed among children less than 1 year of age in the 1 year following RV5 program implementation, with >95% 3-dose RV5 coverage among the same age group.[106] In the United States (U.S.) prior to use of RV1

vaccine, a relative reduction of 39% (95% CI: 29%, 48%) was observed in monthly cause-unspecified AGE hospitalizations among children 0 to 4 years of age in the 1 year following the implementation of an RV5 program, with modest coverage of 56% among children 1 year of age.[107] In Spain, a setting with concurrent RV5 and RV1 use, but without a national immunization program, a 2% (95% CI: 1%, 3%) relative decrease was observed in the trend of weekly all-cause AGE hospitalizations in the 6.5 years following rotavirus vaccine licensure relative to the pre-vaccine period, with reported coverage of approximately 40%.[108] In the U.S. during a period with concurrent RV5 and RV1 vaccination, a 42% (95% CI: 34%, 50%) relative decline in monthly cause-unspecified AGE hospitalizations among children 0 to 4 years of age was observed in the 3-year period post-implementation of a rotavirus vaccine program relative to the pre-vaccine period, with vaccine coverage unspecified.[26]

In Quebec, there has only been one evaluation of the overall effect of the RV1 program, using recent data from two hospitals.[33] While the authors found a significant reduction in the proportion of pediatric emergency department visits attributable to AGE, the analysis was restricted to a simple pre- and post-program comparison via a chi-square statistical test, and the authors did not account for rotavirus secular trends or seasonality in their analyses.[33]

In summary, while there is evidence to support the success of RV1 and/or RV5 vaccine programs, much of the current research has not used methods to adequately account for secular and seasonal variation in rotavirus AGE. Further, when appropriate statistical methods were used to evaluate the overall effect of a RV1 vaccine program, data in the post-vaccine period was limited to less than 2 seasons. Since significant variation in the burden of pediatric rotavirus AGE existed in the pre-vaccine period,[70] data from multiple, post-vaccine seasons is critical to accurately characterize the average overall effect of an RV1-only vaccination program. Further, adequate methods to account for secular and seasonal trends must be used to accurately characterize the overall effect of the RV1 vaccination program in Quebec.

Chapter 3: Effectiveness of monovalent rotavirus vaccine in a high-income, predominant-use setting

3.1 Preface

As described in Chapter 2, there is little research that examines the effectiveness of RV1 in a high-income, non-outbreak setting where RV1 vaccine is predominantly used over RV5 vaccine. Additional research to examine RV1 vaccine effectiveness in this setting is important, since simultaneous uptake of RV5 vaccine in the population can impact rotavirus transmission dynamics and strain circulation, factors which may also influence RV1 vaccine effectiveness.[13] In the following manuscript (Manuscript 1), I examine RV1 effectiveness to prevent emergency department visits and hospitalizations using a test-negative case-control design and data from active rotavirus surveillance of children less than 3 years of age implemented at three hospitals in the Province of Quebec. Additionally, I compare the relative proportion of rotavirus positive specimens in the post-vaccine era over time concurrently with increasing population vaccine coverage, and examine circulating rotavirus genotypes in the post-vaccine era.

Manuscript 1 was published in the peer-reviewed journal, *Vaccine.*[124]

3.2 Manuscript

Effectiveness of monovalent rotavirus vaccine in a high-income, predominant-use setting

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Conflict of Interest: The authors have no conflicts of interest to disclose. GSK did not participate in any of the protocol writing, planning, implementation, analysis or study writing of this study but did review the final version of the manuscript.

Abstract

Background & objectives: We assessed monovalent rotavirus (RV1) vaccine effectiveness in a high-income setting with RV1 predominant use, and examined the burden of pediatric rotavirus gastroenteritis following the implementation of an RV1-only vaccination program.

Methods: We conducted active rotavirus gastroenteritis surveillance among children 8 weeks to less than 3 years of age at three hospitals. Participant information and vaccination histories were collected via parent/guardian interview and medical records. Stool specimens were tested for rotavirus; positive specimens were genotyped. The effect of increasing RV1 coverage on rotavirus prevalence was examined as a weekly time series via binomial regression with a log link function, using either categorical season or mean 2-dose rotavirus seasonal vaccine coverage as the exposure variable. As compared with RV1 vaccine formulation, rotavirus genotypes were classified as homotypic, partly-heterotypic, or heterotypic; prevalence of each was compared by season. A test-negative case-control design was used to examine RV1 vaccine effectiveness against hospitalization or emergency visits.

Results: We enrolled 866 participants in active surveillance; of these, 374 (43.2%) were eligible for vaccine effectiveness analyses. After adjustment for season, we detected a 70.1% (95% CI: 21.9%, 88.6%) relative decrease in rotavirus prevalence in the 2013-14 season compared with 2012-13 season. On average, a 1% increase in ≥2-dose rotavirus coverage among children 1 year of age was associated with a 3.8% (95% CI: 1.8%, 5.8%) relative decrease in rotavirus prevalence. Rotavirus homotypic strain prevalence decreased, with 77% (95% CI: 68%, 89%) versus 8% (95% CI: 0%, 36%) prevalence during the 2011-12 and 2013-14 seasons, respectively. Adjusted 2-dose RV1 vaccine effectiveness was 91.2% (95% CI: 61.6%, 98.0%).

Conclusions: RV1 vaccine was highly effective to prevent rotavirus hospitalizations and emergency visits among children less than 3 years of age in a high-income setting with its predominant use. Our estimates were similar to high-income settings with concurrent RV1 and pentavalent vaccine use.

Keywords: rotavirus, vaccination, effectiveness

Introduction

Rotavirus was the major cause of pediatric gastroenteritis among Canadian children during the pre-vaccine era.[1-7] Before vaccination, up to 1 in 40 Canadian children <5 years of age required hospitalization or emergency care annually for rotavirus gastroenteritis.[7] Two oral rotavirus childhood vaccines are licensed in Canada:[9,10] *Rotarix*® (RV1; trademark of the GlaxoSmithKline group of companies), a monovalent vaccine containing strain G1P[8], administered as a 2-dose series, and *RotaTeq*® (RV5; trademark of Merck & Co., Inc.), a pentavalent vaccine containing strains G1-G4 and P[8], administered as a 3-dose series. As of September 2014, 9 Canadian provinces and territories adopted public reimbursement for RV1-only under provincial insurance plans; the remaining 4 provinces and territories do not reimburse for either vaccine.[125]

Given differences in formulations and dosing, comparison of the direct effect, or vaccine effectiveness, of RV1 and RV5 is of considerable interest.[60-62,64,84-87] Results from post-licensure evaluations in high-income jurisdictions with concurrent RV1 and RV5 use reveal high, indistinguishable effectiveness of each vaccine of >70% to prevent rotavirus hospitalizations and emergency visits.[60-62,64,84-87] RV5 vaccine effectiveness was similar in several high-income locales with exclusive RV5 use - either prior to RV1 licensure, or in a jurisdiction with its exclusive reimbursement.[63,88-93] Since effects of concurrent RV1 and RV5 use may differ from exclusive RV1 use, it is important to evaluate RV1 vaccine effectiveness in settings without concurrent RV5 vaccination. However, to our knowledge, RV1 effectiveness in a high-income, non-outbreak setting where RV1 is predominantly used has only been assessed in Belgium.[120]

We conducted a test-negative case-control study to assess RV1 vaccine effectiveness to prevent rotavirus emergency visits and hospitalizations among young children in a Canadian setting with predominant RV1-use, and examined the effect of increasing vaccination coverage on the prevalence of pediatric rotavirus over time.

Materials and methods

Study setting

In November 2011, Quebec implemented a publicly-funded RV1 vaccination program with its routine administration at 2 and 4 months of age. From February 1, 2012 – May 31, 2014, we conducted prospective, active surveillance for acute rotavirus gastroenteritis at The Montreal Children's Hospital and Centre Hospitalier Universitaire Sainte-Justine, located in Montreal, and

Centre Hospitalier Universitaire de Sherbrooke, located in Sherbrooke. Active surveillance was approved by Research Ethics Boards at each hospital.

Patient recruitment & eligibility

Patients 8 weeks to less than 3 years of age, hospitalized or seeking emergency care for acute gastroenteritis, whose parent or legal guardian consented to be contacted for research were eligible for recruitment. Acute gastroenteritis was defined as (i) diarrhea (liquid stools for >12 hours with ≥3 stools in a 24-hour period), (ii) vomiting (≥1 episode in a 24-hour period), or (iii) an emergency department diagnosis of diarrhea, vomiting, or gastroenteritis; where symptom onset occurred within ≤7 days of presentation. Patients were excluded if rotavirus vaccination was contraindicated per the Quebec Immunization Protocol.[126] Written consent to participate was obtained from a parent or legal guardian of participants.

Data collection & laboratory testing

Participant information was systematically collected via parental phone interview and medical chart review. Participant vaccination history, including vaccine date and type, was obtained in reference to the participant's immunization booklet; if unavailable at the time of interview, permission was requested to contact the participant's medical provider for vaccination information.

Stool samples were obtained at study recruitment from specimens collected at home or retrieved from emergency or hospital care, and stored at -80°C until viral testing. All stool were initially tested for rotavirus via enzyme immunoassay (EIA; Premier™ Rotaclone®, Meridian Bioscience, Inc.). Rotavirus-positives were confirmed via real-time reverse-transcriptase polymerase chain reactions (RT-PCR) according to protocols outlined by Gentsch et al;[127] RT-PCR results were used in the event of discordant EIA results. Rotavirus genotyping was performed as described in Chetrit et al.[128]

Time series analyses of rotavirus burden

Using active surveillance data, we examined rotavirus prevalence over time. We defined rotavirus seasons 2011-12, 2012-13, and 2013-14 as the periods, February 2012 – May 2012, June 2012 – May 2013, and June 2013 – May 2014, respectively. June was chosen as the annual starting month in accordance with previous research examining rotavirus activity in Quebec.[1]

Since our data were limited to the post-vaccine period, we sought to examine the effect of increasing rotavirus vaccination coverage on our dependent variable, the proportion of weekly positive rotavirus cases out of total gastroenteritis cases, among all active surveillance participants. We used binomial regression with a log link function to examine two different characterizations of our exposure: (i) categorical season, and (ii) mean 2-dose rotavirus vaccination coverage among children 1 year (12 to 23 months) of age, for each rotavirus season. A log link function was used instead of a logit because we regarded prevalence ratios as more meaningful than prevalence odds ratios.[129] An annual sine term was used to adjust for seasonal cycles in both models.

For analyses using categorical season, the 2012-13 season was used as the referent period. For coverage analyses, we estimated rotavirus vaccination coverage for each season based upon ≥2-dose rotavirus vaccination coverage among rotavirus-negative, active surveillance participants, 1 year of age. We assessed coverage among rotavirus-negative participants only because we assumed that rotavirus vaccination did not affect the risk of non-rotavirus, acute gastroenteritis etiologies. Coverage was examined among children 1 year of age because this age-group was more frequently hospitalized for acute rotavirus gastroenteritis in Canada,[2,3] and therefore, we hypothesized that vaccination coverage among this age group was more likely to directly impact measured rotavirus gastroenteritis. In these analyses, binomial regression was implemented in a Bayesian hierarchical framework to account for uncertainty in rotavirus coverage estimates. Because of its natural bounds between 0 and 1, a beta distribution was used for each vaccine coverage estimate with parameters for the three seasons selected based upon vaccine coverage data for that period. This approach to modeling is more conservative than using coverage point estimates without accounting for uncertainty from small sample sizes. Non-informative, normal priors with mean=0 and variance=1,000 were used for regression parameters. Parameter estimates were obtained using Markov chain Monte Carlo methods, running three parallel chains for 100,000 iterations, with a burn-in of 10,000 iterations. Convergence was assessed with trace plots and the Gelman-Rubin statistic.[130]

Rotavirus genotypes

Rotavirus genotypes were examined among rotavirus-positive active surveillance cases. Rotavirus strains were classified as vaccine: (i) homotypic (strain G1P[8]), (ii) partly-heterotypic, (any strain inclusive of either G1 or P[8] antigens), and (iii) heterotypic, (any strain exclusive of both G1 and P[8] antigens). Prevalence and 95% confidence intervals were assessed by season.

Monthly prevalence was examined graphically using a simple, backwards, six-month moving average.

Vaccine effectiveness study design & case-control ascertainment

RV1 vaccine effectiveness was investigated using a subset of active surveillance participants age-eligible to receive 2-doses of RV1 vaccine, defined as participants (i) <15 weeks of age as of program implementation (November 1, 2011), and (ii) ≥16 weeks of age at symptom onset. These ages corresponded to the maximum recommended age of administration for the first RV1 dose at program implementation,[131] and the recommended age of second dose administration, respectively.

We used a test-negative case-control study design, where cases were defined as rotavirus-positive and controls as rotavirus-negative participants. This design has been used previously in rotavirus vaccine effectiveness studies.[60-62,64,84] Since we viewed time as a strong potential confounder because of its relationship with both (i) rotavirus vaccine uptake, due to the recent RV1 program implementation, and (ii) risk of severe rotavirus gastroenteritis, due to rotavirus seasonality & changes in circulation over time, we used risk set sampling with variable ratio optimal matching to match up to 8 controls to each case based upon symptom onset date ±15 days; matching was performed using *dist* & *vmatch* SAS macros.[132]

Vaccine effectiveness estimation

We estimated RV1 vaccine effectiveness of 2- versus 0-doses and ≥1- versus 0-dose to prevent rotavirus hospitalization or emergency visits. Only valid RV1 vaccinations administered ≥14 days prior to symptom onset were considered. Children vaccinated with RV5 (private market, minimal penetrance) were excluded.

RV1 vaccine effectiveness was estimated as (1 – exposure odds ratio)*100.[59] Based upon our sampling scheme, the exposure odds ratio from our analyses approximates the rate ratio.[133]

To account for matching, we used conditional logistic regression to estimate the exposure odds ratio. Further, since variable ratio matching was used, we used a schema to weight each control as 1 over the total number of controls matched to "their" respective case to account for differences in the number of controls per case.[134] Multivariable analyses were adjusted for study location, current breastfeeding status, and continuous participant age, confounders determined *a priori*. Given that Quebec daycares and schools do not require vaccination for entry, we did not

view attendance as a potential confounder since it was unlikely to be associated with vaccine uptake.

All analyses were performed using SAS version 9.3 statistical software (SAS Institute, Inc., Cary, NC), or RStudio version 0.98.1103 (Boston, MA). Bayesian modeling was performed using the *R2jags* package[135] that incorporates JAGS statistical program[136] version 3.4.0.

Results

Study population

From February 1, 2012 – May 31, 2014, we enrolled 866 of 4,849 (17.9%) eligible patients with acute gastroenteritis in active surveillance (**Figure 3-1A**). Of these, 728 (84.1%) participants were included in active surveillance analyses; 144 (19.8%) were rotavirus-positive. Rotavirus ≥1-dose coverage was 46.4% (95% CI: 42.8%, 50.1%) among all active surveillance participants; among those vaccinated, 91.4% (95% CI: 87.9%, 93.9%) received RV1 only (*i.e.* not RV5).

Among active surveillance participants, 384 (52.7%) were age-eligible to receive 2 rotavirus vaccine doses; of these, 374 (97.4%) were eligible for vaccine effectiveness analyses (**Figure 3-1B**). Among vaccine effectiveness participants, 32 (8.6%) tested rotavirus-positive and were considered eligible cases.

Characteristics of active surveillance and vaccine effectiveness study participants by rotavirus status are examined in **Table 3-1**. On average, active surveillance rotavirus-positive participants were 7.1 (95% CI: 5.7, 8.6) months older than rotavirus-negative participants. The distribution of rotavirus-positive active surveillance cases differed by study location and onset year, with rotavirus-positive active surveillance participants less likely to present at the Sainte-Justine study location, or in the final year of the study period. Rotavirus-positive active surveillance participants were also more likely to be unvaccinated compared with rotavirus-negative participants. Similar trends were found when comparing rotavirus-positive and -negative vaccine effectiveness participants.

Of the 32 eligible cases for vaccine effectiveness analyses, 30 (93.8%) matched with ≥1 control, with a total of 156 matched controls retained (median: 5.5 controls/case). The absolute mean difference between symptom onset date of cases and controls after matching was 5.0 (95% CI: 4.3, 5.7) days.

Time series analyses of rotavirus burden

The prevalence of rotavirus-positive active surveillance cases and ≥2-dose rotavirus coverage among 1-year old, rotavirus-negative children is presented over time in **Figure 3-2**. Mean age of rotavirus-positive participants was 20.5 (95% CI: 18.3, 22.8), 23.9 (95% CI: 22.1, 25.7) and 25.0 (95% CI: 20.9, 29.1) months for the 2011-12, 2012-13, and 2013-14 seasons, respectively. On average, rotavirus-positive participants in 2011-12 were 3.4 (95% CI: 0.5, 6.2) and 4.5 (-0.1, 9.1) months younger than in 2012-13 and 2013-14 seasons, respectively.

After adjustment for season, we estimated a 70.1% (95% CI: 21.9%, 88.6%) relative decrease in rotavirus prevalence in 2013-14 compared with the 2012-13 season; no relative difference was found between 2011-12 and 2012-13 seasons (RR: 1.2, 95% CI: 0.5, 2.5).

Mean 2-dose rotavirus coverage was 7.3% (95% CI: 2.5%, 19.4%), 35.0% (95% CI: 26.4%, 44.8%), and 82.9% (95% CI: 72.9%, 89.7%) among children 1 year of age during the 2011-12, 2012-13, and 2013-14 seasons, respectively. Figure 3 illustrates these data as beta distributions, incorporated in our hierarchical model. After adjustment for season, we found that on average, a 1% increase in ≥2-dose rotavirus coverage among children 1 year of age was associated with a 3.8% (95% CI: 1.8%, 5.8%) relative decrease in rotavirus prevalence.

Rotavirus genotypes

Rotavirus G- and P-genotypes were typed for 134 of 144 (93%) rotavirus-positive specimens. Vaccine homotypic strains represented 47% (95% CI: 39%, 57%) of specimens, while prevalence of heterotypic and partly-heterotypic specimens was 28% (95% CI: 20%, 38%) and 25% (95% CI: 16%, 34%), respectively. Among heterotypic strains (n=38), 97% (95% CI: 87%, 100%) were G2P[4], and 3% (95% CI: 0%, 13%) were G9P[4]. Among partly-heterotypic strains (n=33), 55% (95% CI: 39%, 71%) were G9P[8], followed by 15% (95% CI: 0%, 32%), 12% (95% CI: 0%, 29%), 12% (95% CI: 0%, 29%), and 6% (95% CI: 0%, 23%) of G12P[8], G10P[8], G3P[8], and G2P[8], respectively.

Rotavirus strains are examined over time in **Figure 3-4**. Generally, homotypic strain prevalence decreased over time with 77% (95% CI: 68%, 89%), 31% (95% CI: 19%, 44%), and 8% (95% CI: 0%, 36%) prevalence during 2011-12, 2012-13, and 2013-14 seasons, respectively. Heterotypic strain prevalence was lowest for the 2011-12 season, representing 8% (05% CI: 0%, 19%) of rotavirus gastroenteritis, in comparison with 46% (95% CI: 34%, 59%) and 23% (95% CI: 8%, 51%) during 2012-13 and 2013-14 seasons, respectively. Partly-heterotypic prevalence

was highest in the 2013-14 season, representing 69% (95% CI: 54%, 98%) of rotavirus-positive specimens, while prevalence during 2011-12 and 2012-13 seasons was 15% (95% CI: 6%, 26%) and 24% (95% CI: 12%, 37%), respectively.

RV1 vaccine effectiveness

The unadjusted vaccine effectiveness of 2- versus 0-doses of RV1 against emergency visits and hospitalizations was estimated as 93.8% (95% CI: 78.3%, 98.2%); adjusted vaccine effectiveness was 91.2% (95% CI: 61.6%, 98.0%). Unadjusted RV1 vaccine effectiveness of ≥1- versus 0- doses was 94.7% (95% CI: 81.5%, 98.5%); adjusted vaccine effectiveness was 92.5% (95% CI: 69.3%, 98.2%).

Table 3-1. Characteristics of active surveillance and eligible vaccine effectiveness study participants by etiology. Data represent n and % (95% CI) unless otherwise specified.

Variable	Active Surveillance: Rotavirus-negative		Active Surveillance: Rotavirus-positive		Vaccine Effectiveness: Rotavirus-negative		Vaccine Effectiveness: Rotavirus-positive	
	N=584	% (95% CI)	N=144	% (95% CI)	N=342	% (95% CI)	N=32	% (95% CI)
Age at onset (months)								
Mean (95% CI)	15.6	(14.9, 16.2)	22.7	(21.4, 24.0)	12.6	(11.9, 13.3)	16.6	(14.3, 18.9)
Sex: Male	306[┼]	53 (49, 57)	73	51 (43, 59)	188[┼]	56 (50, 61)	12	38 (21, 54)
Study Hospital Location								
Montreal Children's	257	44 (40, 49)	73	51 (42, 59)	125	37 (31, 43)	16	50 (34, 69)
Sherbrooke	162	28 (23, 32)	60	42 (33, 50)	81	24 (18, 30)	11	34 (19, 53)
Sainte-Justine	165	28 (24, 33)	11	8 (0, 16)	136	40 (34, 46)	5	16 (0, 35)
Onset Year								
February 2012 - May 2012	106	18 (14, 23)	55	38 (30, 47)	12	4 (0, 9)	4	13 (0, 30)
June 2012 - May 2013	252	43 (39, 48)	75	52 (44, 61)	138	40 (35, 46)	18	56 (41, 74)
June 2013 - May 2014	226	39 (35, 43)	14	10 (1, 18)	192	56 (51, 62)	10	31 (16, 49)
Underlying Condition: Yes	33	6 (4, 8)	13	9 (4, 14)	27	8 (5, 11)	3	9 (0, 19)
Hospitalized: Yes	75[┼┼]	13 (10, 16)	27[┼┼]	19 (12, 25)	45[┼┼]	13 (10, 17)	4	13 (1, 24)
Rotavirus vaccination								
0-doses	253	43 (39, 48)	135	94 (91, 98)	62	18 (14, 23)	24	75 (63, 90)
1-dose	47	8 (4, 12)	1	1 (0, 5)	26	8 (3, 12)	1	3 (0, 18)
≥2-doses	280	48 (44, 52)	8	6 (3, 10)	254	74 (70, 79)	7	22 (9, 37)
Unknown	4	1 (0, 5)	0	0 (0, 4)	N/A	---	N/A	---

[┼]excludes missing data (n=5); [┼┼]excluded missing data (n=1)

Figure 3-1. Flow diagram of active surveillance (*A*) and vaccine effectiveness (*B*) study participants.

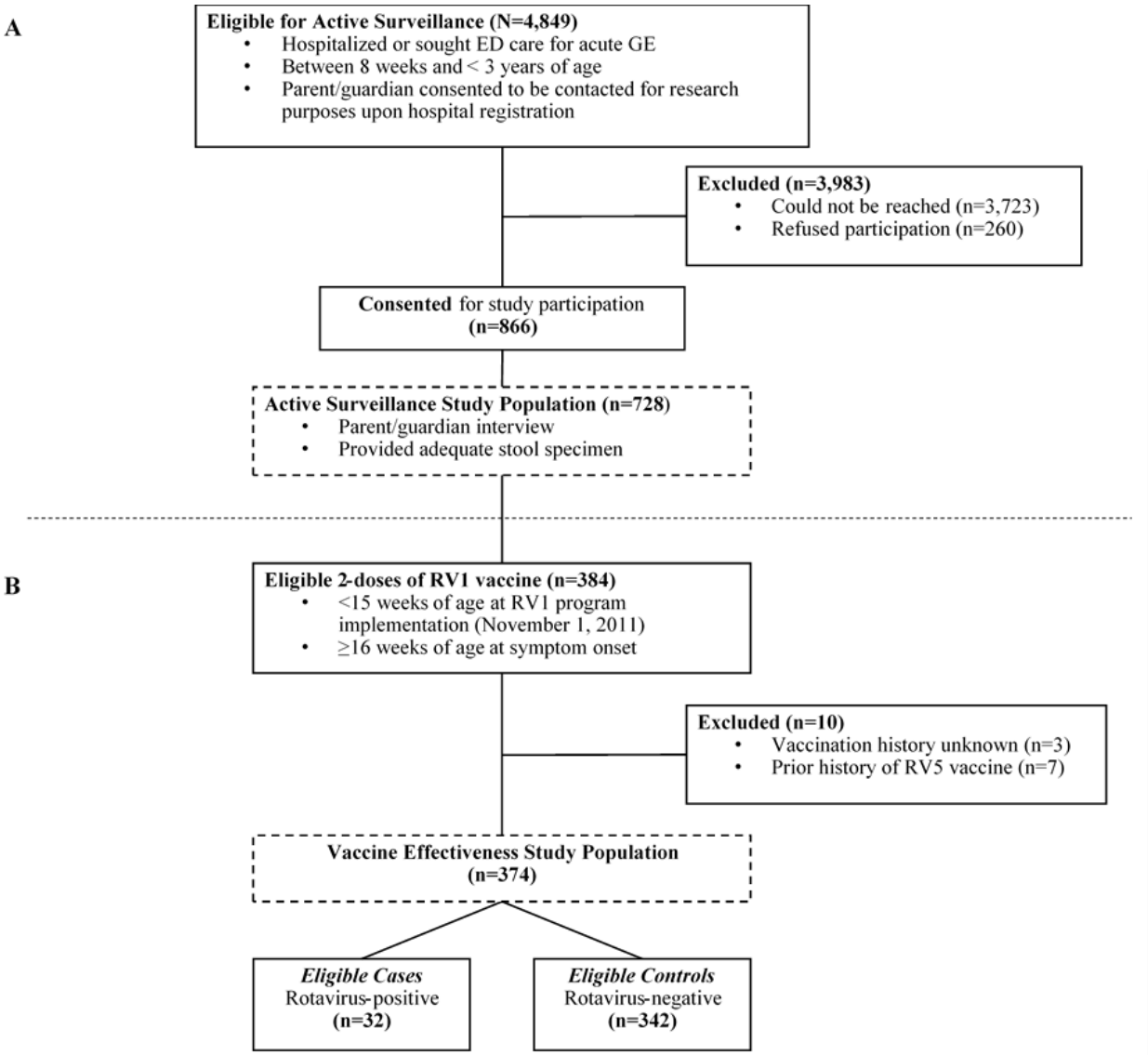


Figure 3-2. Frequency and percentage of rotavirus-positive active surveillance cases and 2-dose rotavirus vaccination coverage over time. Frequencies are illustrated on the left y-axis, while percentages correspond to the right y-axis. Two-dose rotavirus coverage was estimated among rotavirus-negative children aged 1 year at symptom onset and smoothed for display purposes using a simple, 6-month, backwards moving average.

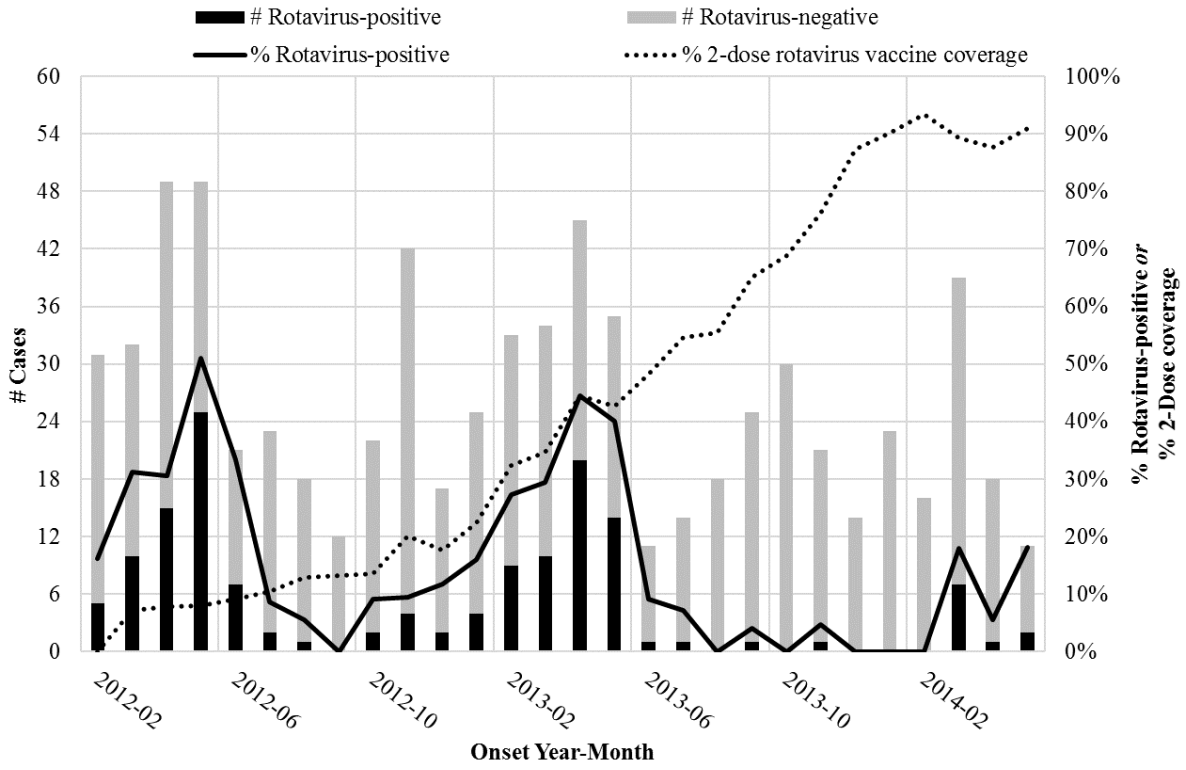


Figure 3-3. Beta distributions for mean annual 2-dose rotavirus coverage among rotavirus -negative participants aged 1-year for each rotavirus season. Beta distributions of rotavirus vaccination coverage were used in place of seasonal coverage point estimates in the hierarchical model to estimate the effect of rotavirus vaccination coverage on rotavirus prevalence.

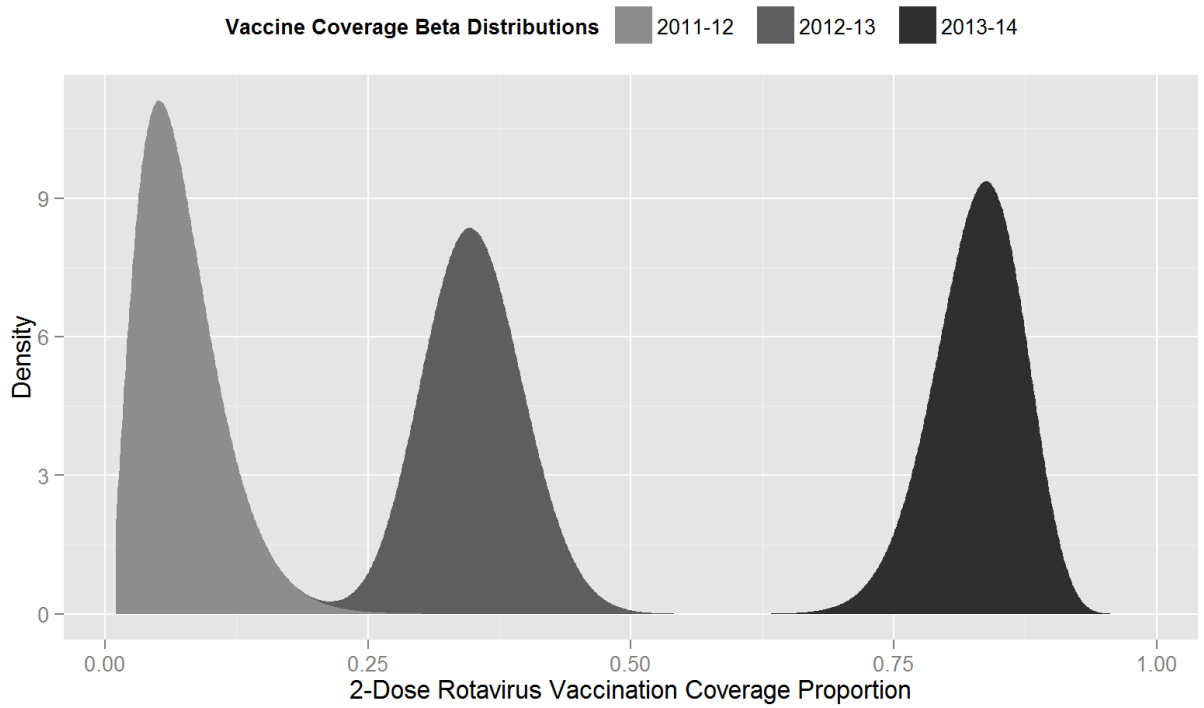
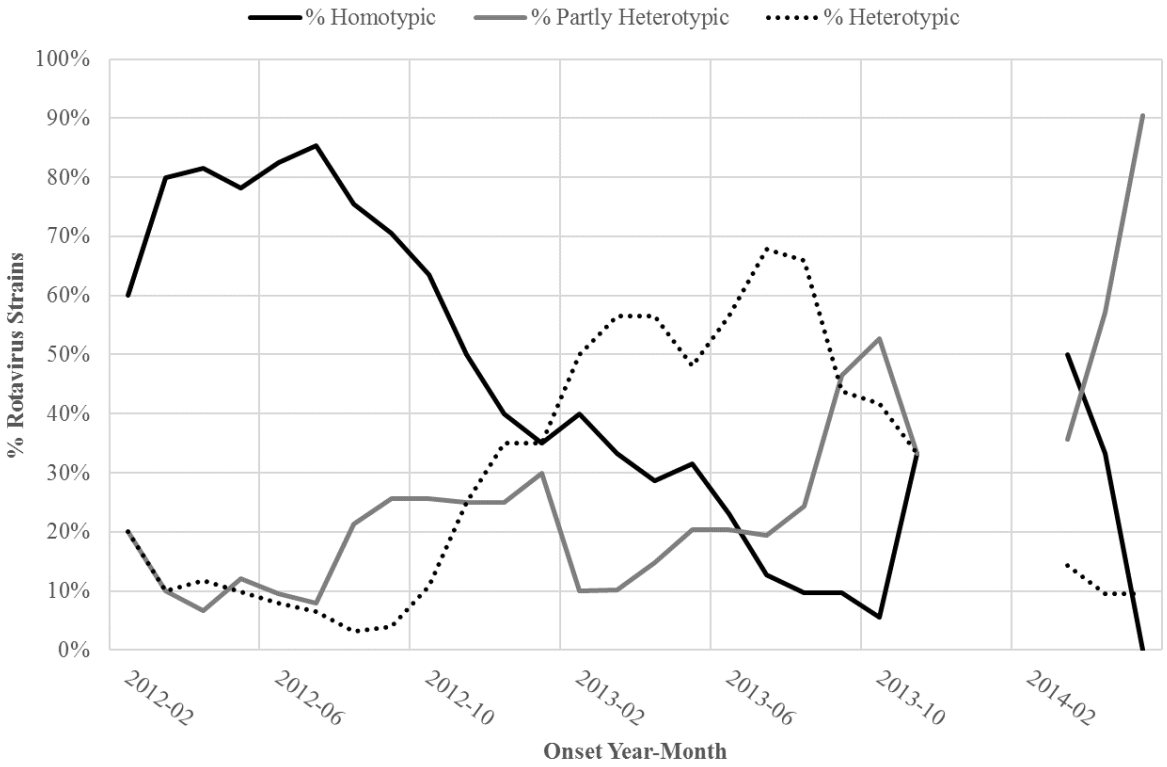


Figure 3-4. Examination of smoothed rotavirus strain prevalence over time by strain category using a simple, 6-month, backwards moving average. Moving averages for periods with ≥3 consecutive months without a rotavirus-positive specimen are represented by missing values.



Discussion

We examined the effect of increasing rotavirus vaccine coverage on rotavirus prevalence and assessed RV1 vaccine effectiveness in a setting with predominant RV1 use. With 2.5 years of post-implementation data, increasing rotavirus vaccine coverage was associated with a decrease in rotavirus prevalence over time, and on average, a 1% increase in 2-dose RV1 coverage among children 1 year of age was associated with a nearly 4% relative decrease in rotavirus prevalence among children less than 3 years of age. RV1 was highly effective in preventing rotavirus hospitalizations and emergency visits, with >90% vaccine effectiveness of ≥1 or 2 doses of RV1.

While rotavirus prevalence did not significantly differ in the first two seasons following RV1 program implementation, we saw a dramatic relative decline of >70% during the 2013-14 season, or 1.5 years following RV1 program implementation. Although we cannot directly compare these data to pre-vaccine seasons, delays between rotavirus vaccination implementation and reductions in pediatric rotavirus gastroenteritis have been observed in other jurisdictions.[93,99,101] The apparent lag may be due to the gradual uptake of vaccine and rotavirus transmission dynamics. In studies from the pre-vaccine era, Canadian children 1 year of age were more frequently hospitalized for rotavirus infection in comparison with children <1 or ≥2 years.[2,3] Among this age group, rotavirus coverage was <40% for seasons 2011-12 and 2012-13, and >80% coverage by the 2013-14 season. Therefore, we hypothesize that a delay may be in part due to the lag between vaccine program implementation and eligible vaccine recipients to grow into a higher risk age group for rotavirus hospitalizations or emergency visits. We also observed an increase in mean age of rotavirus-positive participants over time, likely due to gradual depletion of rotavirus susceptibles among younger age groups, eligible for – and receiving – rotavirus vaccination.

Our RV1 vaccine effectiveness estimates were similar to estimates from studies examining RV1 in high-income settings.[60-62,64,84,85,120] Among jurisdictions with concurrent RV5- and RV1-use, RV1 vaccine effectiveness estimates ranged from 70-98% in preventing rotavirus hospitalizations and/or emergency visits.[60-62,64,84,85] In Belgium, where RV1 vaccine was predominantly used over RV5, 2-dose RV1 vaccine effectiveness was estimated at 90% (95% CI: 81%, 95%) in preventing hospitalization.[120] On the basis of these estimates and our data, RV1 vaccine effectiveness in jurisdictions with predominant RV1 use appears to be similar to concurrent RV5 and RV1 use settings.

We also observed an increase in partly-heterotypic and heterotypic strains over time, coinciding with a decrease in homotypic strains. During the season prior to vaccination, a Quebec study found that heterotypic strain G9P[8] and homotypic G1P[8] predominated, representing 49% and 36% of rotavirus strains, respectively.[137] Although we assessed strain distributions in the 3 seasons post-vaccine implementation, rotavirus strains frequently varied in the pre-vaccine era.[117,138] In Australian jurisdictions with exclusive RV1 programs, predominant strains have also varied in the post-vaccine era, with predominance of genotypes G2 and G9 in 2007-08,[139] G2P[4] in the 2008-09 season,[140] G1P[8] during 2009-10 and 2010-11 seasons,[141,142] G2P[4] in 2012,[143] and finally G3P[8] in 2013.[144] Analyses in Belgium, however, found predominant circulation of genotype G2 during 5 of 6 years post-RV1 vaccination.[145] In the neighboring United States, strain G1P[8] predominated in the first season post-RV5 implementation (2006-07), with increases in G3P[8] and G9P[8] prevalence in subsequent 2007-08 and 2008-09 seasons.[117] Continued strain surveillance in Quebec is essential to understand longitudinal trends of circulating strains during the post-vaccine era.

Our analyses have several limitations. First, active surveillance was limited to the post-vaccine era, and we were unable to directly examine rotavirus vaccine *program* effectiveness. However, we provide meaningful data to inform its impact by examining rotavirus prevalence in relation to vaccination coverage. Second, our data was limited to sentinel hospitals and 3 seasons, which may limit generalizability of our findings. Third, we were only able to enroll ~20% of eligible participants and we were unable to compare characteristics of enrolled versus unenrolled eligible patients. While we cannot exclude the possibility that unenrolled, eligible patients may be different with regard to vaccination status, it is unlikely that enrollment for these individuals differed by etiology; therefore, we believe lower recruitment should not bias our findings. Finally, given the small number of rotavirus cases among children eligible for vaccine, we were unable to produce stratified RV1 vaccine effectiveness estimates by severity or genotype.

Conclusion

With data from 3 seasons following the implementation of an exclusive-RV1 vaccination program, we observed significant declines in the prevalence of rotavirus-associated pediatric gastroenteritis, and estimate that RV1 was >90% effective in preventing emergency visits and hospitalizations among children less than 3 years of age. RV1 vaccine effectiveness did not differ from estimates from comparable jurisdictions with concurrent RV1 and RV5 use. While we

observed an increase in heterotypic and partly-heterotypic rotavirus strains, continued strain surveillance is necessary to monitor longitudinal trends in rotavirus strain circulation in the post-vaccine era.

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Chapter 4: Two birds with one stone: estimating population vaccination coverage from a test-negative vaccine effectiveness case-control study

4.1 Preface

In this manuscript (Manuscript 2), I evaluate rotavirus vaccine coverage among the population eligible for the RV1 vaccine program with active surveillance data used to estimate RV1 vaccine effectiveness in Manuscript 1. Since this method of deriving coverage innovates upon existing methods, in addition to providing coverage results, I describe the underlying assumptions behind the use of this design, examine the effect of diagnostic accuracy on our coverage estimates via simulations, and compare coverage estimates using the design with the current, "gold standard" approach to estimating vaccine coverage in the Province of Quebec, the Institut National de Santé Publique du Québec (INSPQ) provincial vaccine survey.[43]

Although the same active surveillance study is used in this design as was used in Manuscript 1, there are slight differences in the dataset used. The recruitment period for active surveillance in Manuscript 2 was longer than the recruitment period in Manuscript 1, due to the availability of the active surveillance dataset at the time of the manuscript analyses. We also implemented a slight change in the definition of "program-eligible" participants in this manuscript as compared with Manuscript 1, so that coverage was evaluated among children eligible for vaccination at *routine* ages of administration (*i.e.* 2 and 4 months), without the first dose requiring a "catch up" administration. Finally, all active surveillance specimens were tested via real-time polymerase chain reactions (RT-PCR) in Manuscript 2; in Manuscript 1, RT-PCR testing was only available as confirmatory testing for rotavirus enzyme immunoassay-positive patients only.

Manuscript 2 is a pre-copyedited, author-produced version of an article accepted for publication in *Clinical Infectious Diseases* following peer review. The version of record[124] is available online at https://doi.org/10.1093/cid/ciw397. After peer-review, the vaccine section editor, Dr. Stanley A. Plotkin, selected the manuscript to be featured in the "Invited Article" vaccine special section of the journal because he thought the article's message was important and wanted to highlight it as a featured article in the journal.

4.2 Manuscript

Two birds with one stone: estimating population vaccination coverage from a test-negative vaccine effectiveness case-control study

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Running title: Estimating rotavirus vaccine coverage

Article summary: Vaccine program evaluation includes assessment of vaccine uptake and effectiveness. Often examined separately, we propose a design to estimate rotavirus vaccination coverage using control subjects from a rotavirus vaccine effectiveness test-negative case-control study, and examine rotavirus vaccination coverage in Quebec.

Key words: test-negative case-control; vaccine coverage; rotavirus

Abstract

Vaccination program evaluation includes assessment of vaccine uptake and effectiveness. Often examined separately, we propose a design to estimate rotavirus vaccination coverage using controls from a rotavirus vaccine effectiveness test-negative case-control study, and examine coverage following implementation of the Quebec rotavirus vaccination program. We present our assumptions for using these data as a proxy for coverage in the general population, explore effects of diagnostic accuracy on coverage estimates via simulations, and validate estimates with an external source. We found 79.0% (95% CI: 74.3%, 83.0%) ≥2-dose rotavirus coverage among participants eligible for publicly-funded vaccination. No differences were detected between study and external coverage estimates. Simulations revealed minimal bias in estimates with high diagnostic sensitivity and specificity. We conclude that controls from a vaccine effectiveness case-control study may be a valuable resource of coverage information when reasonable assumptions can be made for estimate generalizability; high rotavirus coverage demonstrates success of the Quebec program.

Introduction

With the licensure and implementation of a new vaccine program, it is important to assess vaccine uptake and direct vaccine effectiveness as part of routine program evaluation. Often, separate studies are designed to estimate vaccine uptake and effectiveness, each drawing upon different resources and funding. Although both measures must be estimated, it is expensive to conduct vaccine effectiveness studies and assess coverage, especially in the absence of a vaccination registry.[46,146] These measures may also need to be re-estimated frequently; for example, where a seasonal influenza vaccine is introduced annually, coverage and vaccine effectiveness are estimated yearly for program evaluation.[147]

Case-control studies are commonly used to estimate vaccine effectiveness in post-licensure evaluations.[50] In a case-control study, vaccine effectiveness is estimated as $(1 - odds\ ratio) * 100\%$, where the odds ratio compares the exposure odds of vaccination between cases and controls, and ideally approximates the relative risk/rate of disease comparing vaccinated and unvaccinated subjects in a cohort study, in order to accurately estimate vaccine effectiveness.[13] As with any case-control design, vaccine effectiveness controls should be sampled from the source population in which cases arise.[148]

When proper sampling is achieved, controls from a vaccine effectiveness case-control study are a valuable source of vaccination coverage data, where coverage among the case source population is of interest to public health professionals, and reasonable assumptions can be made to generalize results to a broader population. In this manuscript, we provide a real-world example where we estimate rotavirus vaccination coverage among controls in a test-negative vaccine effectiveness case-control study to examine the success of the Quebec rotavirus vaccination program. We also present our underlying assumptions for using these data as a proxy for vaccination coverage in the general population, explore the effects of diagnostic sensitivity and specificity on coverage estimates, and compare estimates to an external source for validation.

Methods

Study setting

We assessed rotavirus coverage for two cities in Quebec, Canada. Although pentavalent (RotaTeq®, Merck & Co Inc.) and monovalent (Rotarix®, GlaxoSmithKline) rotavirus vaccines were licensed in Canada in August 2006[149] and October 2007[150] respectively, Quebec adopted

public-funding for rotavirus vaccination only in November 2011. At this time, monovalent vaccine was selected for reimbursement and recommended for administration as a 2-dose series at ages 2 and 4 months, with series initiation <15 weeks of age. Pentavalent vaccine is not reimbursed under the publicly-funded program.

Patient eligibility and recruitment

Beginning in February 2012, we conducted prospective, active surveillance for rotavirus gastroenteritis in three children's hospitals: The Montreal Children's Hospital and Centre Hospitalier Universitaire (CHU) Sainte-Justine, located in Montreal, and CHU de Sherbrooke, located in Sherbrooke, QC. Active surveillance continued until December 31, 2014 at Montreal Children's and CHU de Sherbrooke, and June 30, 2014 at CHU Sainte-Justine. Research Ethics Boards at each hospital approved study protocols.

Children were eligible for participation as previously defined.[124,151] Briefly, children hospitalized or seeking emergency care for acute gastroenteritis, between 8 weeks and less than 3 years of age at symptom onset, with parent/guardian consent at hospital registration to allow contact for research, were recruited. Patients were excluded if rotavirus vaccination was contraindicated in accordance with the Quebec Immunization Protocol.[152] Parent/guardian written consent was obtained for all participants.

Data collection

Participant information was collected via medical records and parent/guardian interviews. Vaccination histories (type/administration date) were obtained during interview in reference to the participant's immunization booklet; if unavailable, permission was requested to contact medical providers for immunization information. Stool samples were obtained from specimens collected at home or during routine care and tested for rotavirus via real-time reverse-transcriptase polymerase chain reactions (RT-PCR).[127]

Test-negative design

Active surveillance was used to ascertain eligible cases/controls for enrollment in a test-negative case-control study, designed to estimate vaccine effectiveness. Used mainly in influenza and recently in rotavirus vaccine effectiveness studies,[67,68] the test-negative design defines eligible cases as participants that test-positive, and controls as participants that test-negative, for the disease of interest.

Coverage estimates

We estimated rotavirus vaccination coverage among rotavirus RT-PCR-negative participants (*i.e.* test-negative controls) only. Rotavirus-positive participants were excluded from coverage analyses because rotavirus vaccination is associated with reduced risk of rotavirus hospitalization or emergency care.[61,62,84] Thus, inclusion of rotavirus-positive participants would oversample participants less likely to be vaccinated than the source population, and underestimate vaccination coverage. Among rotavirus-negative participants, rotavirus doses administered to children <6 weeks of age or given <28 days following the previous rotavirus dose were considered invalid; only valid immunizations were used to estimate coverage, ascertained as of symptom onset date.

Rotavirus ≥1- and ≥2-dose coverage were estimated for participants age-eligible and participants age- and program-eligible to receive 2 doses following the Quebec rotavirus vaccination program implementation. For these analyses, age-eligible was defined as participants ≥16 weeks of age at symptom onset; program-eligible was defined as participants <8 weeks of age at program implementation (November 1, 2011). Coverage estimates among age- and program-eligible participants were used to inform uptake among children indicated for immunization under the new program. The Wilson procedure was used to estimate binomial 95% confidence intervals (CI) for coverage point estimates, since *a priori* coverage for all estimates were unknown.[153]

Rotavirus ≥2-dose coverage was examined over time for age-eligible participants, and for age- and program-eligible participants. Time trends were examined as prevalence ratios and 95% CIs representing the average linear change in coverage per consecutive study month, estimated via logistic regression with a log-link function. Among age- and program-eligible participants, ≥2-dose coverage was also stratified by (i) rotavirus season: June 2012 – May 2013 or June 2013 – May 2014, (ii) geographic hospital location: Sherbrooke or Montreal (referent); (iii) parental education: high school, college (referent), or graduate school; (iv) gender: female or male (referent); (v) whether the participant had a primary care physician: none or yes (referent); and (vi) race/ethnicity: Asian, Black, Hispanic, Middle-Eastern, Multiracial, or White (referent). Parental education was based upon the highest reported education level attained by a parent/guardian, and defined as attainment of some/complete education for that level. Having a primary care physician was defined as identification of a pediatrician, family doctor, or clinic as the participant's usual care setting, and none, if an emergency room or no setting were identified for usual care. Parental

reports of participant race/ethnicity were used to determine race/ethnicity categories; if more than one category was selected, the participant was classified as Multiracial. Prevalence differences (PD) and 95% CI were estimated to compare coverage within categorical variables; for all variables, the level with the highest frequency was used as the referent.

All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC) or R version 3.2.1.[154]

Underlying assumptions

In order to generalize coverage estimates to the Quebec population, it is important to clearly identify our underlying assumptions with regard to our study population and design.

First, in selecting participants with acute gastroenteritis that tested-negative for rotavirus, we assumed receipt of rotavirus vaccine had no effect on the risk of non-rotavirus acute gastroenteritis. This assumption is necessary, as an association between vaccine uptake and study inclusion would introduce a selection bias, where persons more/less likely to receive rotavirus vaccination would be overrepresented in our sample. The assumption is also likely satisfied since there is no basis for the vaccine to provide immunity for non-rotavirus etiologies, and to date, no association has been detected between rotavirus vaccination and absolute risk of norovirus,[155,156] the leading cause of medically-attended pediatric gastroenteritis in the post-rotavirus vaccine era.[151,157,158]

Second, we assumed participant characteristics were representative of the general population for variables associated with rotavirus vaccine uptake, or we adjusted for these factors in our analyses. We assessed coverage by time, geographic hospital location, gender, parental education, whether or not the participant had a primary care physician, and race/ethnicity, since we determined these as *a priori* factors potentially associated with both study inclusion and rotavirus vaccine uptake.

Third, we assumed only a low proportion of rotavirus false-negatives were included in the study population based upon high sensitivity of the RT-PCR assay we used to determine rotavirus status.[159] In instances of lower sensitivity, persons with true disease that tested falsely-negative would be included in our study and cause us to underestimate coverage, since these individuals are less likely to be vaccinated. On the other hand, lower diagnostic specificity, where false-negatives are excluded, may also cause us to underestimate coverage when sensitivity is imperfect. Given this interplay (**Figure 4-1**), we explored the effects of imperfect sensitivity and specificity on

coverage estimates via simulations (methods/inputs described in **Appendix 4-1**). We assumed the RT-PCR assay used had a sensitivity and specificity of ≥90%.[159]

Finally, as with all coverage assessments, we assumed rotavirus vaccination histories among participants were measured and recorded with high accuracy and completeness.

External validation of coverage estimates

We estimated rotavirus ≥2-dose coverage among participants born from October 1 – December 31, 2011, and participants born from July 1 –September 30, 2012, who were also age-eligible to receive ≥2 doses of rotavirus vaccine. These estimates were compared with rotavirus coverage estimates obtained from the 2015 Quebec provincial immunization coverage survey, which sampled children from these birth cohorts.[43] Because the Quebec survey does not provide a measure of precision for coverage point estimates, we estimated binomial 95% CIs via the Wilson procedure.[153,160,161] PD and 95% CIs were estimated to assess differences between our estimates and the Quebec survey (referent).

Since the survey is designed to represent the Quebec population, we also examined generalizability of our sample by comparing gender and maternal education characteristics between study and Quebec survey participants using the Pearson's chi-square test statistic (alpha=0.05). Other characteristics were not examined since they were not reported in the Quebec survey.

Results

Study population

Among the 749 active surveillance participants successfully interviewed with stool tested via RT-PCR, 595 (79.4%) were rotavirus-negative and eligible for coverage analyses. Among these, 566 (95.1%) were age-eligible and 336 (56.5%) were age- and program-eligible to receive 2 doses of rotavirus vaccine under the publicly-funded program. Characteristics of participants are detailed in **Table 4-1**.

Rotavirus vaccination coverage

Overall, rotavirus ≥1-dose coverage was 57.7% (95% CI: 53.5%, 61.7%), and ≥2-dose coverage was 52.0% (95% CI: 47.8%, 56.1%) among age-eligible participants. In general, coverage increased over time, with an average relative increase of 2.2% (95% CI: 1.1%, 3.3%) in ≥2-dose coverage per consecutive study month.

When analyses were limited to age- and program-eligible participants, ≥1-dose coverage was 86.8% (95% CI: 82.7%, 90.0%), and ≥2-dose coverage was 79.0% (95% CI: 74.3%, 83.0%). Among these participants, ≥2-dose coverage did not change over time (average relative change/month: -0.2%, 95% CI: -1.4%, 1.0%). By season, ≥2-dose coverage was 80.2% (95% CI: 72.2%, 86.3%) and 79.9% (95% CI: 73.2%, 85.2%) from June 2012 – May 2013 and June 2013 – May 2014, respectively.

Rotavirus ≥2-dose coverage among age- and program-eligible participants is further examined in **Figure 4-2** after stratification by geography, gender, parental education, primary care physician, or race/ethnicity. On average, no differences were found between participants by geographic location (PD: 3.4%, 95% CI: -6.7%, 13.4%) or between participants with/without a primary care physician (PD: -5.3%, 95% CI: -15.4%, 4.7%), though we lacked power to detect small coverage differences. Females had marginally higher coverage compared with males (PD: 9.0%, 95% CI: 0.2%, 17.7%). By parental education, coverage was 15.3% (95% CI: 5.8%, 24.9%) higher among participants whose parents had a high school education compared with college, but no difference was found compared with graduate school (PD: 6.8%, 95% CI: -3.8%, 17.4%). On average, Black and Hispanic participants had 14.1% (95% CI: 2.3%, 26.0%) and 21.1% (11.1%, 31.1%) higher coverage, respectively, than White participants; no differences were detected between Asian, Middle Eastern, or Multiracial participants compared to White participants (PD - *Asian*: -6.0%, 95% CI: -29.5%, 17.5%; *Middle Eastern:* 14.1, 95% CI: -1.6%, 29.8%; *Multiracial*: 5.3%, 95% CI: -9.3%, 19.8%).

Comparison to external estimates

Rotavirus ≥2-dose coverage results were compared with Quebec survey estimates in **Figure 4-3**. No differences were detected between study population and survey estimates, with coverage differences of −6.5% (95% CI: −19.1%, 6.0%) and −2.6% (95% CI: −14.2%, 9.0%) for participants born from October 1 – December 31, 2011 and July 1 - September 30, 2012, respectively.

Further, no differences were detected in the distribution of gender or maternal education characteristics between Quebec survey and age-eligible (gender, p=0.96; maternal education, p=0.25) or age- and program-eligible (gender, p=0.27; maternal education, p=0.23) study participants.

Role of diagnostic accuracy

Based upon RT-PCR sensitivity and specificity of 90%, we estimated the mean bias in our coverage estimates was -2.7% (95% CI: -3.4%, -2.0%); for a sensitivity and specificity of 95%, mean bias in coverage was estimated as -1.3% (95% CI: -1.7%, -1.0%). We further explored mean bias in coverage for various sensitivity and specificity scenarios in **Table 4-2**. Bias was generally low in scenarios of high sensitivity and specificity. No bias was observed among coverage estimates in situations where sensitivity was 100%. Where sensitivity was <100%, imperfect sensitivity or specificity consistently led to an underestimation of coverage.

Table 4-1. Characteristics of age-eligible and age- & program-eligible coverage study participants. Data represent % (95% CI) unless otherwise specified; sample sizes are provided for each category in order to account for missing data.

Variable	Rotavirus RT-PCR Negative Participants	
	Age-Eligible	**Age- & Program-Eligible**
	N=566	**N=336**
	% (95% CI)	% (95% CI)
Age (months): Mean (95% CI)	16.0 (15.4, 16.7)	12.0 (11.4, 12.7)
Geographic Location	n=566	n=336
Montreal	73.0 (69.2, 76.5)	77.4 (72.6, 81.5)
Gender	n=560	n=330
Male	52.5 (48.4, 56.6)	55.8 (50.4, 61.0)
Primary care physician	n=560	n=332
Yes	69.6 (65.7, 73.3)	71.4 (66.3, 76.0)
Parental education	n=564	n=334
High school	19.9 (15.8, 24.2)	18.9 (13.5, 24.3)
College/university	57.5 (53.4, 61.8)	58.1 (52.7, 63.6)
Graduate school	22.7 (18.6, 27.1)	23.1 (17.7, 28.5)
Race/Ethnicity	n=564	n=334
Asian	5.1 (1.4, 9.2)	4.8 (0.0, 10.0)
Black	10.5 (6.7, 14.5)	11.1 (6.3, 16.3)
Hispanic	8.3 (4.6, 12.4)	7.2 (2.4, 12.4)
Middle Eastern	5.1 (1.4, 9.2)	5.4 (0.6, 10.6)
Multiracial	9.6 (5.9, 13.6)	10.5 (5.7, 15.7)
White	61.4 (57.6, 65.4)	61.1 (56.3, 66.3)

Table 4-2: Mean bias (95% confidence intervals) in vaccination coverage estimates estimated via simulations for varying levels of diagnostic sensitivity and specificity.

Test characteristic	Specificity					
Sensitivity	**50%**	**60%**	**70%**	**80%**	**90%**	**100%**
50%	-18.9 (-23.1, -14.4)	-16.4 (-20.3, -12.5)	-14.6 (-18.0, -11.0)	-13.1 (-16.1, -9.9)	-11.8 (-14.7, -9.0)	-10.8 (-13.5, -8.2)
60%	-15.9 (-19.6, -12.1)	-13.8 (-17.0, -10.4)	-12.1 (-15.0, -9.2)	-10.8 (-13.4, -8.1)	-9.8 (-12.1, -7.4)	-8.9 (-11.1, -6.7)
70%	-12.6 (-15.7, -9.6)	-10.8 (-13.4, -8.2)	-9.5 (-11.8, -7.1)	-8.4 (-10.5, -6.3)	-7.6 (-9.5, -5.7)	-6.9 (-8.6, -5.2)
80%	-8.9 (-11.1, -6.7)	-7.6 (-9.5, -5.7)	-6.6 (-8.3, -4.9)	-5.9 (-7.3, -4.4)	-5.3 (-6.5, -4.0)	-4.8 (-6.0, -3.6)
90%	-4.8 (-6.0, -3.6)	-4.0 (-5.0, -3.0)	-3.5 (-4.4, -2.6)	-3.0 (-3.8, -2.3)	-2.7 (-3.4, -2.0)	-2.5 (-3.1, -1.8)
100%	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)

Figure 4-1. Illustrated representation of the role of imperfect diagnostic characteristics (sensitivity and specificity) on vaccination coverage estimates derived from controls in a test-negative case-control vaccine effectiveness study.

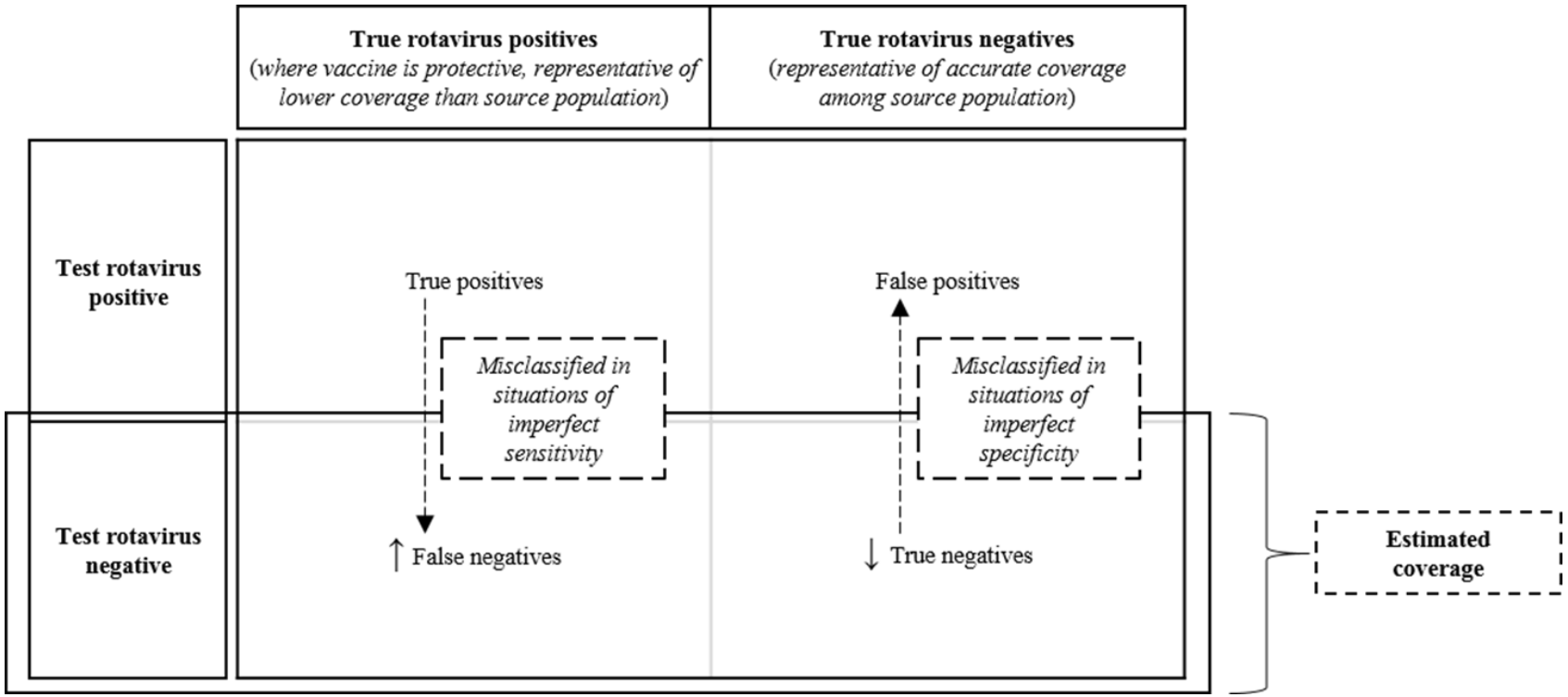


Figure 4-2. Rotavirus ≥2-dose coverage by subgroup among participants eligible for 2 doses of rotavirus vaccination under the Quebec rotavirus vaccination program. Coverage estimates and 95% CI were estimated stratified by hospital geographic location, gender, parental education, whether the participant had a primary care physician, or race/ethnicity.

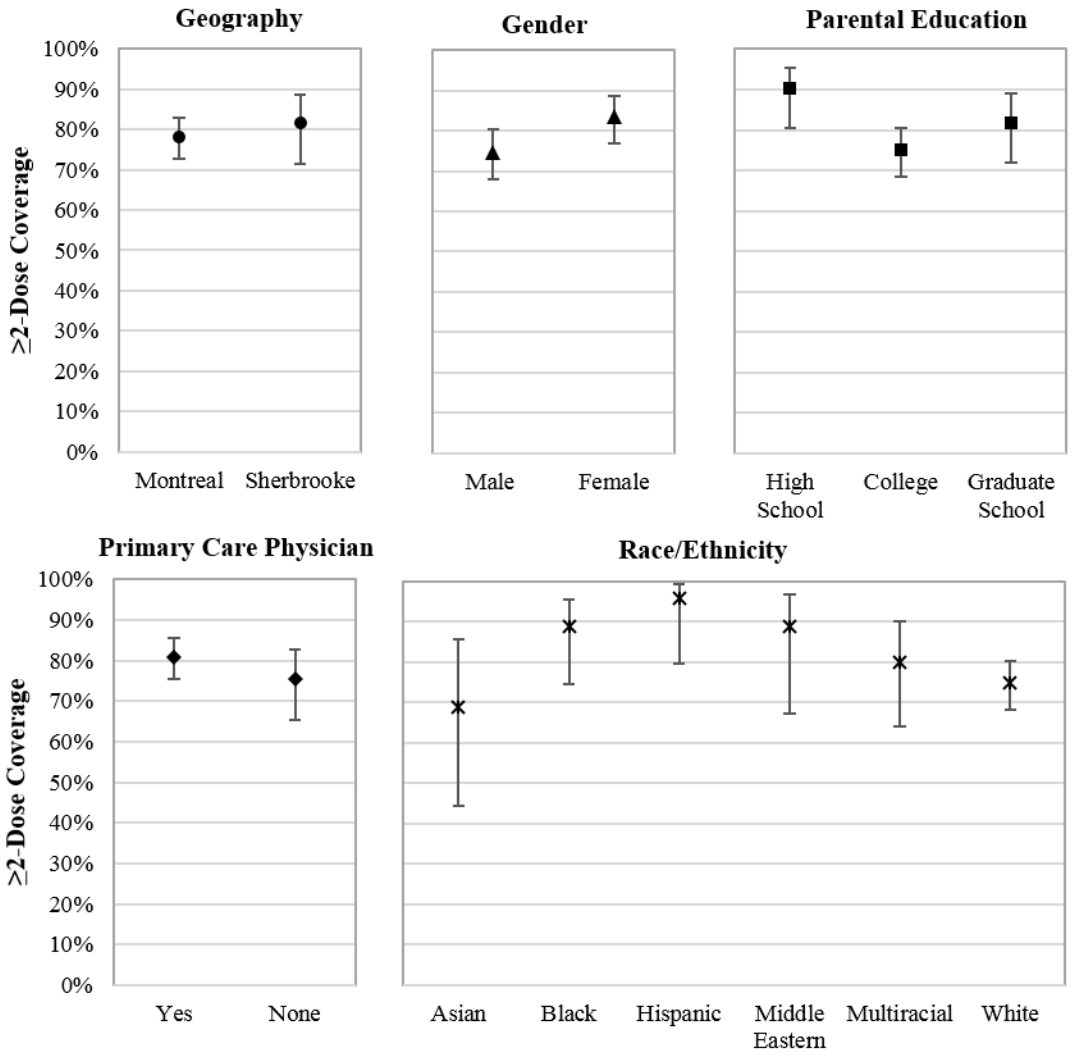
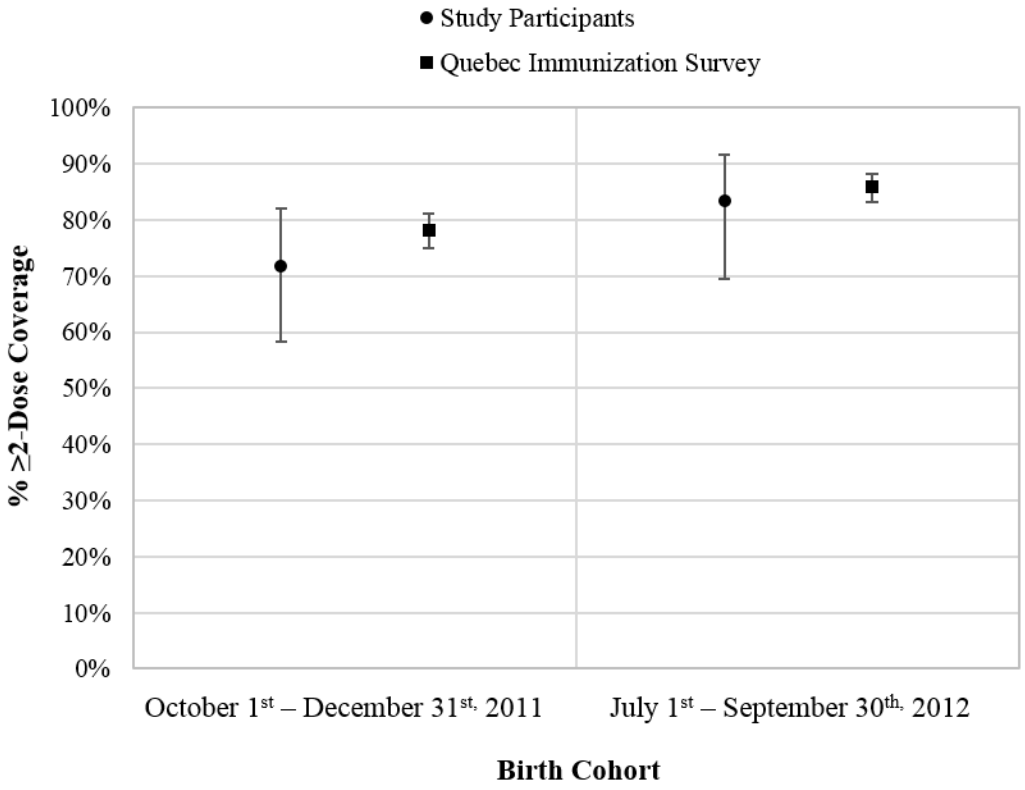


Figure 4-3. Comparison of rotavirus ≥2-dose coverage estimates from study participants and the 2015 Quebec provincial immunization survey. Coverage and 95% CI are compared separately for each birth cohort of participants born from either: (i) October 1st – December 31, 2011, or (ii) July 1st – September 30, 2012.



Discussion

In this manuscript, we demonstrate how vaccination data collected from controls in a vaccine effectiveness case-control study can be used to estimate population vaccination coverage. Specifically, we assessed rotavirus vaccination coverage among eligible controls in a test-negative case-control vaccine effectiveness study as a proxy for coverage among Quebec children. When we compared our estimates to results from an external study designed to estimate immunization coverage, we found no significant differences between coverage estimates. Further, we demonstrate that there was minimal bias in coverage estimates when test-negative controls were identified via a diagnostic assay with high sensitivity and specificity. These results suggest test-negative vaccine effectiveness study controls are a useful source of immunization coverage data, when reasonable assumptions can be made to generalize results to a greater population, and a highly accurate test is used to differentiate cases from controls.

Among participants for whom vaccination was recommended under the Quebec rotavirus vaccination program, we found 87% ≥1-dose coverage and nearly 80% ≥2-dose coverage, with no average change in monthly coverage detected over time. These data demonstrate the rapid, relative success of the Quebec program, with high initial vaccine uptake and sustained coverage during the first 3 years of program implementation. In comparison, 3 years after United States (U.S.) program implementation, average rotavirus ≥1-dose coverage was 72% among sentinel locations, ranging from 48% to 86%.[118]

Although high rotavirus coverage was found among age- and program-eligible children, differences in coverage were detected among subgroups. Coverage among males was 9% lower than females, while participants with a college-educated parent had 15% lower coverage than those with a high school-educated parent. White participants had 14% to 21% lower coverage in comparison with Black and Hispanic participants. These findings are similar to characteristics of unvaccinated children found in U.S. studies, with unvaccinated children more likely to be White, male, or have a college-educated mother/parent.[162-165]

Our results should be interpreted in the context of several limitations. First, non-rotavirus gastroenteritis participants may have symptoms caused by influenza, and if infected with a vaccine-preventable strain, these participants are less likely to receive influenza vaccination, and potentially other vaccines. Thus, inclusion of these participants may underestimate rotavirus vaccine coverage (as well as vaccine effectiveness). While we cannot rule out inclusion, it is

unlikely that influenza was predominantly responsible for non-rotavirus gastroenteritis in our sample for several reasons: approximately 40% of participants tested positive for alternate, non-vaccine-preventable gastroenteritis etiologies, norovirus or sapovirus,[151] we did not test for other pathogens characterized as significant contributors of pediatric acute gastroenteritis,[166-168] and among children with influenza, gastroenteritis is not a predominant clinical presentation with <33% of cases experiencing diarrhea or vomiting symptoms[169-173] and <5% presenting with gastroenteritis as the cause of admission.[169,172]

Second, persons seeking healthcare may differ from the general population in ways related to vaccine uptake. Although differential uptake of vaccine among healthcare seekers versus non-seekers could bias results, we believe it is less likely to occur in a setting where care is sought for emergency services, among an age group more commonly requiring emergency visits/hospitalizations for acute gastroenteritis, and where public insurance coverage for primary and emergency care is universally available. However, our study's strengths are that we compared coverage estimates and sample characteristics with the Quebec survey, which did not rely on participant recruitment from a healthcare facility, and we stratified estimates by presence/absence of a primary care physician.

Third, comparison of our estimates to Quebec survey estimates required us to limit our data to mutually examined cohorts; thus, we lacked sufficient power to detect small differences in coverage between study and survey estimates. Nonetheless, our point estimates were close to those in the survey, and we examined validity of our estimates via simulations.

Fourth, we only examined coverage at 3 university hospitals located in 2 Quebec cities. If coverage differed by hospital catchment and/or city, our estimates may have limited generalizability to other geographic areas; however, our results were similar to the Quebec survey, and we did not find coverage differences stratified by geographic location.

Fifth, rotavirus vaccination coverage was measured only among participants for whom the vaccine was not contraindicated. Although we suspect rates of contraindication are relatively rare at the population-level (*i.e.* history of intussusception prior to vaccination, history of hospitalization between 2 months and >104 days of age, or severe immunosuppression), our estimates are not generalizable to these populations.

Finally, although coverage estimates derived from test-negative controls may be a useful addition to vaccine program evaluation, they should not be viewed as a replacement of traditional

coverage surveys, which can incorporate rigorous sampling methods to reliably and precisely estimate coverage among both general and sub-populations of interest.

Conclusion

Controls from a vaccine effectiveness case-control study design may be a valuable resource for estimating vaccination coverage. Using eligible controls from a rotavirus test-negative study, we found high ≥2-dose rotavirus coverage of nearly 80% among children eligible for vaccination in Quebec, 3 years after implementation of a provincial rotavirus vaccination program. While high coverage demonstrates the relative success of the program, coverage levels varied by subgroup, potentially leaving pockets of rotavirus susceptible children in the community.

Notes

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Conflict of Interest

The authors have no conflicts of interest to disclose. Caroline Quach has received funding from GlaxoSmithKline, Pfizer, Sage and AbbVie (all for research grant or support). The remaining authors have no financial relationships relevant to this article to disclose.

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Appendix 4-1. Simulations to explore the role of diagnostic accuracy on coverage estimates

Methods

We adapted simulation methods previously described by Jackson and Rothman[67] to explore the role of diagnostic sensitivity and specificity on the accuracy of vaccination coverage estimates derived from controls of a test-negative study design. We used the following six parameters for our simulations:

- **True coverage**: rotavirus vaccination coverage among children <3 years in the population
- **$IP_{rotavirus}$**: incidence proportion (risk) of severe gastroenteritis, defined as gastroenteritis requiring hospitalization or an emergency department visit, caused by rotavirus among unvaccinated children <3 years
- **IP_{other}**: incidence proportion (risk) of severe gastroenteritis due to non-rotavirus etiologies among children <3 years
- **VE**: direct vaccine effectiveness of rotavirus vaccine to prevent severe gastroenteritis caused by rotavirus
- **Sensitivity**: sensitivity of diagnostic test (variable)
- **Specificity**: specificity of diagnostic test (variable)

We ran 10,000 simulations with a generated population of 20,000 children <3 years of age for each diagnostic test scenario. The design of simulations is provided for reference in **Supplemental Figure 4-1**. Briefly, the population was created by initial stratification into vaccinated and unvaccinated population subgroups (based upon true coverage), and then divided further into groups of either: (i) severe gastroenteritis due to non-rotavirus etiologies, (based upon IP_{other}), (ii) severe rotavirus gastroenteritis (based upon $IP_{rotavirus}$, in consideration of vaccination status and VE), or (iii) no severe gastroenteritis (based upon 1 - IP_{other} - $IP_{rotavirus}$, in consideration of vaccination status and VE). After stratification, vaccinated and unvaccinated children with severe rotavirus gastroenteritis were combined to encompass "true rotavirus positives", and vaccinated and unvaccinated children with non-rotavirus severe gastroenteritis were combined to encompass "true rotavirus negatives". Sensitivity and specificity scenarios were applied to each of these groups to determine the number of children that would test rotavirus-negative, comprised of false rotavirus negatives and true rotavirus negatives, and thus, be classified as controls in a test-

negative study. Coverage was estimated among all children that tested rotavirus-negative (*i.e.* test-negative controls) for each simulated population; bias in coverage for each simulation was estimated as [estimated coverage/true coverage - 1] * 100%. Mean bias for each diagnostic scenario was estimated as the average bias in coverage across the 10,000 simulations; lower and upper 95% CI were estimated as bias in the 2.5% and 97.5% probability quantiles, respectively, for each diagnostic scenario.

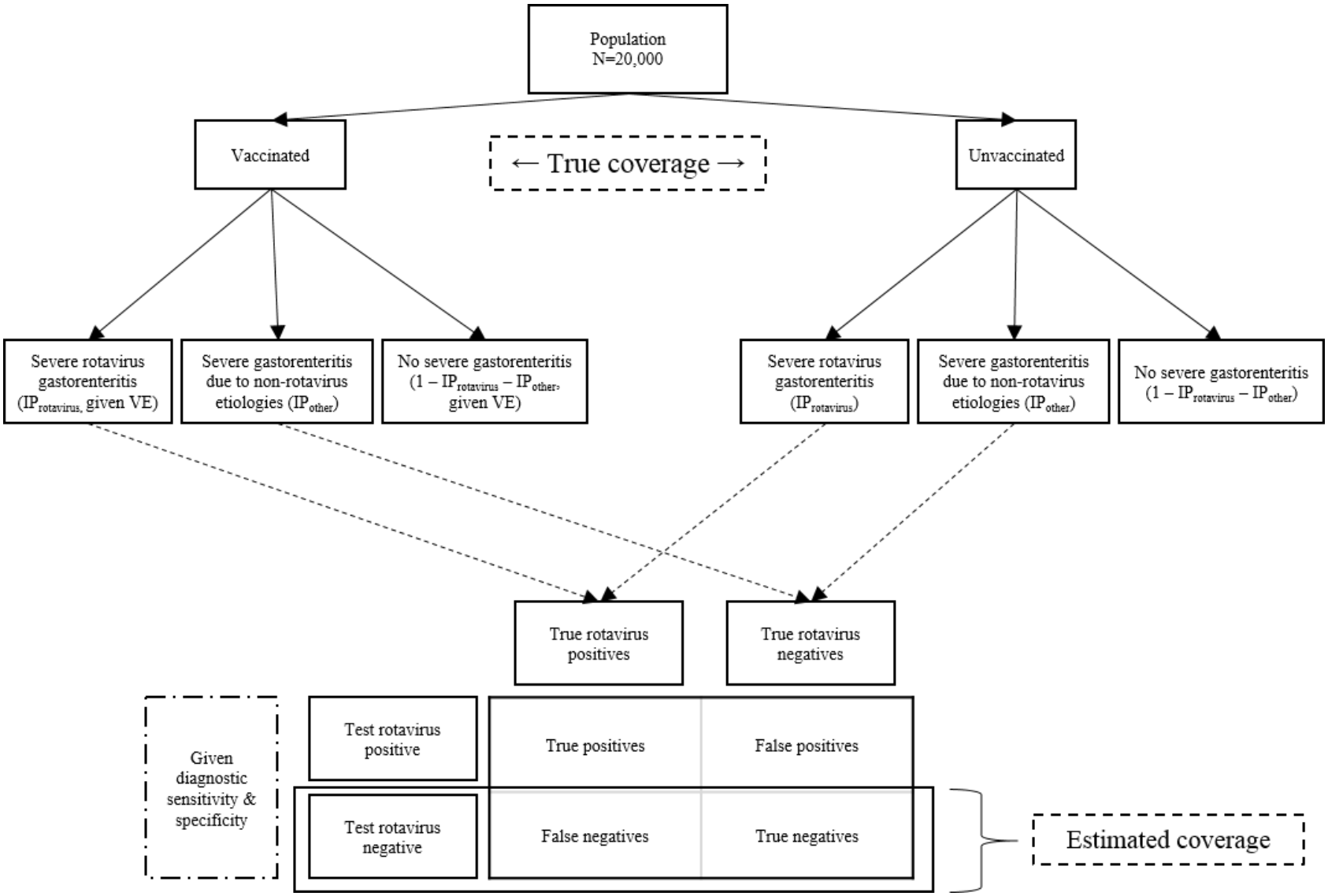
We generated outcome datasets using known probabilities of vaccination status and the risk of severe gastroenteritis (rotavirus or otherwise). Each simulated population had a fixed sample size of n=20,000. The number of vaccinated children was binomially distributed, with the probability equal to the expected true coverage of 50%. Non-vaccinated children were equal to 20,000 – number vaccinated. The subset of the population that experienced severe non-rotavirus gastroenteritis was binomially distributed, with n=20,000, and the probability equal to IP_{other} of 2.5%. The subset of the unvaccinated population that experienced severe rotavirus gastroenteritis was binomially distributed, with n equal to the number of unvaccinated children, and probability equal to $IP_{rotavirus}$ of 1.5%. Lastly, the subset of the vaccinated population that experienced severe rotavirus gastroenteritis was also binomially distributed, but with n equal to the number of vaccinated children and probability equal to $IP_{rotavirus}$, accounting for an expected VE of 85%. Estimates for $IP_{rotavirus}$ and IP_{other} were chosen in consideration of the risk of emergency department visits caused by rotavirus ($IP_{rotavirus}$), and the risk of emergency department visits caused by all-cause diarrhea excluding rotavirus (IP_{other}), among children <5 years of age from Quebec during the pre-vaccine era.[7] For these estimates, we used risks for emergency department visits only, since we assumed the majority of hospitalized children would pass through an emergency department prior to hospitalization. The input for VE was selected based upon monovalent rotavirus VE estimates to prevent severe gastroenteritis from recent studies ranging from 70 to 98%.[60-62,64,84-87]

In order to encompass a large range of diagnostic testing scenarios, we examined diagnostic sensitivities of 50% to 100% in 10% increments, with simultaneous diagnostic specificities of 50% to 100% in 10% increments.

Similar to methods detailed by Jackson and Rothman,[67] we excluded other potential sources of bias in order to focus on the role of diagnostic accuracy, and assumed (i) vaccination coverage was binary (*i.e.* either vaccinated or non-vaccinated), and (ii) disease groups of severe

rotavirus gastroenteritis and severe gastroenteritis due to non-rotavirus etiologies were mutually exclusive at a given point in time.

Supplemental Figure 4-4. Schematic representation of simulated populations to assess mean bias in coverage.



Chapter 5: Estimation of the overall effect of a rotavirus vaccine program attributable to a per-unit change in rotavirus vaccine coverage in the population

5.1 Preface

In this manuscript (Manuscript 3), I examine the overall effect of the RV1 vaccination program in Quebec on weekly rates of all-cause AGE hospitalizations among a population-based sample of children 8 months to less than 3 years of age residing in Montreal, using a time series analysis. I estimate the overall effect of the program as a whole, using standard methods to compare rates of all-cause AGE in the post-vaccine period relative to the pre-vaccine period. I also characterize the overall effect as the effect attributable to a per-unit change in vaccine coverage, using population vaccine coverage as the exposure variable. The latter measure is not traditionally used in vaccine program evaluation; therefore, I also discuss reasons why it may be a useful addition to standard methods to measure the overall program effect.

As explained in the manuscript, this analysis is performed using a population-based cohort of approximately 25% of the Montreal census area population, created via linkages in healthcare administrative databases for research on health indicators. Population vaccine coverage for the sample was estimated as a time series via the same study design and dataset from Manuscript 2, combined with age-standardization methods, in order to ensure that coverage was representative of the age-distribution of children in the population-based cohort.

Manuscript 3 is currently under review at the peer-reviewed journal, *American Journal of Epidemiology*.

5.2 Manuscript

Estimation of the overall effect of a rotavirus vaccine program attributable to a per-unit change in rotavirus vaccine coverage in the population

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Data sharing: Aggregate time series data and R code will be made available as a supplemental appendix on the journal website.

Key words: rotavirus; vaccine program; overall effect; program evaluation

Abstract

Background: Estimation of the overall effect of a vaccine program is essential, but it is typically estimated as an effect attributable to an entire program. We estimate the overall effect of a rotavirus vaccine campaign and the effect for each 10% increase in rotavirus vaccine coverage on pediatric all-cause acute gastroenteritis (AGE) hospitalizations.

Methods: We conducted a time series analysis of weekly rates of all-cause AGE hospitalizations among children 8 to 35 months of age between June 1, 1998 and December 28, 2014 in Montreal, Quebec. We implemented negative binomial regressions to estimate the overall effect of the Quebec rotavirus vaccine program as: (i) a dichotomous variable, representing pre- and post-program periods, and (ii) a continuous variable, representing rotavirus vaccine coverage, and adjusted our estimates for seasonality, long-term trends, and infection dynamics.

Results: Using a dichotomous exposure, we estimate the vaccine program was associated with a 29.3% (95% CI: 16.5%, 40.1%) relative decline in adjusted weekly rates of all-cause AGE hospitalizations in the post-vaccine period. Using a continuous exposure, we found that a 10% increase in rotavirus ≥1-dose coverage was associated with a 6.8% (95% CI: 3.9%, 9.5%) relative decline in adjusted weekly rates, with an increase in coverage to 87.0% associated with a 45.6% (95% CI: 29.2%, 58.2%) relative decline.

Conclusions: Estimation of the overall effect attributable to a per-unit change in vaccine coverage may be a useful addition to standard measurement of the overall program effect, allowing estimates to be generalized across settings with discrepant vaccine coverage.

Introduction

No vaccine program is created equal. With the adoption of a vaccine, policy-makers must make numerous decisions regarding its allocation, which can influence the overall effect, or impact, of a vaccine program on the burden of disease. For example, program decisions regarding the choice of vaccine(s), the population(s) and age group(s) targeted, and the recommended schedule and dosage can all influence the effect of a vaccine program on a disease outcome from a population perspective.[35]

Prior to program implementation, mathematical models are useful for evaluating the potential effects of different program scenarios in a jurisdiction,[13,69,174] but estimates from these models are often uncertain.[69,175,176] Evaluation of the overall effect, using real-world, post-implementation data, is therefore warranted,[13,69,175] and comparison of these data from similar jurisdictions with different vaccine programs may provide insights into the consequences of program decisions on population health outcomes.

Yet, estimates of the overall program effect from jurisdictions with differing levels of vaccine coverage are not easily compared. The comparison is not straightforward because the overall program effect represents the average of effects in vaccinated and unvaccinated individuals, *weighted* by their respective proportion in the population (*i.e.* as determined by vaccine coverage).[11,13,14,50] One strategy for making measures of overall program effect comparable is to characterize the relative reduction in a disease outcome **attributable to a per-unit change in vaccine coverage**. Doing so separates the effectiveness of the vaccine program from vaccine coverage, and should make jurisdictional estimates of the overall effect more easily comparable.

In this manuscript, we provide a real-world example of estimating the effect of a vaccine program as a function of coverage, where we estimate the overall effect of a rotavirus vaccine program on pediatric hospitalizations for all-cause acute gastroenteritis (AGE) via a time series analysis in Quebec, Canada. In our analyses, we demonstrate how the overall effect can be estimated as a rate ratio attributable to a 10% change in rotavirus vaccine coverage. We also characterize the overall effect of the vaccine program as a whole, in accordance with standard practice, and discuss the utility of our non-standard approach.

Methods

To estimate the overall effect of the Quebec rotavirus vaccine program, we conducted a time series analysis of weekly all-cause AGE hospitalizations between June 1, 1998 and December 28, 2014 among children 8 to 35 months of age residing in greater Montreal, Quebec.

Study setting

The Province of Quebec implemented a publicly-funded rotavirus vaccine program in November 2011. Under the program, monovalent (Rotarix®; GlaxoSmithKline) rotavirus vaccine was available at no cost to Quebec residents, with routine vaccination recommended at 2 and 4 months of age, and series initiation and completion by 20 weeks and 8 months of age, respectively [31]. Prior to the program, pentavalent (RotaTeq®, Merck & Co Inc.) and monovalent rotavirus vaccines were licensed in Canada in August 2006[149] and October 2007[150], and recommended for use by the National Advisory Committee on Immunization (NACI) in January 2008[177] and July 2010,[178] respectively; however vaccine recipients were required to pay out of pocket for vaccination.

Greater Montreal is the largest metropolitan area in Quebec and the second largest in Canada, with a population of approximately 4 million residents in 2016.[179] In general, all Quebec residents are covered by provincial health insurance, with few exceptions for temporary residents.[180]

Study population

We included greater Montreal residents 8 to 35 months of age who were members of the Montreal Population Health Record (PopHR) cohort in our analyses. As described elsewhere,[181] the Montreal PopHR cohort was created for research on health indicators, and represents an open, population-based, de-identified sample of approximately 25% of greater Montreal residents with provincial health insurance. Healthcare utilization data are tracked longitudinally for each cohort member from the date of cohort entry until either death, movement outside of Montreal, or cohort end date. Each year, cohort losses from death and emigration are replaced with a random sample of births and immigrants to maintain the population sampling fraction. The initial PopHR cohort was selected in 1998, with annual updates through 2014 at the time of our analyses.

Data sources

The PopHR cohort was created via linkages of provincial health insurance administrative databases maintained by the government organization, *Régie de l'assurance maladie du Québec* (RAMQ). Year and month for each cohort member's dates of birth, cohort entry and exit are provided, and member healthcare utilization data is tracked via an anonymized, unique identifier.

Hospitalization data for each cohort member is fed via the software system that captures administrative, clinical, and demographic information on hospital discharges, *Maintenance et exploitation des données pour l'étude de la clientèle hospitalière* (MED-ECHO),[182] used by all Quebec hospitals. In MED-ECHO, administrative codes are recorded for each hospital stay based on the International Classification of Diseases (ICD) 9th Revision, adapted for Quebec (ICD-9-QC) until 2006, and ICD 10th Revision, adapted for Canada (ICD-10-CA) from 2006 onwards.

Exposure ascertainment

In separate analyses, we characterized the Quebec rotavirus vaccine program (exposure), as either: (i) the presence or absence of the vaccine program, or (ii) the percentage of rotavirus vaccine coverage in the population.

Rotavirus vaccine program

We divided the study period into pre- and post-program periods, with the pre-program period designated as weeks before November 14, 2011, and the post-program period as weeks on or after this date. We designated November 14, 2011 as the effective program start date in consideration of the program's implementation date, and a lag of 2-weeks to account for the biological delay in the immune response to rotavirus vaccine, which is a duration typically used in rotavirus direct vaccine effectiveness studies.[61,62,120,124]

Vaccine coverage

We estimated weekly ≥1- and ≥2-dose rotavirus vaccine coverage among Montreal residents 8 to 35 months of age using coverage data from control participants enrolled in an external test-negative case-control study of rotavirus vaccine effectiveness in Quebec.[124] For reasons previously described,[183] we assumed that rotavirus vaccine coverage among these study participants was a reasonable proxy to estimate population rotavirus vaccine coverage. We used these coverage data since an immunization information system did not exist in Quebec before June 2014,[119] and provincial coverage survey estimates were not available as a time series.[43]

In our main analyses, we used coverage data from eligible controls recruited at hospitals in Montreal and Sherbrooke, Quebec, since coverage did not vary by geographic location.[183] Only controls 8 months of age or older at the time of participation in the external study were eligible for inclusion in our coverage estimates. This age cut off was chosen because a control's rotavirus vaccine history was assessed as of their participation date, and was not expected to change after 8 months of age.[184] Using these eligibility criteria, we formed a retrospective cohort to assess weekly rotavirus vaccine coverage, with controls entering and exiting the cohort at 8 and 36 months of age, respectively. We assessed ≥1- and ≥2-dose rotavirus coverage each week to form a weekly time series. Due to concerns that the age distribution of cohort members may differ from the PopHR cohort over time, weekly coverage estimates were age-standardized via direct standardization using the weekly distribution of children 8 to less than 12 months, 1 year, and 2 years of age in the PopHR cohort, via the R *epitools* package.[185] Using these methods, the earliest date that we could derive age-standardized coverage estimates was April 11, 2011, or approximately 29 weeks before the implementation of the Quebec rotavirus vaccine program. Prior to that date, we assumed rotavirus vaccine coverage was 0%, but modified this assumption in sensitivity analyses (described below).

Outcome ascertainment

We examined weekly counts of hospitalizations due to all-cause AGE as our outcome of interest. We used all-cause AGE in consideration of potential changes in laboratory testing practices for rotavirus and/or ICD coding directives for AGE over time.[186] To identify relevant hospitalizations, we examined the primary diagnosis ICD-9-QC or ICD-10-CA code recorded for each hospital stay, and counted hospitalizations with a matching primary code for all-cause AGE, as previously defined by Quebec researchers Bernard et al.[7]

Statistical analyses

We used negative binomial generalized linear models with a log-link function to estimate the overall effect of the Quebec vaccine program on weekly counts of all-cause AGE hospitalizations among children 8 to 35 months of age. A negative binomial distribution was selected over Poisson, based upon preliminary analyses that revealed overdispersion in our outcome data. A continuous, linear term indicating the week number of the time series, subsequently referred to as week time, was included in all models. All models also included a

weekly offset term to account for the denominator of children 8 to 35 months of age in the PopHR cohort.

In separate models, we characterized our exposure as: (i) a dichotomous variable, representing the presence or absence of the vaccine program, and (ii) a continuous variable, representing vaccine coverage in the population.

For exposure (i), we coded pre-program weeks as 0 and post-program weeks as 1. The exponentiated model coefficient for exposure (i) represented the rate ratio (RR) comparing weekly rates of all-cause AGE hospitalizations in the post- versus pre-vaccine periods. In addition to the RR, we report the percent relative decrease in weekly rates, or vaccine program effectiveness, estimated as (1 – RR)*100, to facilitate the interpretability of our estimates.

For exposure (ii), we input weekly age-standardized percentages of either ≥1- or ≥2-dose rotavirus vaccine coverage (in separate models), with weeks before April 11, 2011 coded as 0. The exponentiated model coefficient for exposure (ii) therefore represented the RR of weekly all-cause AGE hospitalizations corresponding to a 1% increase in vaccine coverage. To promote its interpretability, we also report RR and the percent relative decrease in our weekly outcome associated with a 10% increase in vaccine coverage, and with an increase to the maximum level of vaccine coverage observed during the study period.

We considered several different approaches to adjust for rotavirus seasonality, and implemented a series of models with season characterized as either: (i) time strata (*i.e.* binary, tertiary, quarterly, or monthly categorical variables), (ii) Fourier transformation of week time (using combinations of annual and biennial sine and cosine terms), (iii) cubic B-spline transformation of calendar week time (*i.e.* using a January start date for week number; with the number of annual knots varying between 3 and 10), or (iv) a combination of approaches (i)-(iii).[72] We also considered adjustment for long-term trends by inclusion of a linear annual term for rotavirus season with June as a starting month, as used previously in Quebec.[1] Additionally, for our dichotomous exposure model, we considered adjustment for a change in trend in the post-program period,[69,187] via inclusion of a term either accounting for the number of weeks or the number of annual rotavirus seasons since program implementation.

Due to the annual dynamic between the susceptible-infected-recovered populations within a rotavirus season, we also considered adjustment for the "population immune to rotavirus", defined as the cumulative number of participants hospitalized for all-cause AGE per annual

rotavirus season.[71,74] This approach assumes that: (i) hospitalizations for all-cause AGE are a surrogate for rotavirus hospitalizations, and (ii) people that contract rotavirus within each season are immune for the remainder of the season after recovery. While these assumptions represent an oversimplification, they are unexpected to be problematic since: (i) rotavirus was the predominant cause of pediatric acute gastroenteritis in Canada in the pre-vaccine period [1-7], and (ii) approximately one-half of our cohort was replaced each rotavirus season by an incoming birth cohort, which presumably represented children susceptible to rotavirus.

Additionally, to address residual autocorrelation, we considered inclusion of one of the following autoregressive terms, lagged by 1-week: (i) model residuals, (ii) our outcome, (iii) the logarithm of our outcome + 1, or (iv) the logarithm of our outcome + 0.5. This approach has been suggested by several authors to reduce strong residual autocorrelation in infectious disease time series induced by the contagious nature of the outcome.[71,73,188] We chose a lag of 1-week in consideration of the short incubation period of rotavirus.[189] For terms (iii) and (iv), the addition of 1 or 0.5 to outcome counts was implemented to prevent taking the logarithm of zero.

We selected the best-fitting model for each exposure by minimizing the Akaike information criterion (AIC),[190,191] and compared model fit among the final selected models for each exposure by calculating the difference between their respective AIC. We used the general criteria recommended by Burnham and Anderson[192] and denoted AIC differences of 1-2, 4-7, and >10 as models with similar, moderately better, or conclusively better fit, respectively. We assessed residual autocorrelation via autocorrelation and partial autocorrelation functions,[193] and examined model fit via plots of the residuals over time and plots of predicted versus observed values.[193] We also inspected the appropriateness of using the negative binomial distribution by examining the relationship between the theoretical and actual residual variance for fitted values using the method developed by Ver Hoef et al.,[194] as implemented by Imai et al.[71]

Sensitivity analyses

We conducted multiple sensitivity analyses to examine the robustness of our findings. First, to investigate the characterization of our binary exposure variable, we excluded the annual 2011-12 rotavirus season to account for a delay in vaccine uptake. In this analysis, we defined the time periods before and after the season as pre- and post-program periods, respectively.

To account for missing population vaccine coverage data in our continuous exposure variable during the pre-program period, we conducted a complete case analysis excluding weeks

between: (i) June 21, 2008, or the earliest date that the initial NACI recommendation for rotavirus vaccination could affect vaccine uptake among children 8 months of age, and (ii) April 11, 2011, or the start date of our weekly rotavirus coverage estimates. In another analysis, we imputed weekly coverage estimates for the population between these dates assuming a linear change in coverage during the period, and baseline coverage equal to 0%. In yet another sensitivity analysis, we only used coverage data derived from external study participants recruited at a Montreal hospital.

For each exposure, we also compared 95% confidence intervals (CI) derived via standard procedures with those estimated via a heteroskedasticity and autocorrelation consistent (*i.e.* robust) covariance matrix estimator, implemented via the R *sandwich* package.[195,196] This procedure is recommended by King and Roberts[197] to evaluate potential model misspecification.

Finally, we also compared estimates derived from our final models using a Quasi-Poisson distribution. All analyses were performed in RStudio version 0.98.1103 (Boston, MA) with R version 3.2.5.[154]

Ethics approval

This study was approved by the McGill University Institutional Review Board (IRB). Formation of the PopHR cohort was also approved by the McGill University IRB, while the external vaccine effectiveness study was additionally approved by IRBs at each hospital.

Results

An average of 24,058 children 8 to 35 months of age were under surveillance in the PopHR cohort each week (range: 21,396 to 27,061). The total number of all-cause AGE hospitalizations over the study period was 2,505, with the number of weekly hospitalizations ranging from 0 to 18.

As of the rotavirus vaccine program effective start date, age-adjusted rotavirus ≥1- and ≥2-dose vaccine coverage among children 8 to 35 months of age was 6.9% (95% CI: 2.6%, 17.0%), and 6.6% (95% CI: 2.5%, 16.8%), respectively. Between the start date of our coverage estimates and the study end date, age-adjusted ≥1-dose vaccine coverage ranged from 3.9% to 87.0%, while ≥2-dose vaccine coverage ranged from 3.9% to 72.5%. Time series plots of weekly all-cause AGE hospitalization rates are presented in conjunction with the dichotomous and continuous representations of our exposure in **Figure 5-1**.

Model selection

For both exposures, the final selected models included the following terms to adjust for seasonality, long-term trends, and infection dynamics: a linear term for week time, cubic B-spline transformation of calendar week time with 6 annual knots, annual sine and cosine terms, a biennial sine term, a linear term for annual rotavirus season, and a linear term for the population immune to rotavirus. To account for residual autocorrelation detected in the final models, we selected an autoregressive term of 1-week lagged model residuals, which fit the data better than other autoregressive terms evaluated. After implementation of the autoregressive term, there was little evidence of residual autocorrelation in the fully-adjusted models.

For our continuous exposure, the model with ≥1-dose rotavirus coverage had similar fit as the model with ≥2-dose rotavirus coverage (AIC difference=0.2). Models with either ≥1- or ≥2-dose coverage, however, had better fit than the dichotomous exposure model (AIC differences=4.3 and 4.5, respectively). Plots of the predicted counts and 95% CI from each exposure model versus observed counts of all-cause AGE hospitalizations are presented in **Figure 5-2**. Analyses of the theoretical and actual residual variances for fitted model values indicated that the negative binomial distribution was appropriate for all exposures.

Overall effect of vaccination

On average, weekly rates of all-cause AGE hospitalizations in the pre- and post-program periods were 1.341 (95% CI: 1.238, 1.443) and 0.696 (95% CI: 0.606, 0.786) per 10,000 children, respectively, accounting for a relative decrease of 48.1% (95% CI: 37.6%, 56.8%) in crude weekly rates of all-cause AGE hospitalizations in the post-program period. After adjustment, the Quebec vaccine program was associated with a 29.3% (95% CI: 16.5%, 40.1%) relative decline in weekly rates of all-cause AGE hospitalizations among children 8 to 35 months of age.

Prior to the uptake of any vaccine (*i.e.* 0% coverage), the mean weekly rate of all-cause AGE hospitalizations was 1.369 (95% CI: 1.263, 1.474) per 10,000 children 8 to 35 months of age. We estimated that a 10% increase in ≥1-dose rotavirus coverage was associated with an 11.9% (95% CI: 8.8%, 14.9%) relative decrease in crude weekly rates of all-cause AGE hospitalizations, or a 6.8% (95% CI: 3.9%, 9.5%) relative decrease in adjusted weekly rates of all-cause AGE hospitalizations. Where the continuous exposure was characterized as a 10% increase in ≥2-dose coverage, we estimated a crude relative weekly rate reduction of 13.8% (95% CI: 10.3%, 17.3%), or a relative decline in adjusted rates of 7.9% (95% CI: 4.6%, 11.2%). When we generalized our

adjusted estimates to the maximum coverage levels observed during the study period, we estimated a relative decline in weekly all-cause AGE hospitalization rates of 45.6% (95% CI: 29.2%, 58.2%) for an increase in ≥1-dose coverage to 87.0%, or 45.1% (95% CI: 29.0%, 57.6%) for an increase in ≥2-dose coverage to 72.5%. Adjusted model coefficients, RRs and 95% CI are presented in **Table 5-1**.

Sensitivity analyses

The results of our sensitivity analyses are presented in **Figure 5-3**. In general, estimates were consistent with our primary analyses, except for our analysis excluding the 2011-12 rotavirus season, which found a larger relative reduction in our outcome associated with the rotavirus vaccine program (adjusted relative decline: 34.1% 95% CI: 20.9%, 45.1%). We observed little difference between 95% CI estimated via standard procedures versus a robust covariance estimator.

Table 5-1. Adjusted model coefficients, rate ratios (RR) and 95% confidence intervals (CI) for the dichotomous and continuous representations of our exposure, the Quebec rotavirus vaccine program. Model coefficients represent the log(RR) for each exposure derived from fully-adjusted negative binomial generalized linear models implemented with a log link function.

Exposure	Model coefficient (95% CI)	RR (95% CI)	Unit
Dichotomous	-0.34646 (-0.51299, -0.17993)	0.707 (0.599, 0.835)	---
Continuous			
>=1-dose coverage	-0.00700 (-0.01003, -0.00397)	0.993 (0.990, 0.996)	*per 1% increase*
	---	0.932 (0.905, 0.961)	*per 10% increase*
	---	0.544 (0.418, 0.708)	*per increase to max coverage (87.0%)*
>=2-dose coverage	-0.00828 (-0.01183, -0.00473)	0.992 (0.988, 0.995)	*per 1% increase*
	---	0.921 (0.888, 0.954)	*per 10% increase*
	---	0.549 (0.424, 0.710)	*per increase to max coverage (72.5%)*

Figure 5-1. Weekly rates of all-cause acute gastroenteritis (AGE) hospitalizations among children 8 to 35 months of age, June 1998 – December 2014. The top chart depicts the pre- and post-vaccine program periods used for the dichotomous characterization of our exposure; the bottom chart depicts the estimated percentage of rotavirus ≥1- and ≥2-dose vaccine coverage, used for the continuous representation of our exposure.

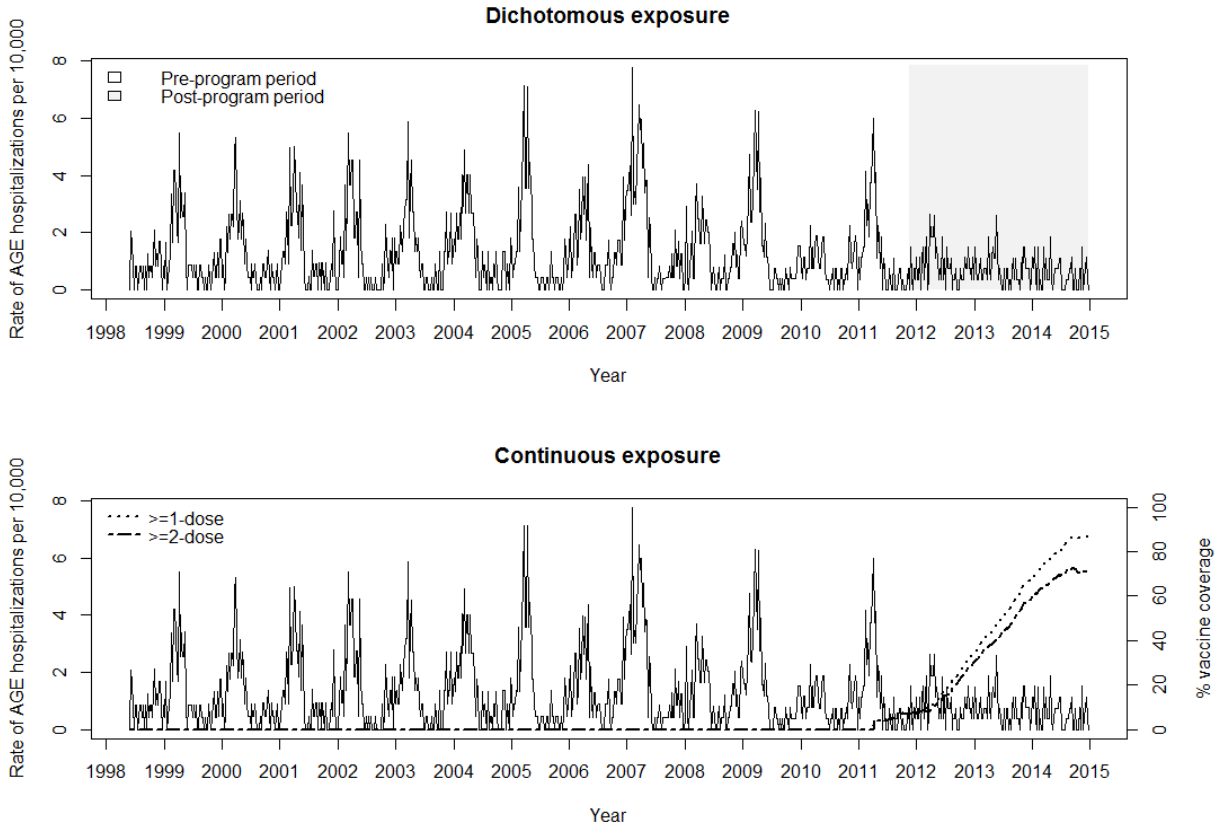


Figure 5-2. Observed counts versus predicted model estimates and 95% confidence intervals (CI) of weekly all-cause AGE hospitalizations over time. Plots of predicted values are derived from fully-adjusted models with the exposure characterized as either: (i) a dichotomous variable representing presence or absence of the program, (ii) a continuous variable representing ≥1-dose rotavirus vaccine coverage, or (iii) a continuous variable representing ≥2-dose rotavirus vaccine coverage.

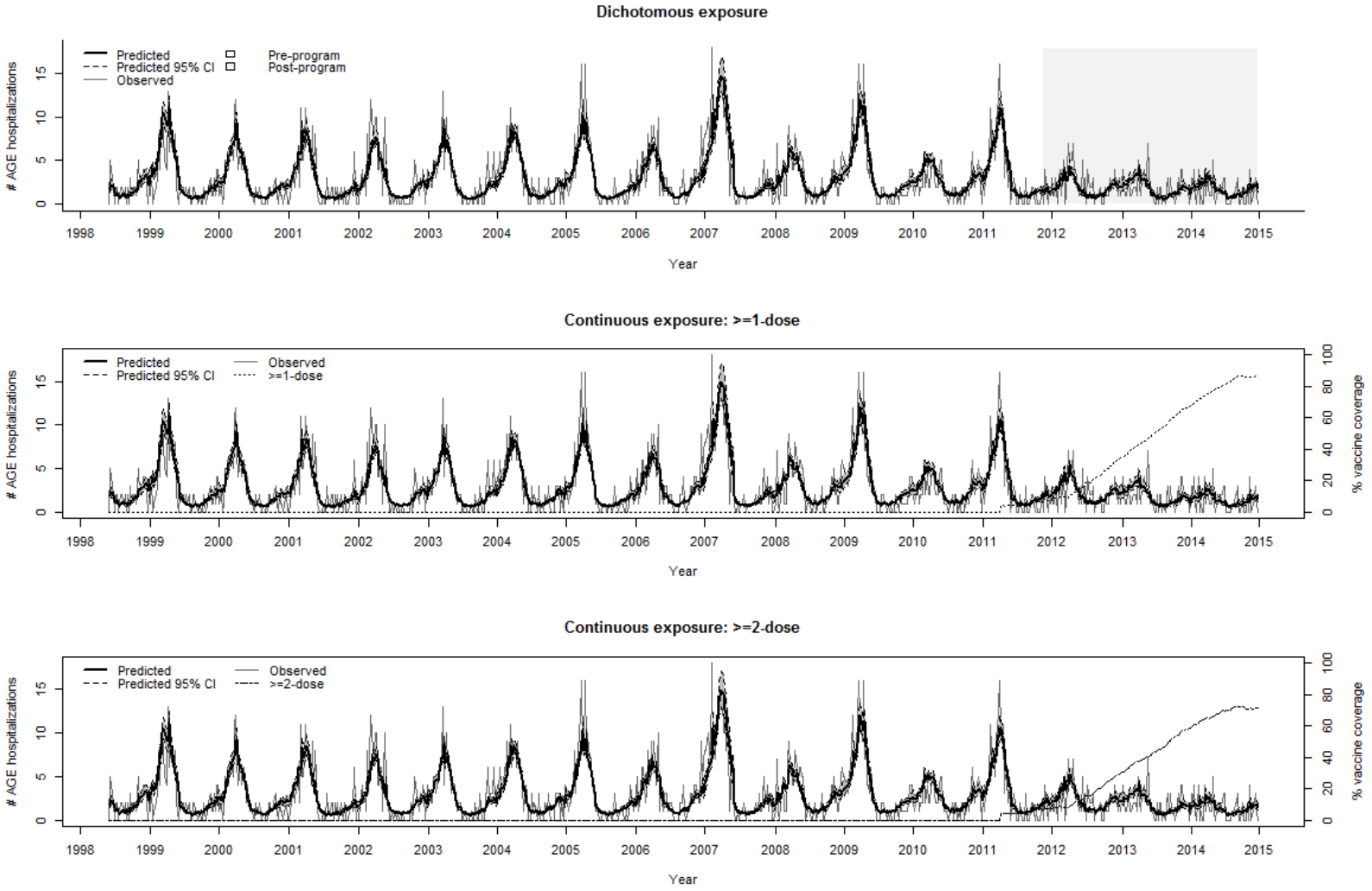
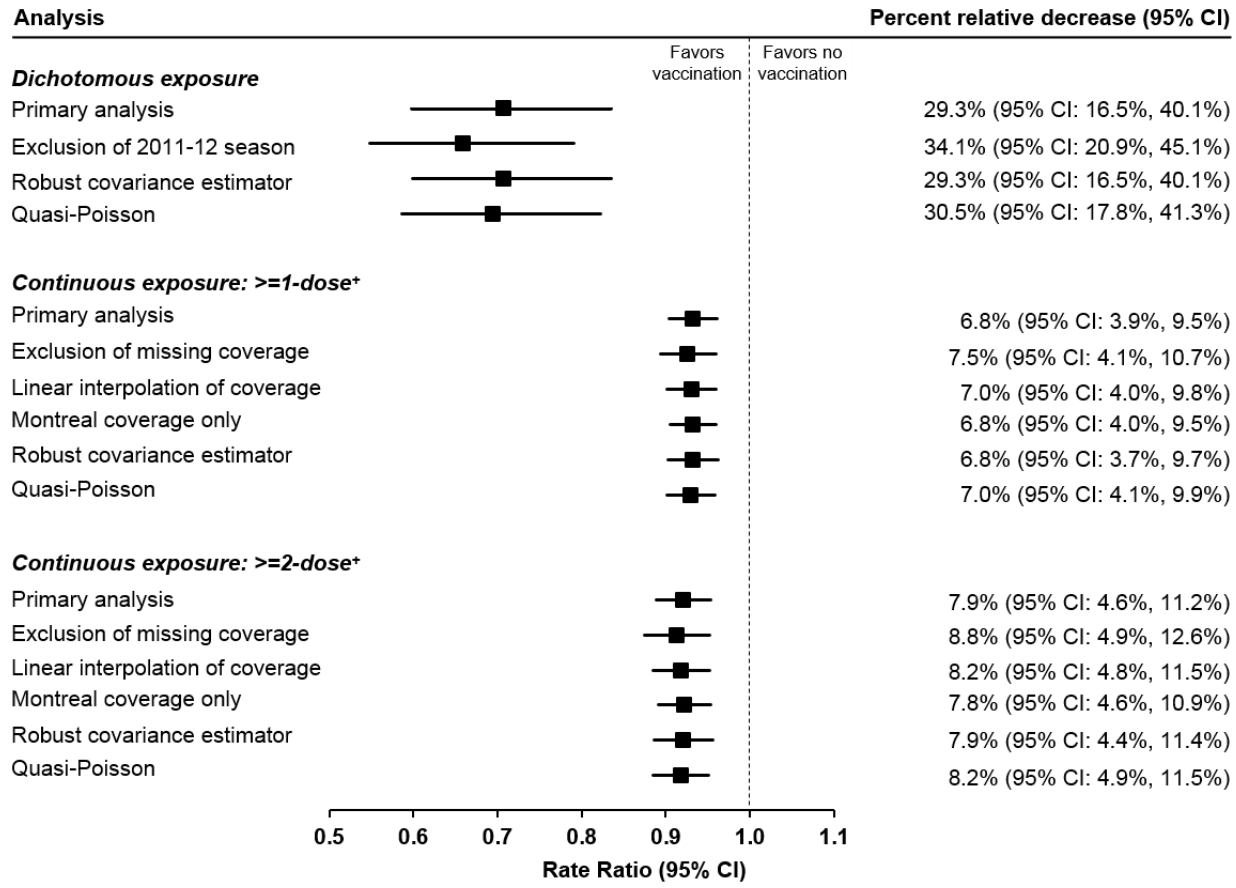


Figure 5-3. Sensitivity analyses examining the adjusted overall effect of the Quebec rotavirus vaccine program on the weekly rate of all-cause AGE hospitalizations. [+]For continuous exposures, rate ratios and percent relative decrease are estimated for a 10% increase in population rotavirus coverage.



Discussion

After adjustment for seasonality and other factors, we estimated that a 10% increase in ≥1-dose rotavirus vaccine coverage was associated with a nearly 7% relative decrease in the weekly rate of all-cause AGE hospitalizations among children 8 to 35 months of age. For an increase to 87% rotavirus ≥1-dose coverage, or the highest coverage level in the population during the study period, we estimated that adjusted weekly rates of all-cause AGE hospitalization declined by nearly 46%.

By comparison, for the dichotomous representation of the vaccine program, as traditionally used to estimate the overall effect of rotavirus vaccine programs in time series analyses,[24,27,28,69,198] we estimated that weekly rates of all-cause AGE hospitalizations declined in the post- versus pre-vaccine period an average of 29%, using an effective program start date of November 14, 2011, or 34%, excluding the 2011-12 season as a transition period. While these analyses are valid to ascertain the mean weekly effect attributable to the vaccine program since its implementation, the results are not easily generalizable to post-program periods, particularly if there is a change in population vaccine coverage.

Direct comparison of the overall program effect to otherwise similar jurisdictions with differing vaccine coverage is also not straightforward, since interpretation of program-related reductions must be made in the context of population vaccine coverage. While most systematic reviews and/or meta-analyses (SR/MA) that compare overall effects between vaccine programs report jurisdictional vaccine coverage in their narrative or a results table,[76-80] it is difficult for readers to synthesize this information. Other SR/MA account for differences in vaccine coverage in their analyses by stratifying overall effect estimates by coverage;[81,82] while this is a better method for comparison, coverage strata in these SR/MA were overly broad (*i.e.* coverage <50% vs. ≥50%, or low/moderate/high coverage), which may be insufficient to adjust for differences in program effects due to vaccine coverage.

While it is also possible to directly adjust for vaccine coverage in meta-analyses using statistical models,[83] the overall effect estimates from primary studies may not reflect a post-program period with uniform vaccine coverage. This may be particularly true for the evaluation of new vaccine programs, such as rotavirus, where program estimates represent a period in which rotavirus vaccine coverage is rapidly changing in the population;[24,25,27,28,75] thus, direct adjustment for vaccine coverage in pooled analyses of the overall effect may not be possible or accurate.

In each of these scenarios, estimates of the overall effect attributable to a per-unit change in vaccine coverage may be particularly useful to extrapolate estimates to other coverage levels, directly compare estimates between otherwise similar jurisdictions, or to incorporate into statistical models pooling program effect estimates from differing jurisdictions. For these reasons, we suggest that the overall effect attributable to a per-unit change in vaccine coverage may be a useful measure to supplement traditional methods to estimate the overall effect of a vaccine program. Where vaccine coverage data are available, authors may consider estimating both the overall program effect attributable to the vaccine program as a whole, and a per-unit change in vaccine coverage, in order to enhance the generalizability of their results.

Limitations

Our analyses have some limitations. First, in modeling our continuous exposure, we assumed that the increase in the log of weekly all-cause AGE hospitalization rates associated with a 1% increase in coverage was the same across all levels of observed vaccine coverage in the population (*i.e.* assumption of a log-linear relationship). This may be an oversimplified representation of the dynamic relationship between vaccine coverage and inducement of indirect (*i.e.* herd) effects, and is an area for future research. Second, our approach ignores the potential implications of vaccination in other population subgroups on indirect effects; though this is not an issue in the present study because our study population represents the entire population eligible for vaccination, we recommend that researchers consider adjustment for population vaccine coverage should analyses be restricted to a subgroup of the vaccine eligible population. Third, we did not include sampling error for coverage estimates in our analyses; nonetheless, we conducted multiple sensitivity analyses that explored the effect of differing coverage estimates, and did not find meaningful differences in our results. Lastly, we were unable to ascertain the effect of the program on rotavirus hospitalizations directly; however, broadening our definition to all-cause AGE hospitalizations should only attenuate our effect estimates.

Conclusion

In the evaluation of a vaccine program, researchers should consider estimating the overall effect attributable to a per-unit increase in vaccine coverage in the population, in addition to estimating the overall effect of the program. In our examination of the effect of the Quebec rotavirus vaccine program, we estimated that each 10% increase in ≥1-dose rotavirus vaccine

coverage was associated with a nearly 7% relative decrease in the rate of weekly all-cause AGE hospitalizations among children 8 to 35 months of age. Using this approach of estimating the incremental effect of increasing coverage as part of measuring the program effect should promote generalizability of vaccine program effectiveness estimates across settings with differing coverage.

Chapter 6: Summary & Conclusions

6.1 Summary of Research

The goal of my doctoral thesis was to advance scientific knowledge regarding rotavirus vaccine programs and epidemiologic methods related to vaccine program assessment through the evaluation of the Quebec RV1 rotavirus vaccine program. Specifically, the first objective of my thesis was to examine the vaccine effectiveness, or direct effect, of the RV1 vaccine to prevent pediatric emergency department visits and hospitalizations. The second objective of my thesis was to estimate rotavirus vaccination coverage among the Quebec population eligible for vaccination, and innovate upon existing methods of vaccine coverage assessment. Finally, the third objective of my thesis was to evaluate the population impact, or overall effect, of the Quebec rotavirus vaccine program to prevent all-cause AGE hospitalizations, and characterize the effect attributable to the program as a whole, according to standard practice, and the effect attributable to a per-unit change in vaccine coverage, a newly proposed measure that may help to promote the generalizability of overall effect estimates.

In the first manuscript entitled, "Effectiveness of monovalent rotavirus vaccine in a high-income, predominant use setting", I implemented a test-negative case-control study design to estimate RV1 vaccine effectiveness among eligible children seeking emergency care for acute gastroenteritis who were enrolled in active rotavirus surveillance at 3 Quebec hospitals. Prior to this work, there was little research that examined RV1 vaccine effectiveness in a high-income setting, where it was predominantly used over RV5 vaccine. I estimated that the adjusted ≥1-dose RV1 vaccine effectiveness was 92.5% (95% CI: 69.3%, 98.2%) to prevent emergency department visits and hospitalizations among children less than 3 years of age, and concluded that RV1 vaccine effectiveness was similar to RV1 vaccine effectiveness in other high-income settings with concurrent RV1 and RV5 vaccine use.[60-62,64,84,85] In this manuscript, I also examined longitudinal trends in rotavirus strain circulation in Quebec in the three seasons post-program implementation, and found an increase in heterotypic and partly-heterotypic rotavirus strains over time.

In the second manuscript entitled, "Two birds with one stone: estimating population vaccination coverage from a test-negative vaccine effectiveness case-control study", I demonstrated how population rotavirus vaccine coverage may be estimated using coverage data from control subjects enrolled in a test-negative rotavirus vaccine effectiveness case-control study,

and estimated that rotavirus ≥1-dose coverage was 86.8% (95% CI: 82.7%, 90.0%) among participants eligible for vaccination under the Quebec rotavirus vaccine program. I also present the underlying assumptions required to generalize rotavirus vaccine coverage estimates to a broader population, validated coverage estimates with comparison to estimates from the Quebec immunization survey, and used simulations to explore the effect of diagnostic accuracy to discern control subjects on coverage estimates. I concluded that controls from a test-negative vaccine effectiveness case-control study may be a valuable resource for vaccine coverage information, when reasonable assumptions can be made to generalize coverage estimates.

In the third and final manuscript entitled, "Estimation of the overall effect of a rotavirus vaccine program attributable to a per-unit change in vaccine coverage in the population", I evaluated the impact, or overall effect, of the Quebec rotavirus vaccine program to prevent all-cause AGE hospitalizations among a random sample of approximately 25% of children 8 to 35 months of age residing in the Montreal census metropolitan area, using a time series study design. In accordance with standard practice, I estimated the overall effect of the vaccine program as a rate ratio comparing adjusted rates of our outcome in the post- versus pre-vaccine periods. Additionally, I demonstrated how the overall effect may be characterized as the effect associated with a 10% increase in rotavirus vaccine coverage in the population by using continuous rotavirus vaccine coverage as the exposure variable, derived from the application of the study design highlighted in objective 2. I estimated that the vaccine program was associated with a mean 29.3% (95% CI: 16.5%, 40.1%) relative decline in adjusted weekly rates of all-cause acute gastroenteritis hospitalizations in the post- versus pre-vaccine period, or that a 10% increase in rotavirus ≥1-dose vaccine coverage was associated with a 6.8% (95% CI: 3.9%, 9.5%) relative decline in adjusted weekly rates. I also discussed the utility of measuring the overall effect associated with a per-unit change in vaccine coverage, and concluded that researchers may consider estimating this measure, in addition to standard measures, to promote the generalizability of their estimates to other coverage levels and settings.

6.2 Limitations

In addition to the specific limitations outlined within each of the three manuscripts located within Chapters 3-5, there are limitations relevant to the collective findings of this thesis that are important to highlight. First, a reoccurring limitation among all three manuscripts is that this evaluation is limited to three rotavirus seasons in the post-vaccine era. During this period,

we demonstrated that rotavirus ≥1-dose coverage vaccine coverage in the population rapidly increased to 86.8% (95% CI: 82.7%, 90.0%) among participants eligible for vaccination under the Quebec rotavirus vaccine program. Although the introductory period of a new vaccine program is ideal to measure vaccine effectiveness given the potential for residual confounding when the population vaccine coverage is too low or too high,[51] data from three rotavirus seasons following program implementation may be insufficient to accurately characterize the average overall effect of a vaccine program in the post-vaccine period, or sufficiently examine circulating rotavirus strains in the post-vaccine era. Nonetheless, our time series evaluation of the overall effect of a RV1-only vaccine program on all-cause AGE hospitalizations included a greater post-vaccine period than time series evaluations from other high-income jurisdictions with RV1-only programs, to date.[24,28] Further, documenting early changes in pediatric rotavirus AGE is useful to justify the scope and financial costs of the program, and prioritize areas of future research.

Similarly, another limitation of this research is that the study populations were restricted geographically. In the examination of the RV1 vaccine effectiveness and vaccine coverage, we were only able to include data collected from 3 university hospitals located in 1 urban and 1 rural location in the Province of Quebec, while the evaluation of the overall effect of RV1 vaccination was limited to a sample of residents from the Montreal census metropolitan area. In general, adjusted RV1 vaccine effectiveness is not expected to differ across regions of Quebec, given that characteristics of the vaccinated population and rotavirus transmission dynamics throughout the province are likely similar. While vaccine coverage may differ geographically, stratified estimates of coverage did not reveal coverage differences between the regions surveyed, or differences from provincial estimates from the Quebec immunization survey. Where vaccine coverage does vary by Quebec region, however, we would expect the overall effect attributable to the vaccine program as a whole to also differ geographically. Nonetheless, the characterization of the overall effect attributable to a per-unit change in vaccine coverage may be more generalizable across provincial settings with varying vaccine coverage.

6.3 Implications and Directions for Future Research

This research makes several important contributions to further the current scientific understanding of rotavirus vaccination programs or evaluative methods for vaccine programs, generally. Specifically, findings of RV1 vaccine effectiveness to prevent emergency department visits and hospitalizations from the first manuscript further supports the implementation of RV1-

only vaccine programs, given that RV1 vaccine is similarly effective to prevent severe gastroenteritis as RV1 and RV5 concurrent settings. Additionally, we provide early data to examine the prevalence of circulating rotavirus strains in Quebec, following the implementation of an RV1-only vaccination program. In this analysis, we observed an increase in heterotypic and partly-heterotypic rotavirus strains, underscoring the importance of continued strain surveillance to monitor longitudinal trends in rotavirus strain circulation in Quebec.

In manuscript 2, we suggest an alternative design to evaluate vaccine coverage, documenting its assumptions and bias under varying scenarios of diagnostic accuracy. While this method should not be considered a replacement to traditional vaccine coverage surveys, it may be a useful addition to evaluate vaccine coverage, particularly for a newly implemented vaccine program, where survey methods may not be readily used to rapidly examine the uptake of vaccine, and a test-negative vaccine effectiveness case-control study is planned. As a result of this work, we hope that other researchers consider using this design to evaluate vaccine coverage where appropriate, and continue to explore alternative methods for the evaluation of vaccine coverage.

In manuscript 3, we provide estimates of the overall effect of a RV1 vaccination program, fully adjusted for secular and seasonal trends, with the inclusion of three years of data following the implementation of a RV1 vaccine program. Data from this evaluation support the sustained reduction in the burden of pediatric rotavirus AGE hospitalizations, similar to reductions found in the first year following the implementation of RV1-only vaccine programs in other jurisdictions.[24,28] An additional contribution of this work is the proposal that researchers consider characterization of the overall effect as the effect attributable to a per-unit change in vaccine coverage, with a discussion of the utility of this non-standard approach. As a result of this work, we hope that other researchers consider using this alternative measure to characterize the overall effect, as it may facilitate comparisons between similar jurisdictions with different vaccine programs, and provide insights into the consequences of program decisions on population health outcomes.

6.4 Conclusions

Collectively, the results from this thesis research demonstrate the relative success of the Quebec monovalent rotavirus vaccine program, with (i) greater than 90% effectiveness of monovalent rotavirus vaccine to prevent emergency department visits and hospitalizations due to rotavirus gastroenteritis, (ii) achievement of more than 85% ≥1-dose rotavirus vaccine coverage

among the population eligible for vaccination under the new program, and (iii) a near 30% average relative decline in adjusted weekly rates of all-cause acute gastroenteritis hospitalizations since the implementation of the program among children 8 to 35 months of age. This research also makes two important methodological contributions to the field of vaccine program evaluation with its suggestion of an alternative design to estimate vaccine coverage in the population, and an additional measure to estimate the overall effect of a vaccine program. While this research highlights the initial success of the Quebec rotavirus vaccine program, ongoing research is necessary to evaluate the program's continued achievements.

Back Matter

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