DETERMINANTS OF IMMUNIZATION AND DAYS UNDER-IMMUNIZED IN A QUEBEC COHORT: 2012-2014

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October, 2017

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science in Epidemiology

Abstract

In high-income countries well-established immunization programs have resulted in the decrease and even elimination of vaccine preventable diseases. Nevertheless, notable declines in vaccine uptake have been reported in the last 20 years. Within the current body of literature, factors determined to influence uptake of vaccines are contextual, individual, social, and vaccine-specific. Despite the concerning decline in uptake of childhood vaccines, most children receive at least some vaccines. Therefore, it can be argued that children who have partial or delayed coverage for age represent a larger and perhaps more important population to study than those who receive no vaccines at all. Thus, the overall aim of my Master's thesis is to identify those determinants associated with the immunization status of a Quebec cohort of pre-schoolers and their cumulative time spent under-immunized through a secondary analysis of previously collected data.

The current body of literature has failed to find conclusive global determinants of vaccine uptake. To fill this knowledge gap, the first manuscript of this thesis is a systematic review that identified determinants of immunization status, uniquely in high-income countries. Using a search strategy developed on May 12, 2016 for Ovid MEDLINE and adapted across other databases, I identified 4475 articles of which 43 were reviewed. Among the selected articles several core determinants were found to be conclusive barriers to routine immunization within high-income countries represented in the review. This list includes birth order or increasing number of children per household (n=20, 46.5%), single motherhood (n=9, 21%), younger

maternal age (n=8, 18.6%), high mobility (n=5, 11.6%), parental smoking (n=4, 9%), and late initiation of immunization (n=5, 11.6%). Several determinants were found to be inconclusive barriers to immunization such as maternal education, the type of healthcare or immunization provider, and belonging to a racial or linguistic minority group, indicating that the importance of these determinants would be detected at a more local level.

In Quebec, 75% of children are vaccinated by public health nurses in regional and borough health centers. This underlines the importance of public health programs to adapt locally relevant strategies to increase age-specific immunization coverage according to the provincial guidelines. My second manuscript was a secondary analysis of a cohort of pre-school aged children recruited through active surveillance for gastroenteritis from three Quebec pediatric emergency departments from 2012-2014. First I aimed to indentify factors associated with under-immunization in the province of Quebec. Second, I calculated the number of days during which children were delayed in their immunization schedule in their first 24 months of life (days under-immunized). . Cumulative days under-immunized due to delay in the immunization schedule were calculated for: diphtheria and tetanus toxoids, acellular pertussis vaccine, poliovirus vaccine and *Haemophilus influenzae* type b vaccine (DTap-IPV-Hib), pneumococcal conjugate vaccine (PCV-7,10 or 13), measles, mumps, and rubella with one containing varicella (MMR (v)), and meningococcal type C vaccine (Men-C-C). In this cohort analysis, of 246 eligible children, 180 (73%) had complete doses for age. The following factors were significantly associated with an up-to-date (UTD) status at 24 months and the risk of being ≥6 months cumulatively delayed for one or more vaccines: timely initiation of immunization was

associated with an almost 6-fold chance of being UTD (OR=5.85; 95% CI: 2.80-12.22) and an almost 90% decreased chance of being delayed for being ≥6 months cumulatively (OR=0.13; 95% CI: 0.07-0.24). The same was seen for failure to co-administer 18-month vaccines (OR =0.15; 95% CI: 0.10-0.21) and (OR=3.29; 95% CI: 2.47-4.39), and having a household with ≥3 children under 18 years (OR= 0. 0.50; 0.28-0.86) and (OR=2.99; 1.45-6.22), respectively. The mean cumulative days under-immunized for MMR was 107 days, for PCV, 209 days, for Men-C-C, 145 days, and for DTaP-VPI-Hib, 227 days. Overall, 149 children (60%) experienced delay for at least 1 vaccine.

Paired with a lower than expected vaccination coverage at 24 months of life, Quebec children spent a significant amounts of time under-immunized; increasing time at risk for illness and their complications. A large number of studies were summarized to identify core determinants of vaccine hesitancy in a high-income setting. I believe the findings to be generalizable to other high-income countries not represented in the review. However, the role of inconclusive determinants such as healthcare provider and minority status are most likely determinants that are locality specific. Knowledge gained from my Master's thesis will contribute to the increasing body of evidence used to understand the cultural epidemiology of vaccine hesitancy in high-income countries and as a launch point for several future research projects, exploring the impact of incomplete childhood immunization.

Abrégé

Dans les pays à revenu élevé, les programmes de vaccination bien établis ont entraîné la diminution et même l'élimination des maladies évitables par la vaccination. Néanmoins, des baisses notables de l'acceptation vaccinale ont été signalées au cours des 20 dernières années. L'hésitation à la vaccination, ou le fait d'hésiter à donner à son enfant une partie ou l'ensemble des vaccins recommandés en dépit de la disponibilité des services de vaccination, est un sujet de recherche récent. Dans le corpus actuel de la littérature, les facteurs influençant l'acceptation vaccinale sont liés aux contextes, aux individus, aux facteurs sociaux et sont spécifiques à chacun des vaccins. Malgré la diminution dans l'acceptabilité de vaccins infantiles, la plupart des enfants reçoivent au moins certains vaccins. Par conséquent, on peut soutenir que les enfants qui ont une couverture vaccinale partielle ou avec des retards selon l'âge représentent une population plus grande et peut-être plus importante à étudier que ceux qui ne reçoivent aucun vaccin. En l'absence d'un registre vaccinal, l'occasion unique d'analyser le statut vaccinal d'une population peut être d'intérêt pour les autorités de santé publique. Ainsi, l'objectif général de ma thèse de maîtrise est d'identifier les déterminants associés au statut vaccinal dans une cohorte québécoise d'enfants d'âge préscolaire et leur temps cumulatif, sous-immunisés (retards selon le calendrier de vaccination) au moyen d'une analyse secondaire de données recueillies antérieurement.

Le corpus actuel de la littérature couvrant l'hésitation vaccinale n'a pas permis d'identifier de déterminants globaux décisifs de l'acceptation des vaccins. Pour combler ce fossé dans les connaissances, le premier manuscrit de cette thèse est une revue systématique qui a identifié les déterminants du statut vaccinal, uniquement pour les pays à haut revenu. En utilisant une

stratégie de recherche développée le 12 mai 2016 pour Ovide MEDLINE, Cochrane, PubMed, Ovide: MEDLINE (1946 à mai 2016), Web of Science, et EBSCOhost: CINHAHL, j'ai identifié 4475 articles dont 43 ont été examinés. Plusieurs déterminants se sont révélés être des obstacles décisifs à la vaccination systématique dans les pays à haut revenu représentés dans l'étude. Cette liste comprend l'ordre de naissance ou le nombre croissant d'enfants par foyer (n = 20 46,5%), la monoparentalité (n = 9, 21%), un âge maternel plus jeune (n = 8, 18,6%), une mobilité élevée (n = 5, 11,6%), le tabagisme parental (n = 4, 9%) et le début tardif de l'immunisation (n = 5, 11,6%). Plusieurs déterminants se sont révélés être des obstacles non concluants à l'immunisation, comme l'éducation maternelle, le type de soins de santé ou de vaccination, et l'appartenance à un groupe racial ou linguistique minoritaire, ce qui indique que ces déterminants influencent la couverture vaccinale d'une façon plus contextuellement spécifique.

Au Québec, 75% des enfants sont vaccinés par des infirmières en santé publique dans les centres locaux de services communautaires (CLSC). Cela souligne ainsi l'importance des programmes de santé publique pour adapter les stratégies locales pertinentes et ainsi accroître la couverture vaccinale selon l'âge recommandé dans les lignes directrices provinciales. Avec les principaux déterminants de l'immunisation identifiés dans ma revue systématique, j'ai cherché à savoir si ces mêmes facteurs étaient associés à la sous-immunisation dans la province de Québec. Deuxièmement, je voulais connaître le nombre de jours pendant lesquels les enfants ont été en retard dans leurs vaccins au cours de leurs 24 premiers mois de leur vie (jours sous-immunisés), visant à comparer cet indicateur avec la mesure standard de la

couverture en évaluant l'espacement (intentionnel ou non) dans le calendrier de vaccination. Pour répondre à ces questions, mon deuxième manuscrit a été une analyse secondaire d'une cohorte d'enfants d'âge préscolaire recrutés par le biais d'une surveillance active de la gastro-entérite dans trois services d'urgence pédiatriques du Québec de 2012 à2014. Le statut vaccinal des enfants âgés d'au moins 24 mois a été déterminé à l'aide des directives provinciales sur l'immunisation. Les jours cumulatifs sous immunisés en raison d'un retard dans le calendrier d'immunisation ont été calculés pour le diphtérie-coqueluche-tétanos-hépatite B- poliomyélite - *Haemophilus influenzae* type b (DCaT-VPI-Hib), le pneumocoque (PCV), le rougeole-rubéole-oreillons-varicelle (RRO-v) et le méningocoque C (Men-C). Dans mon analyse de cohorte, des 246 enfants admissibles, 180 (73%) avaient des doses complètes pour l'âge. Des facteurs importants associés à la fois à un statut à jour pour l'âge à 24 mois et qui associés simultanément à un risque de retard dans l'immunisation ≥ 6 mois respectivement, incluaient l'initiation de l'immunisation sans aucun délai (RC = 5,85; 95% IC: 2,80-12.22) et (RC = 0,13; 95% IC: 0,07-0,24), défaut à administrer concomitamment les vaccins de 18 mois (RC = 0,15;) (95% IC: 0,10-0,21) et (RC = 3.29; 95% IC: 2, 47-4,39), et ayant un foyer avec ≥ trois enfants de moins de 18 ans (RC = 0.50; 0,28-0,86) et (RC = 2,99; 1,45-6.22). La moyenne de jours cumulatifs sous-immunisés pour le RRO étaient de 107 jours, pour le PCV, de209 jours, pour Men-C-, de-145 jours, et pour le DCaT-VPI-Hib, de 227 jours. En tout, 149 enfants (60%) ont connu un retard d'au moins 1 vaccin.

Jumelés à une couverture vaccinale inférieure à celle prévue à 24 mois de vie, les enfants du Québec ont passé une quantité importante de temps sous immunisés et ainsi, plus de temps à

risque pour la maladie et leurs complications. Un grand nombre d'études ont été résumées afin d'identifier les principaux déterminants de l'hésitation vaccinale dans un contexte de pays à haut revenu. Je crois que les conclusions sont généralisables à d'autres pays à haut revenu qui ne sont pas représentés dans l'étude. Cependant, le rôle des déterminants non concluants tels que le fournisseur de soins de santé et le statut de minorité sont des déterminants probablement locaux. Les connaissances acquises grâce à ce mémoire contribueront à l'ensemble des données probantes utilisées pour comprendre l'épidémiologie culturelle de l'hésitation vaccinale dans les pays à haut revenu et comme point de départ pour plusieurs projets de recherche futurs, explorant l'impact de la vaccination infantile incomplète.

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List of abbreviations

Abbreviation/Acronym	Definition
AGE	Acute Gastroenteritis
CLSC	Centre Local de Services Communautaires
cNICS	Canadian childhood National Immunization Coverage Survey
CSSS	Centre de Santé et Service Sociaux
FSA	Forward Sortation Area
GNI	Gross National Income
PHAC	Public Health Agency of Canada
PIQ	Protocole d'immunization du Québec
SAGE WG	Strategic Advisory Group of Experts Working Group
UTD	Up-to-Date
WHO	World Health Organization

Preface and Contribution of Authors

I developed the original research questions for this thesis in collaboration with my thesis supervisor, Dr. Caroline Quach. I also developed the thesis objectives, which were approved by my thesis supervisor and by my thesis committee (Dr. Eve Dubé). Under the supervision of Dr. Quach I developed the study protocols for the two thesis objectives and subsequently carried out the pre-planned analyses for each study.

Dr. Quach previously obtained the cohort data used in this thesis. I processed all the data and built a specific database for the cohort analysis manuscript presented in this thesis. Accordingly, I carried out all statistical analyses and was primarily responsible for the interpretation and elaboration of results. Once I presented the results to my thesis supervisor and thesis committee member, I drafted the manuscript which was revised and edited by my supervisor, committee member, and co-authors. I then wrote all chapters of this Master's thesis.

Specific co-author contributions for the two manuscripts included in this thesis are detailed below:

1. Shauna O'Donnell, Noushon Farmanara, Caroline Quach. **Determinants of immunization status in pre-school children in high income countries: A Systematic Review.** Submitted to *Archives of Disease in Childhood.*

Conception: S. O'Donnell approved by C. Quach; *Data acquisition:* S.O'Donnell and N. Farmanara; *Data administration:* S. O'Donnell; *Analysis:* S. O'Donnell; *Data interpretation:* S.

O'Donnell*; writing:* S. O'Donnell*; critical revision:* S. O'Donnell, N. Farmanara, G.Gore, C.Quach; *supervision*: C.Quach.

2. Shauna O'Donnell, Eve Dubé, Bruce Tapiero, Arnaud Gagneur, Margaret K. Doll, Caroline Quach. **Determinants of under-immunization and cumulative time spent under-immunized in a Quebec cohort**. Vaccine; 35(43)

Conception: S. O'Donnell approved by C. Quach; *Data acquisition:* C. Quach (MUHC-vaccine study center); *Data administration:* S.O'Donnell, M. Gonzales, M.K.Doll; *Analysis:* S. O'Donnell; *Data interpretation:* S. O'Donnell; *writing:* S.O'Donnell; *critical revision:* S. O'Donnell, E. Dubé, B. Tapiero, A. Gagneur, M. K. Doll, M. Gonzales, C. Quach *supervision:* C. Quach.

Acknowledgements

This Master's Thesis would not be possible without the commitment and continued support from Dr. Caroline Quach. Her unrelenting belief in my competencies helped me not just survive but thrive through this academic process. You remain as ever, an inspiration. I must also acknowledge Dr. Eve Dubé, for her expert advice in untangling the complex topic of vaccine hesitancy.

Acknowledgments are due to my colleagues and friends at the MUHC Research Institute. I would like to especially impart warm gratitude to Ms. Mila Gonzales and Ms. Margaret K. Doll for database queries and trouble shooting. To Ms. Gen Gore, expert librarian, for her invaluable assistance in organizing my search strategy. Many thanks to my colleagues, teachers and friends at the Department of Epidemiology, Biostatistics & Occupational Health.

To Gareth-my partner in the truest sense; thank you for your steadfast belief in me. To my children, Elisabeth and Owen; my raisons d'etre, I did this for you. "I knew when I met you an adventure was going to happen." Winnie the Pooh [A.A. Milne]

Statement of support

My time spent Master's program was generously supported by a student stipend award from my supervisor Dr. Caroline Quach in addition to support to attend scientific conferences throughout my training.

Statement of Ethics

Research involving Forward Sortation Area (FSA) geography (i.e., postal codes) must include the following statement:

Chapter 1 Introduction

Rationale

Immunization is widely considered one of the most important accomplishments in the global fight against morbidity and mortality from infectious disease [1]. Globally, it is estimated that 2 to 3 million deaths per year are prevented due to vaccines [1]. In Canada, vaccines have significantly reduced or eliminated many vaccine preventable diseases. All infectious diseases now represent less than 5% of Canadian mortality, compared to over 100 years ago when it was the leading cause of death [2]. As such, the Canadian Public Health Association reported vaccinations as one of the top 12 public health achievements in Canada [3]. Vaccines have been shown to be a cost-effective intervention in saving lives and improving quality of life [1]. In addition, immunization has provided health care savings, increased life expectancy, and enhanced equity [4].

Despite proven safety and efficacy, rates of childhood immunization have been on the decline to just below threshold herd immunity levels since the turn of the century[5]. Notwithstanding this concerning decline in uptake, the majority of Canadian children are immunized against vaccine preventable diseases. The proportion of Canadian children whose parents or guardians reported they had never received any immunization in 2013 was 1.5% across all age groups[6]. Therefore, it can be argued that children who have partial or delayed coverage for age represent a larger and perhaps more important population to study than those who receive no vaccines at all. It is imperative to understand the drivers behind declining vaccine acceptance in order for public health organizations to provide and increase coverage of this fundamental preventive care service. In the absence of a vaccine registry, any unique opportunity should be

seized, to estimate coverage, under-immunization, gaps in immunization, and the associated risk factors[7]. Recent systematic reviews conducted at the global scale have been unable to identify common determinants of incomplete immunization and this, due to the highly complex and contextual nature of the decision process in choosing to vaccinate [8, 9]. Through grouping populations such as those in high-income countries we can control for some of these contexts and uncover common, core determinants of immunization that will be informative at a broad scale.

Thesis objectives

This thesis will address some gaps in the literature pertaining to factors associated with vaccine uptake and under-immunization. The primary objectives of this thesis were to determine the factors associated with vaccine coverage in Quebec pre-schoolers and the amount of time they spent under-immunized in the first 24 months of life. The secondary objective was to determine through a systematic review, the core determinants of incomplete immunization in high-income countries.

Outline

This thesis is composed of 8 chapters. This first chapter provides a brief introduction to the topic of study, objectives of this thesis, and an outline of the document. The second chapter contains information on the origins of vaccination, the Montreal connection, and the global response to vaccine decline. The third chapter is the first manuscript, a systematic review of the literature that analyzes determinants associated with immunization in high-income countries. The fourth chapter bridges the two manuscripts. The fifth chapter discusses methods and a

foreword for the 2nd manuscript. Chapter 6 is the second manuscript [10], a cohort analysis of Quebec pre-schoolers and the determinants of immunization and time spent under-immunized. In the seventh chapter, the objectives of this thesis are reiterated, and the findings of this research are summarized and discussed. The final chapter enumerates the full collection of references used throughout this thesis, including those cited in the manuscripts.

Chapter 2 Background

This chapter will illustrate how, through inception to present, vaccination has stimulated continuous discourse at the local and global level.

Vaccination

In the absence of an effective treatment for smallpox, there began a shift in approach from attempts at curative measures to those of prevention. These early attempts at prevention came in the form of *variolation* in the early 18th century[11]. The *variolation* process involved taking a small amount of smallpox, called variola, from an infected patient and inoculating a healthy person with the disease. This practice, originating in China, spread slowly to the Middle East then to Europe and North America[12]. *Variolation* is credited for a drastic reduction in smallpox death rates in the English population in the first decade of its wider practice (1721-1729) [13, 14].

English physician and scientist, Edward Jenner is credited with creating the first vaccine; that of smallpox and formally testing his vaccine in 1796. The word vaccine derives from Jenner's work and its root from the Latin vaccinus, meaning "pertaining to cows, from cows"[15]. A vaccine is the product injected through the act of vaccination and immunization is the process by which the immune system mounts a response to resist or decrease severity of future infection[16]. By the end of 1800, over 100,000 individuals in Europe were successfully vaccinated using cowpox sera. Variolation rapidly fell into disuse in favour of vaccination and was banned in England in 1849 because of the risk of spreading contagion[17, 18].

Despite evidence of efficacy there was opposition and resistance to vaccination since its very beginning. Fears were such that vaccinations would lead to minotaurization (the development of cattle-like features in humans)[19, 20]. At the time, anti-vaccination proponents also claimed that vaccines could cause tuberculosis, syphilis, blood poisoning, diabetes, and a host of other diseases. Serious opposition was based on concerns about infections through bacterial contamination of the vaccines or the equipment. These fears were not unfounded and unsanitary conditions used to produce vaccine and vaccinate commonly led to infections, which resulted in morbidities and mortalities. Despite errors, many controversies and proliferation of anti-vaccination groups, there was swift adoption of vaccination[20]. By 1821, vaccination was required by law in Bavaria, Norway, Sweden, and Denmark. In 1853, England rendered primary vaccination of infants compulsory with a penalty of 20 shillings for noncompliance[11].

The Montreal Experience

Montreal has a long history of divisive views on vaccination, split along linguistic lines, and by clergy and physicians, that began with the smallpox epidemic of 1885.

By 1880, vaccination had been available in Canada for more than 50 years[21]. In Montreal, municipal vaccinators had been offering free vaccines to the underprivileged since 1862. Unfortunately, at the dawn of the 1885 smallpox outbreak most of the population remained unvaccinated [21].

In Montreal, disease incidence divided the population. Several factors played into this divide; Anglophones were well accustomed to the practice of vaccination and wealthy Francophones were able to vaccinate and treat cases of smallpox in the privacy of their own homes. The poor

working class, already sceptical of any government interventions, were largely unreceptive to preventive actions. Importantly, there were serious economic reasons for under-immunization in this population. Prevention was costly, due to inadequate numbers of public vaccinators, and temporary unemployment from illness meant starvation. Thus, cases of smallpox were hidden to avoid hospitalization and quarantine[21]. Most interestingly, the lower-class French Canadians held a somewhat fatalistic approach to disease; believing that surviving the scourge led to an overall strengthened state. Mothers went so far as to intentionally expose children, as they understood surviving the disease would impart immunity[21]. Of the thousands that died during the epidemic, a disproportionate number were poor French Canadians.

The media, religious leaders and even physicians played a large role in both promoting vaccination and propagating anti-vaccination sentiment[21, 22]. The English media often sided with businessmen who wanted their employees vaccinated to keep up productivity; often overstating the benefits of vaccination[21]. In contrast the French media focused on reporting episodes of adverse events associated with contaminated vaccine and the unsanitary conditions under which they were administered. Clergy and some doctors rejected vaccination on both medical and ideological grounds, favouring sanitary and environmental improvements to curb the epidemic. Lastly, at the beginning of the epidemic, there was an extended period during which a lack of leadership and general apathy from municipal public health resulted in prolonged inaction to halt the epidemic. When mandatory vaccination was proposed, the absence of a compulsory birth registry made enforcing vaccination next to impossible[21].

The epidemic ended by the close of 1885 but not without riots and civil unrest, opposing mandatory immunization. Most notable, was the failure of public health to vaccinate upward of 30-40,000; most of them children from lower class families[21, 22].

Over a century after the 1885 smallpox epidemic, Quebec experienced in 2011, the largest measles outbreak in a decade [23]. Despite a robust provincial public health system offering free or low cost immunization, there were 21 imported cases of measles of which four resulted in an outbreak of 725 local cases. The majority of cases were unvaccinated or under-immunized [23]. Vaccination is still not mandatory in the province of Quebec and there is not yet a fully functional province-wide vaccine registry[24].

The present

More than 200 years since Jenner first tested his vaccine and a century since the smallpox epidemic in Montreal, the issues surrounding the decision to vaccinate and the implications of not vaccinating remain considerably similar. Some common and important factors that influence vaccination are largely: socio-economic, media, culture, leadership, and vaccine materials and ingredients. Therefore, it is imperative to address caregiver concerns and gaps in user knowledge with the aim to increase voluntary uptake of preventive care in our ever interconnected and globalized world.

In 1967, the World Health Organization (WHO) launched the global initiative for the eradication of smallpox. Under the guidance of D. H. Henderson, the WHO recruited thousands of healthcare providers to organize a comprehensive network for efficient reporting, containment of outbreaks, and distribution of vaccine[20]. On October 26, 1977, the last naturally occurring

case of smallpox was reported, and on December 9, 1979, the WHO's Global Commission for the Certification of Smallpox Eradication decreed that smallpox had been eradicated[11].

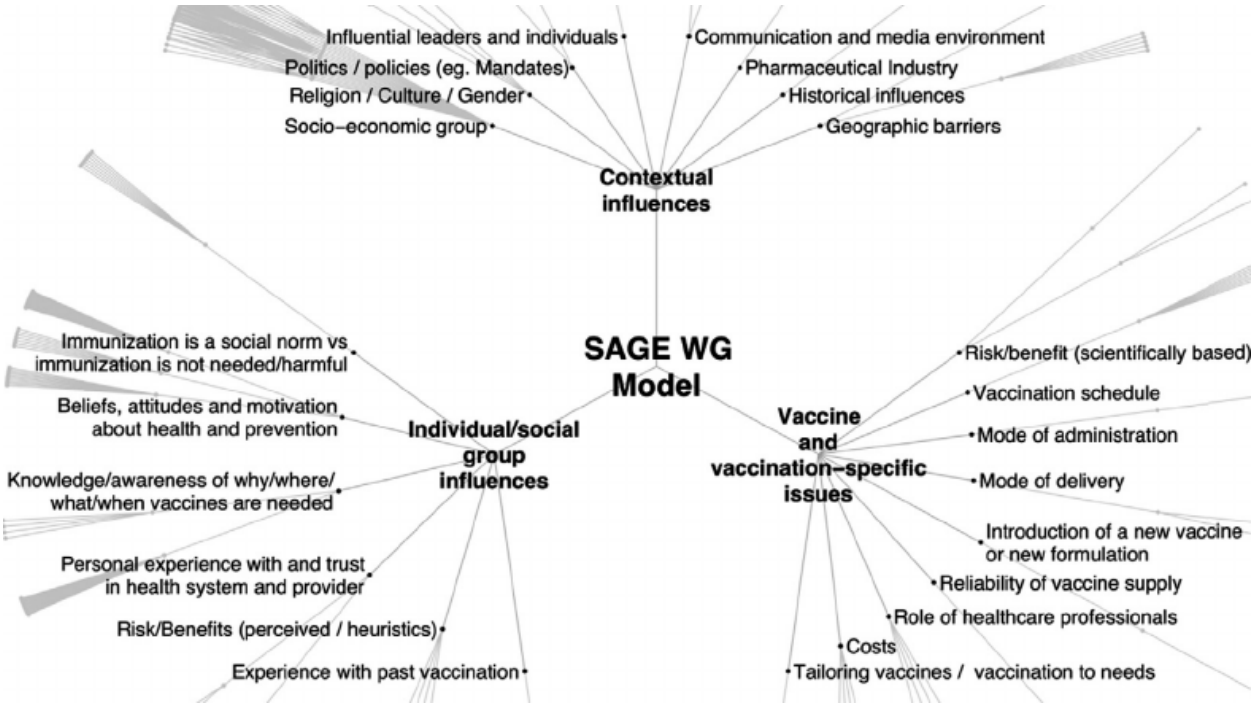
The Strategic Advisory Group of Experts (SAGE) on Immunization was established by the Director-General of the WHO in 1999. SAGE is the principal advisory group to WHO for vaccines and immunization. It is tasked with advising WHO on overall global policies and strategies, ranging from vaccines and technology, research and development, to delivery of immunization and its linkages with other health interventions. In 2012, recognizing the growing global importance of waning vaccine acceptance and uptake, a working group was mandated to examine the evidence and provide advice to SAGE on how to address vaccine hesitancy[25]. Childhood immunizations are often delayed well past the recommended ages leaving children vulnerable to preventable illness. Caregiver attitudes and beliefs can be broken down into acts of complacency, convenience, and hesitancy[26]. *Vaccine complacency* is where the perceived risks of vaccine-preventable diseases are low and vaccination is not thought to be a necessary preventive action[26]. *Vaccination convenience* exists where the decision to vaccinate is dependent on the quality of the service (real and/or perceived) and delivery at a time and place that is considered appealing, affordable, convenient and comfortable[26]. When caregivers choose not to vaccinate or delay vaccination, despite availability of immunization service, it is called *vaccine hesitancy[5]*. The following are a few key definitions that drive research into this area of cultural epidemiology.

- "Vaccine hesitancy is a term used to describe refusal or delay in regular immunization schedules due to concerns about vaccination" PHAC[27]

- "Vaccine hesitancy is present when vaccine acceptance is lower than would be expected in the context of information provided and the services available" Dubé, E., et al.[28]

Building on the above definition, the working group also drafted a "Model of determinants of vaccine hesitancy" (Fig. 1) organized around three key domains: 1. *Contextual influences* that include historic, socio-cultural, environmental, health system/institutional, economic or political factors; 2. *Individual and group influences* that encompass influences arising from personal perception of the vaccine or influences of the social/peer environment; and, 3. Vaccine and vaccination-specific issues which are directly related to the characteristics of the vaccine or the vaccination process[8].

Figure 1[1] Model of determinants of vaccine hesitancy



[1] The SAGE Working Group [WG] "Model of determinants of vaccine hesitancy"][8] Larson HJ, Jarrett C, Eckersberger E, Smith DM, Paterson P. Understanding vaccine hesitancy around vaccines and vaccination from a global perspective: a systematic review of published literature, 2007-2012. Vaccine. 2014;32:2150-9.

Public confidence in vaccination is essential to the success of immunization programs in all corners of the world[29]. The work in this thesis, relates directly back to this model and the various spheres of influence associated with vaccination coverage and incomplete immunization. The scope of this thesis incorporates the relevant elements of this model in the context of high-income countries and in the analysis of a cohort of urban Quebec pre-schoolers. The systematic review aimed to summarize caregiver characteristics and healthcare usage. The Quebec cohort analysis aimed to compare findings in the systematic review to those caregiver characteristics available for analysis in the Quebec cohort database.

Chapter 3 manuscript 1: as submitted to BMJ-Archives of Disease in Childhood

Determinants of immunization status in pre-school children in high income countries: A Systematic Review

At the time of submission of this thesis, the following manuscript was submitted to BMJ-ADC

ABSTRACT

Background: In high-income countries, well-established immunization programs have resulted in the decrease of vaccine-preventable diseases. However, recent declines in vaccine uptake have been reported. We aimed to summarize characteristics and behaviors of caregivers associated with immunization statuses for pre-school children, in high-income countries.

Methods: We searched Ovid MEDLINE, Cochrane, Pubmed, Web of Science, Ebscohost: CINHAHL. We limited our review to articles published in English or French that reported data from January 1997 to May 2017 and used regression modelling where the outcome was immunization status with independent risk factors for complete, incomplete, or timely immunization.

Results: Of 4475 articles identified, 43 met inclusion criteria and were reviewed. We identified several core determinants found to be barriers to routine immunization: birth order or number of children (20 articles, 46.5%), low maternal education (11 articles, 25.6%) single motherhood (9 articles, 21%), younger maternal age (8 articles, 18.6%), high mobility (5 articles, 11.6%), and smoking (4 articles, 9.3%). Late initiation of immunization was associated with subsequent

incomplete immunization for age in 5 articles (11.6%). Usage of a healthcare or immunization provider, belonging to a racial or linguistic minority, and maternal employment were found to be inconclusive determinants of immunization status at this scale of analysis.

Conclusion: Determinants of vaccine uptake are complex and contextually driven. In high-income countries, immunization programs should adapt and provide outreach and education to ensure preventive care for families with multiple children, single mothers and mothers with low education as well as to mobile families with young children.

Introduction

Vaccination is one of the greatest public health achievements. Governments spend billions of dollars each year on vaccination programs to reduce the burden associated with vaccine-preventable diseases, making it a cornerstone in the effort to promote public health. Vaccination programs and new vaccines have contributed to significant declines in the occurrence of vaccine-preventable diseases and recently, the elimination of measles in the Americas [30]. Nevertheless, there is still notable heterogeneity in vaccination coverage globally. Furthermore, incomplete immunization may jeopardize or reduce the effect of new and established vaccines on the burden of disease[31].

The concepts of *vaccine hesitancy, convenience and complacency* are relatively recent and can be understood as a, " *delay in acceptance or refusal of vaccines despite the availability of vaccination services*", and is the most apt definition for this study setting[28]. Recent systematic reviews have been conducted at the global scale to identify common and country-specific determinants of vaccine hesitancy [8, 9, 31]. In parallel, the World Health Organization's (WHO) Strategic Advisory Group of Experts (SAGE) on Immunization, sponsored a global survey

of immunization providers to better understand the drivers of vaccine hesitancy in different settings[28]. The overarching conclusion of these studies was that determinants of vaccine uptake are complex and context-specific. Variations across time and geography, indicate a need to identify the locally relevant causal factors and to develop adapted strategies to address them.

Previous studies have identified factors associated with vaccination that are related to socio-economic contexts, family characteristics, health care providers and immunizers and child characteristics, such as prematurity [9, 32]. Given the complexity of factors associated with vaccine hesitancy, this systematic review aimed to narrow the scope of relevant determinants by reviewing literature from high-income countries. We hypothesized that grouping findings from countries with similar income profiles would account for some of the contextual factors identified by the SAGE working group such as: socio-economic factors, communications and media environments, and geographic barriers.

High-income countries represent 25% of all countries and are defined by the World Bank Lending Group as those with a gross national income (GNI) of > $ 12,736 [33]. One common characteristic of populations in high-income countries is the early adoption of internet technology. Reports emerged as early as 2002 indicating that 13% of American internet users had searched online for information about immunizations or vaccination[34]. Therefore, we were interested in scoping study populations that were exposed to internet search engine technology and social media; with Google and Facebook registered as a public domain in 1997 and 2006, respectively. Seminal literature describes exposure to anti-vaccine content viewed on the internet, depending on search terms and its influence on vaccine hesitancy [5, 35, 36]. The

shared characteristics and between-country similarity among high-income countries will allow for a large number of studies to be summarized and critically appraised. This review will bridge the knowledge gap by describing those determinants associated with incomplete immunization in high-income nations while concurrently identifying inevitable regional differences.

In keeping with the study rationale, the three objectives of this study were to:

1. Identify statistically significant caregiver characteristics associated with healthy pre-schooler's overall routine immunization status and to evaluate the impact of these determinants as barriers to complete immunization in a high-income setting.

2. Describe determinants that were inconclusive (i.e. that were identified as both barriers and promoters of immunization across the selected articles).

3. Identify the ways in which selected studies described vaccine hesitancy and differentiate between vaccine refusal and hesitancy.

Methods

This systematic review was written in accordance with the PRISMA guidelines[37]. The search strategy was developed on May 12, 2016 for Ovid MEDLINE (1946 to May 2016) and adapted across other disciplinary databases: Cochrane Library, PubMed, Web of Science, and CINAHL on EBSCOhost (1981 to May 2016) (Table 3.1 supplementary content.) Hand-searches of seminal articles and past systematic reviews were also conducted using database search terms. A search update was conducted on May 10, 2017.

Articles were included if they were in English or French. Studies needed to use multivariate regression analysis (logistic, Cox, or Poisson) to identify parental, social, healthcare or child characteristics that were significantly associated with complete or timely immunization. Studies that reported vaccination status of children up to and including age 6 were selected, as we expected many studies to evaluate pre-school immunization status at school entry. All study designs – prospective or retrospective – that collected data from January 1997 to present were included. Studies were excluded if they were unpublished or only provided abstracts, were published in a language other than English or French, and did not evaluate complete, incomplete, or timely immunization. Studies were excluded if they only evaluated immunizations schedules beyond the pre-school years or were from low- or middle-income countries. Studies were also excluded if they only analyzed pediatric populations with chronic illnesses or who were refugees. Studies that did not report 95% confidence intervals (CI) for the multivariable analyses were also excluded. Two researchers, SO and NF, independently assessed the eligibility of each study for inclusion in the systematic review. Conflicts were resolved by consensus or through a third reader.

Each reviewer conducted data extraction and quality assessment independently. Data were collected for the following study characteristics: country of study, year of study data collection, source of data, study design, sample size, vaccination series description, age of study population, parental/healthcare/child characteristics, effect measures and their 95% CIs. Articles were reviewed and data were extracted using Distiller SR software (DistillerSR, Evidence Partners, Ottawa, Canada). Study quality assessment was completed using the Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analyses[38].

Vaccination schedules differ across countries and age groups. We included original articles that assessed a vaccination schedule with at least two vaccine types and that described the age at vaccination, the vaccinations series, and the method of vaccination ascertainment. Completeness of basic vaccination schedules were described in each article according to regional recommendations.

Parental and caregiver characteristics

We collected descriptive information and effect measures for the following variables: socio-economic status (i.e. neighbourhood wealth index, family income, families receiving government aid), maternal employment, birth order or number of children, maternal and paternal education, racial or linguistic minority status, indigenous status, rural dwelling, high mobility before or after birth, parental smoking, maternal depression, maternal age and marital status, and prematurity. We additionally looked at factors associated with the following caregiver behaviors: breastfeeding, pre-natal care, preventive care for premature infants, delay in initiating immunization, and failure to co-administer vaccines.

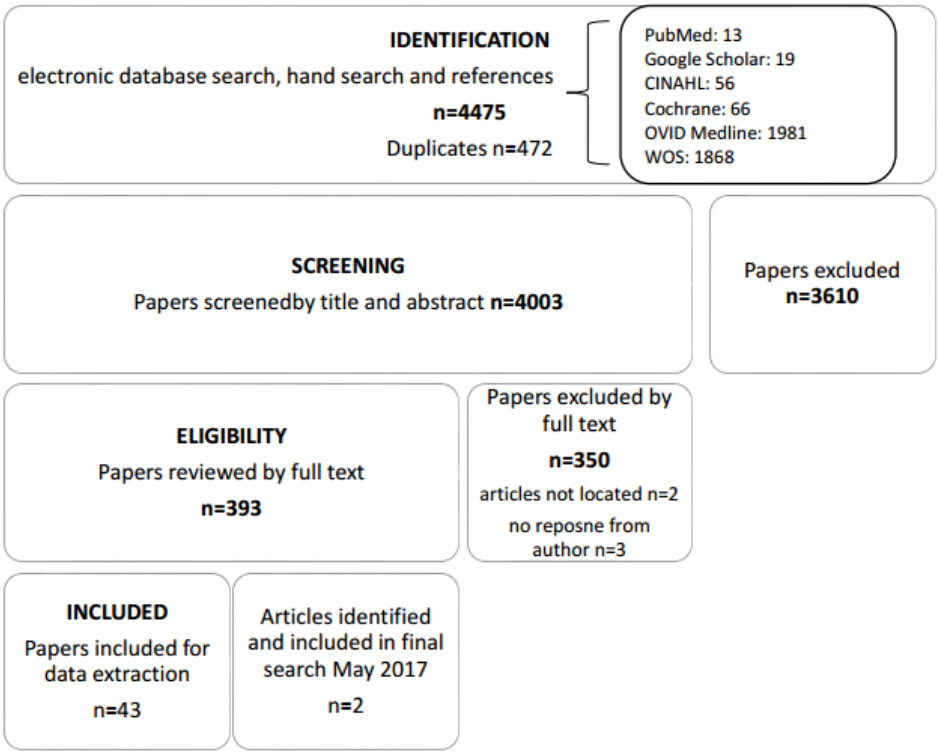
Finally, we collected data on healthcare service type or vaccination provider (i.e. public, private, pediatrician, family physician, and no usual care), and lack of insurance. The healthcare systems were categorized as mainly public, mainly private and mixed.

Risk factors and associated effect measures for incomplete immunization for age were reported by study type in forest plots. No meta-analysis was carried out due to high heterogeneity of the data. We hypothesized that the largest source of bias originated from non-objective ascertainment of vaccination status. Finally, selection bias was a potentially large source of bias, as the majority of the reviewed studies were cross-sectional in design.

Results

An initial search identified 4475 articles (Figure1). After removing duplicates (n=472) and articles that did not meet inclusion criteria (n=3610), 393 articles were included for full-text review. An additional 350 articles were excluded during the full-text review; of these, two could not be located through library services and three had missing information. Efforts to contact authors for clarification were unsuccessful. Two additional articles were identified in a final article search in May 2017, resulting in a total of 43 relevant articles for data extraction. Of these, 26 articles (59.1%) were cross-sectional, 14 (31.8%) were cohort studies, and three (7%) were case-control designs.

Figure 3.1 Study selection flow



Study Characteristics

Of the 43 studies selected, there was representation across 5 of the 6 inhabited continents: South America (Argentina n=1), Australia n=3, Europe (United Kingdom, n=2, Ireland, n=2, Greece, n=2, Germany, n=1, and Belgium, n=2), Asia (Japan, n=1) and North America (Canada, n=5 and United States n=24) (Table 3.2-Supplementary content)

Over half of the studies (n=24) were based in American populations. Of these studies, 15 analyzed a random sample of specific subsets of the National Immunization Survey (NIS) with data ranging from 1997 to 2012. The NIS is an ongoing, list-assisted, random-digit-dialing telephone survey[39]. The NIS provides annual estimates of vaccine coverage for children 19-35 months of age for each of the 50 states and 28 selected urban areas. The remainder of the studies used data from national cohort studies (n=13), hospital or insurance databases (n=9), regional immunization registries (n=4) and school/daycare surveys (n=2). Four papers assessed determinants associated with timeliness of vaccination, exclusively, whereas three papers assessed both timeliness and completeness. The remaining studies assessed completeness of the vaccination schedule.

Summary of results

Significant factors and their effect measures associated with immunization status and the quality assessment ratings in the 43 studies, summarized by study type can be found on Table 3.3-supplementary content.

Figures A-L, summarize and compare, through Forest plots, the most commonly identified factors associated with incomplete immunization. The family characteristics most frequently cited as barriers to complete or timely vaccination were an increasing number of children in the home (n = 20 articles, 46.5%) and low maternal education defined as ≤12 years of education (n

= 11 articles, 25.6%)[24, 40-61]. Among studies that reported an increasing number of children in the home as a barrier to immunization, 10 articles cited having 4 or more children in the home as a significant barrier to complete or timely immunization; three studies (two cohort and one case control), reported a three-fold increase in the odds of incomplete immunization for age. Cross-sectional studies (n=7), consistently demonstrated smaller effects (Fig. A). The effect measures of low maternal education can be seen in Fig. B, with one cohort study and ten cross sectional studies reporting up to a two and a half-fold increase in the risk of incomplete immunization for age [24, 40-61]. Single parenthood (never married/widowed or divorced), younger maternal age, and moving residence before or after birth were reported 9, 8, and 6 times respectively [40, 42, 44-48, 50, 52, 54, 55, 58, 62-66] as barriers to complete immunization. The majority of studies that evaluated the effect of single motherhood found a less than 50% increase in risk. One case control study found an almost four-fold increase in the risk of incomplete immunization for age among single mothers (Fig. C)[63]. The reference age varied for studies that reported maternal age as a factor in immunization uptake (Fig. D). For studies in which more than one age category was analyzed, there was a clear gradient of higher risk among the youngest age groups [55, 64]

Moving just before, or in, early infancy appears to have an impact on immunization status. Five articles found high mobility to be associated with incomplete immunization for age. One case control study found a four-fold increased risk of incomplete immunization, [65]while cohort and cross-sectional studies showed smaller but consistent effect measures (Fig. E).

Six articles reported that belonging to a racial or linguistic minority, as compared to Caucasian non-Hispanic or non-minority groups, was negatively associated with complete immunization

for age (Fig. F) [45, 47, 54, 55, 57, 67]. Four articles reported parental smoking as a barrier to immunization with up to a two-fold risk of incomplete immunization for age (Fig. G) [46, 55, 68, 69]. Low income status and maternal employment was reported as a barrier in 3 studies each (Figs. H and I) [43, 48, 50, 59, 63, 69]. Higher paternal education, rural dwelling, indigenous status, maternal depression, breastfeeding, and lack of daycare attendance were each reported once as being negatively associated with complete or timely immunization[40, 57-59, 69-71].

The behaviors most frequently associated with incomplete immunization were late initiation of immunization (five articles) and failure to co-administer vaccines (one article)[24, 63, 67, 68, 72]. In five studies, delay in initiating immunization, usually before three months old, was associated with a four- to nine-fold increase in the risk of not completing subsequent age-appropriate immunizations (Fig. J). Three cohort studies found a two-fold risk in incomplete immunization for age when there was a lack of pre-natal care (Fig. K). Two articles found prematurity to be a risk factor for incomplete immunization for age or timely immunization [55, 68, 72, 73].

There was no constant association found between usual healthcare provider or immunizer and that of a child's immunization status. Three studies (two American and one Belgian) found that being followed and immunized by a family physician was a barrier to complete immunization for age when compared to care from a pediatrician (n=2) and a public health clinic (n=1). Three studies (two American and one Canadian) also found that using a hospital clinic was a barrier to complete immunization for age when compared to private practices (n=2) and a public health clinic (n=1). Two American studies found that using a public health clinic for healthcare or immunizations was a barrier to immunization as compared to private practice. Lack of

insurance was found to be a barrier to complete immunization for age in four American studies (Fig. L) [52, 67, 68, 74]

Figure B

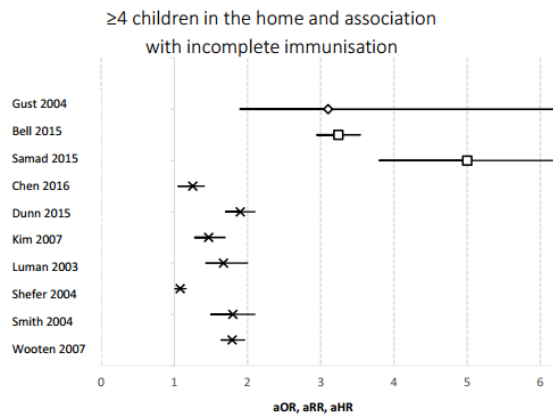


Figure C

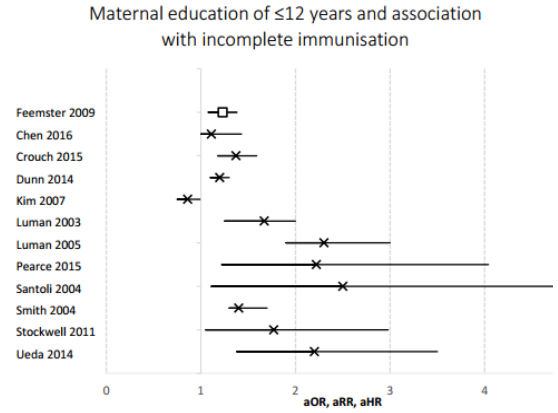


Figure D

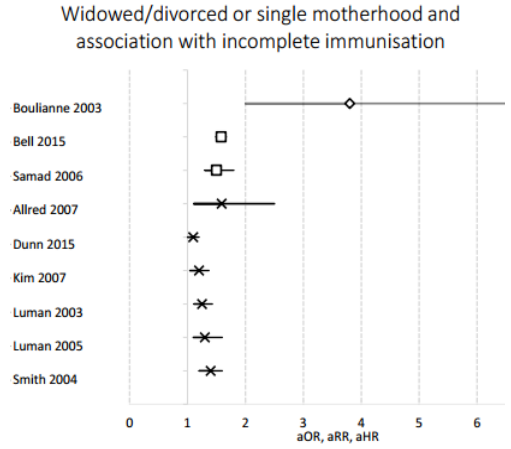


Figure E

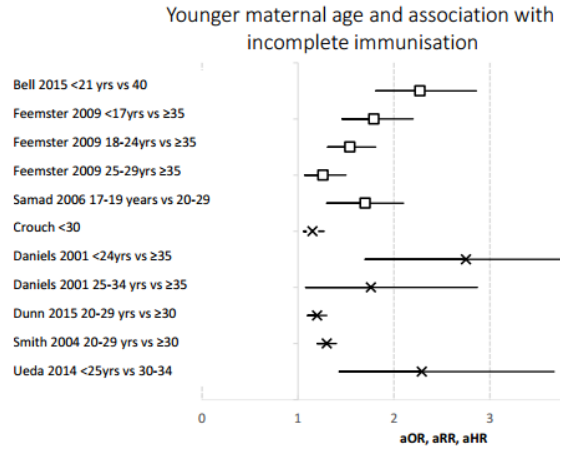


Figure F

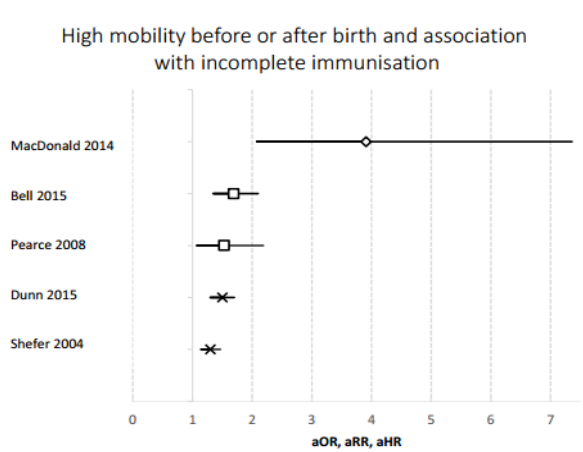


Figure G

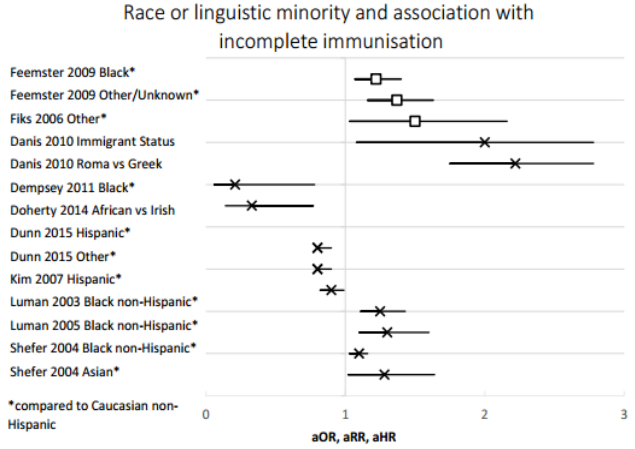


Figure H

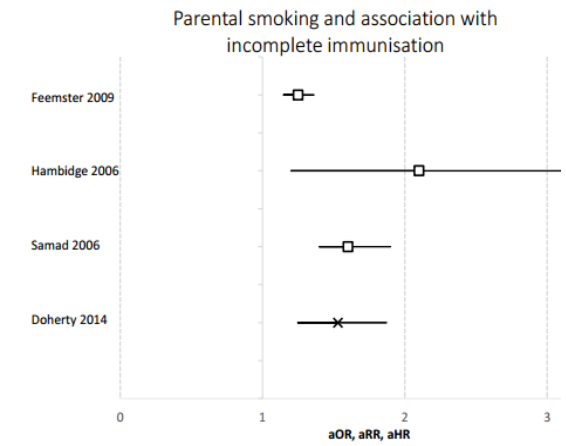


Figure J

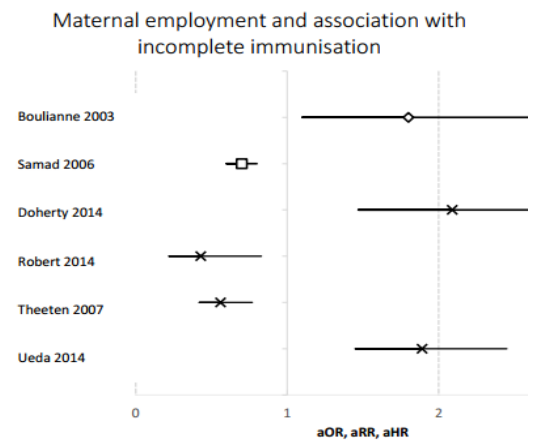


Figure L

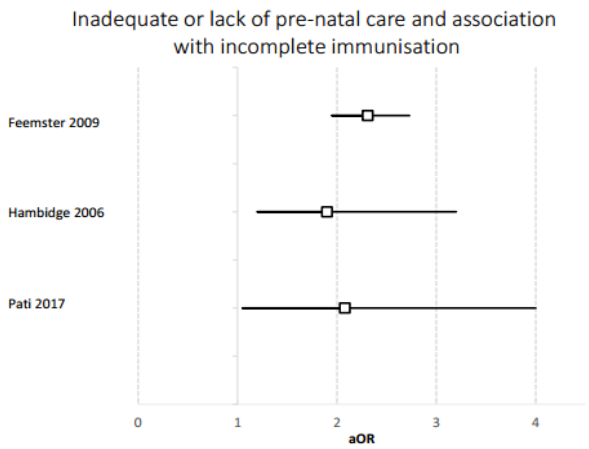


Figure I

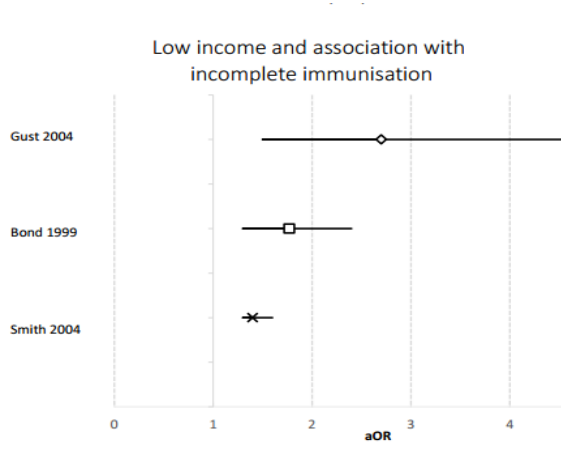


Figure K

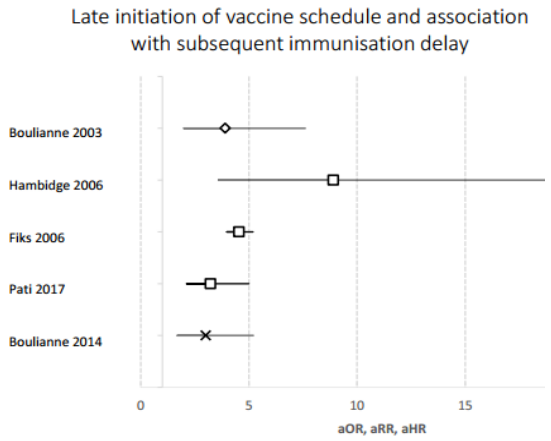
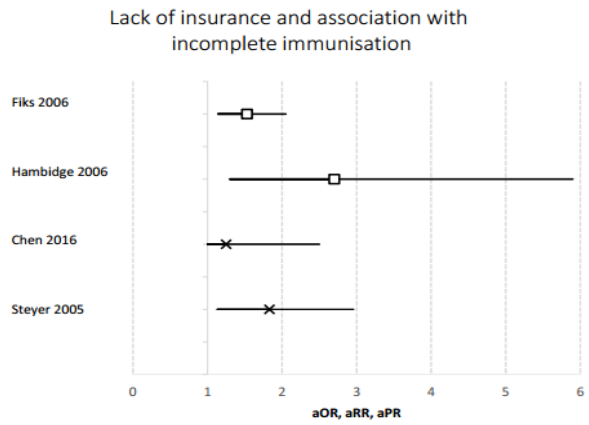


Figure L



Inconclusive determinants of incomplete immunization

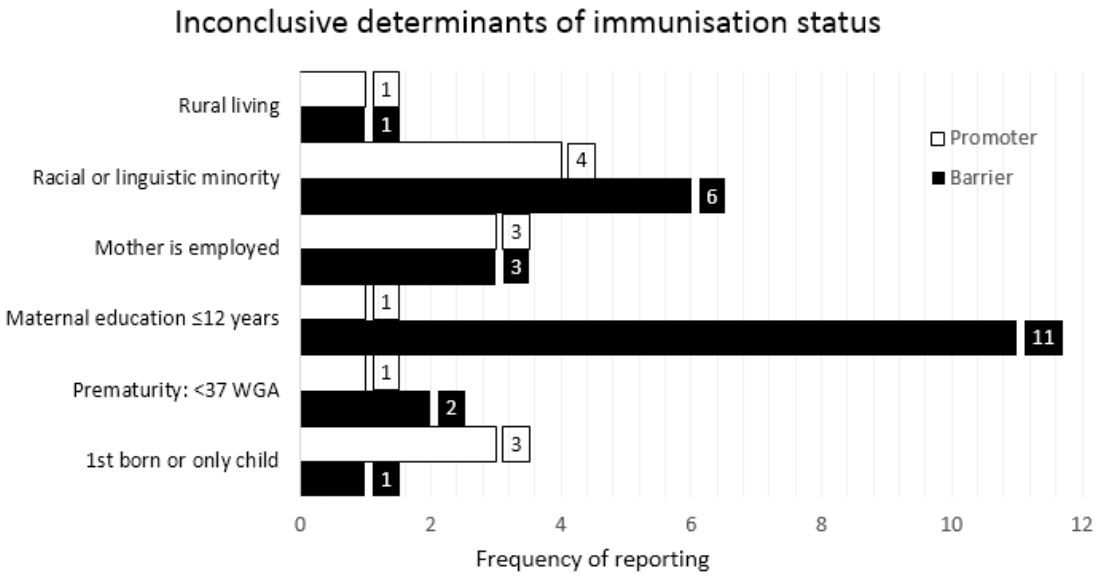
In keeping with the second study objective, we observed that several determinants reviewed in the studies were not conclusively found to be barriers or promoters of complete immunization for age (Figure 2). Ten studies evaluated the association between belonging to a racial or linguistic minority, as compared to Caucasian non-Hispanic or non-minority populations, on complete or timely childhood immunizations. Six studies (five American and one Greek), identified belonging to a racial/linguistic minority as a barrier to complete immunization [45, 47, 54, 55, 57, 67]. In contrast, four studies (three American and one Irish) reported a positive association between belonging to a racial or linguistic minority and complete immunization [42, 44, 69, 75].

Three studies each reported maternal employment as either a barrier or promoter for complete immunization. Studies in countries that reported a negative association between working mothers and complete immunization were Canada, Japan, and Ireland [50, 63, 69]. In contrast, working mothers were positively associated with immunization in 2 Belgian studies and one British [46, 76, 77].

Low maternal education was a barrier in 11 studies (n=10 USA, n=1 Australia) but a promoter in one American study[42, 44, 45, 47, 48, 52, 54, 55, 58-61]. Rural dwelling was split between two North American studies; a barrier in a Canadian study and a promoter in an American study [40, 51]. Three studies analysed the association between prematurity and complete or timely immunization. One American study and one Irish study found prematurity to a barrier to

complete immunization, while a second American study found a positive association between prematurity and complete immunization[67, 68, 73]. In two American and one Belgian study, being first born or an only child at time of study was found to be positively associated with immunization [76, 78, 79]. In contrast, one American study found being first-born to be a barrier to complete or timely immunization[58].

Figure 3.2 Inconclusive determinants of immunization status



Vaccine hesitancy key words in the review literature

To satisfy the third objective of this study, we asked if the term “vaccine hesitancy” or simply “hesitancy” was used in either the title or abstract of any of the selected articles. We found that none of the selected articles used these terms in either the title or abstract. We also assessed whether studies described the concept of vaccine hesitancy. We drew elements from Dubé et al ,[5] related to decision-making processes, risk perceptions, people or groups as influencers, and social barriers, to answer this question. We identified eight (18.2%) articles that met this

criterion (Table 5). Seven of the eight articles that described the phenomenon of vaccine hesitancy were published in the last ten years. Importantly, many studies aimed to distinguish between partial immunization and refusal.

Table 3 vaccine hesitancy as described in reviewed studies

Source	**Year**	**Quote from article text**
Smith et al.(USA)	*2004*	*"…determine the characteristics that distinguish unvaccinated children from under vaccinated children. This information is important in designing interventions that are tailored for differences between these groups… differences regarding safety concerns and people who are important in influencing parents' decision on whether to vaccinate their children."*
Feemster et al.(USA)[55]	*2009*	*"Despite unprecedented high levels of vaccination coverage rates for children, delays in receipt of vaccines according to the recommended schedule persist, especially in early childhood."*
Jessop et al. (Ireland)[73]	*2010*	*"Most studies have grouped partially and unimmunised children together, but recent work has found that there may be differences between these groups."*
Dempsey et al. (USA)[75]	*2011*	*"Increasing numbers of parents use alternative vaccination schedules that differ from the recommended childhood vaccination schedule for their children."*
MacDonald et al. (Canada)[65]	*2014*	*"…there is the potential to improve vaccine uptake among "children whose parents either are open to immunization but encounter barriers to obtaining vaccines or hesitate because of fears and concerns about safety."*
Bell et al.(Canada)[40]	2015	"*Typically, vaccination coverage is classified as either 'complete' or 'not-complete'. However, this system ignores the distinction between children whose parents have refused all vaccines and those who have received some but not all of the vaccines recommended for their age. Given that the latter group comprises the largest number of under-protected children, a better understanding of this cohort is essential. Parents of these children may be selectively opting out of specific vaccines or they may be starting the vaccine series, but failing to complete the recommended doses."*
Crouch et al. (USA)[58]	*2015*	*"This study explores some of the underlying variables that influence a family's choice to immunize their children in 2007"*
Pearce et al. (Australia)[59]	*2015*	*"Two broad groups of non-immunising parents are described in the literature. The first are 'conscientious objectors' or hesitant parents with concerns about immunization who may decline, delay or be selective in the vaccines they accept; these parents tend to be more*

		affluent and educated. The second group comprises families experiencing barriers to access, which may relate to social disadvantage and logistical barriers"

Risk of bias within studies

Non-objective exposure and outcome ascertainment was the largest threat to study quality. Five studies (11.4%) had non-objective vaccination status ascertainment: in three studies, parents reported the vaccination dates in the child's immunization booklet or, the study did not clarify who collected the data [50, 56, 57]. In one study, parents were shown an immunization booklet and asked which vaccines the child had received and another accepted the vaccination card or any other written proof of vaccination [41, 46]. This reporting bias was captured in the quality assessment via questions that dealt with ascertainment of exposure and validation of the study outcome.

Discussion

The principal aim of this systematic review was to summarize the results of available studies on the determinants of childhood immunization in high-income countries. We hypothesized that a large number of studies from high-income countries, that also share a common exposure to media influences, could be summarized to identify the most frequent determinants of incomplete immunization (intentional or not). A secondary aim was to discuss the determinants that remain inconclusive as either a barrier or promoter to the completion of routine childhood immunization.

Previous reviews in lower- and middle-income countries have identified that the most common barriers to immunization were often healthcare related in terms of accessibility, and that delays

were more protracted in rural areas compared to urban [31]. Equally, Gauri and Khaleghian,[80] found that the role of wealth inequality in child and maternal services varied by country and interestingly by the political model in developing countries. In contrast, our review found that the most common determinants were related to parental and caregiver characteristics and behaviors.

We identified several core determinants that were concluded to be barriers to routine immunization among the studies reviewed within high-income countries. This includes birth order or increasing number of children in the home, single motherhood, younger maternal age, smoking, and high mobility. The authors recognize that while we have identified these characteristics as risk factors they are not modifiable – with the exception of smoking, and therefore no intervention is possible to modify these characteristics. Nevertheless, having identified these barriers, adapted strategies built into national and regional immunization programs should facilitate access to preventive care for children of larger families, young mothers and single parents. Bell et al,[40] suggested that the combination of characteristics such as single marital status, young maternal age, large number of children, and multiple household moves are indicative of a potentially chaotic lifestyle. Further, that together these factors may be synergistic in nature and generate barriers to scheduling and attending vaccination appointments. Similar conclusions were drawn by MacDonald et al,[65] suggesting that high mobility may result in practical barriers, such as not knowing where to go for immunizations or not receiving appointment reminders, in addition to the challenging aspects of maintaining accurate immunization records. Another study by Dunn et al,[42] estimated immunization coverage among American military families. The authors also found that high

mobility was a significant determinant of delayed immunization after controlling for other important factors [40, 42, 47, 65, 66]. In contrast to the chaotic lifestyle theory, Dunn's findings highlighted that even with stable employment and access to medical services, families encountered obstacles to completing the standard immunization calendar when they were highly mobile in the early childhood years.

Low income was only found to be a significant barrier to complete immunization in three studies [48, 56, 81]. Although many studies included income as a covariate in their models, based on literature and findings from global studies, the authors were not surprised to find that income was not a common significant determinant of immunization in high-income countries. In their study of under-immunized African American children, Daniels et al,[64] failed to find an association between income and completion of immunization series. They suggested that in low-income settings, social interventions and education were key components to preventive care alongside of low- or no-cost vaccines [64]. Furthermore, several studies have shown that most deficits in immunization were a result of missed opportunities, rather than issues with access to [82-85]. This results of this review were consistent with these findings: five studies found that missed opportunities to initiate vaccination at two months of age, or failing to co-administer vaccines, were independent risk factors for incomplete immunization at a subsequent age [24, 63, 67, 68, 72]. Even after controlling for income, many studies reported that low maternal education remained a significant independent risk factor for incomplete immunization[42, 45, 48, 50, 52, 54, 55, 58-61]. Conversely, Polonijo and Carpiano,[86] proposed that vaccine knowledge was highly associated with maternal education. However, after controlling for receiving a recommendation from a healthcare professional, they found

that education was no longer a risk factor. Indeed, of the 11 articles that cited low maternal education as a risk factor, eight controlled for income or poverty level,[42, 44, 45, 48, 52, 58-60] but only three studies controlled for provider type [45, 55, 60]. Only one study included in our review found both low income and low education to be independent risk factors for incomplete immunization [48]. Furthermore, two studies controlled for healthcare or vaccine provider but not for income, where low maternal education was still found to be a significant barrier to complete immunization [50, 61]. One study by Santoli et al,[60] controlled for both income and health services and still found an independent association between low maternal education and immunization. These findings open up a new discussion on Polonijo and Carpiano's theory for diminished importance on low maternal education when we can account for provider influence[86].

Usage of several types of healthcare and/or immunization provider types was found to be a barrier to immunization. We found this variable to be the least homogeneous. Four countries reported significant findings for healthcare or immunization providers: Australia, Canada, Belgium and the USA. Except the USA, all countries share the characteristic of having a largely public healthcare system. In two American studies, the use of a public health clinic was negatively associated with complete or timely immunization compared to a private family practice [54, 55]. Conversely, in countries where the healthcare system is more accessible with less healthcare inequality, family physicians and hospital clinics were found to be barriers to complete immunization when compared to public health providers[24, 77]. This is not to imply that this is a result of poverty or marginalization, but instead illustrates the role of insurance coverage in mainly private healthcare models. A plausible argument can be made that the use

of retail clinics located in pharmacies and department stores in the US limits continuity of care, despite being less expensive for the uninsured along with offering flexible hours[87]. Indeed, our review found that four American studies reported a negative association between lack of insurance and complete immunization for age [52, 67, 68, 74].

The determinants reported in our findings that found inconclusive associations with a child's immunization status can largely be explained by individual or local behaviors and beliefs. Belonging to a racial or linguistic minority has been well studied among Hispanic Americans using NIS data[88]. A study examining vaccination coverage among children of Hispanic ancestry found that immunization practices varied largely by group[88]. This is consistent with this review, where racial or linguistic identity, as a determinant of immunization, was highly contextual. Eight out of ten studies describing the association between belonging to a racial or linguistic minority and complete immunization were American[42, 44, 45, 54, 55, 67, 75, 89].

Study quality was assessed using the Newcastle Ottawa scale of non-randomized studies. This scale assesses bias, based on a maximum star allocation for three main criteria: the selection of study groups, the comparability of study groups, and the ascertainment of either the exposure or outcome of interest for cohort, case-control and cross-sectional studies. Many of the articles included in our study used large populations in their analysis and therefore, we chose not to penalize these studies for not reporting sample size calculations. Conversely, with the majority of studies being cross-sectional in design, there is the potential for bias where non-responders systematically differed from respondents. We were largely able to capture this potential for bias through the assessment tool using smaller studies that reported response rates. Additionally, we expect that non-objective exposure and outcome ascertainment was

adequately captured in the quality assessment reporting. Overall, we found no reason to exclude any studies for poor quality.

Taken together, the findings of this review demonstrate that it is possible to narrow the lens on a particular context to identify common determinants of a health outcome. On the other hand, it is necessary to underline the important findings of previous work that soundly concluded that determinants of vaccine hesitancy are complex and highly contextual. In summary, we believe our review captured important, common characteristics and behaviors of caregivers in high-income countries as well as identifying lessor assessed determinants such as smoking, high mobility, prematurity, and maternal depression. Most notable is the lack of "*vaccine hesitancy",* as a key search term and that few studies attempted to differentiate groups in their immunization practices. Future reviews should seek to evaluate determinants among comparable groups in order to provide informative and actionable results for vaccine program developers. Finally, data collection should be expanded to include social networking habits. This information may provide an enhanced understanding of how parents seek and obtain information on vaccination and whether or not partial immunization is intentional or not.

There were several limitations in our review. Efforts were made to include all relevant material although review methods may not have captured all articles during the specified review period. As we were only able to review studies published in English or French, this may have resulted in the exclusion of other potentially relevant studies. Use of two independent reviewers and a third in case of non-consensus, and the use of a per protocol inclusion/exclusion criteria, assisted in minimizing any subjectivity.

Table 3.1 Database search strategy

1. vaccination/
2. "Patient Acceptance of Health Care"/
3. 1 and 2
4. ((vaccin* or immuniz* or immunis*) adj3 (parent* consent or decision making or uptake or hesita* or intent* or delay* or timely* or timeliness* or status* or characteristic* or choice* or accept*)).mp.
5. 3 or 4
6. exp child/; 7. child$.mp.;8. exp pediatrics/; 9. pediatric$.mp.; 10. paediatric$.mp.; 11. neonat$.mp.; 12. newborn$.mp.;13. new born$.mp.; 14. infan$.mp.; 15. bab$.mp.; 16. toddler$.mp.; 17. boy$.mp.; 18. girl$.mp.; 19. kid$1.mp.; 20. school$.mp.; 21. infan$.jw.; 22. child$.jw.; 23. pediatric$.jw.; 24. paediatric$.jw.; 25. exp parents/; 26. mother*.mp.; 27. maternal*.mp.; 28. parent*.mp.; 29. caregiv*.mp.; 30. legal guardian*.mp.;
31. or/6-30
32. 5 and 31
33. survey*.mp.
34. questionnaire*.mp.
35. "surveys and questionnaires"/ or health care surveys/ or health surveys/ or self report/
36. epidemiologic studies/ or exp case-control studies/ or exp cohort studies/ or controlled before-after studies/ or cross-sectional studies/
37. cohort.mp.
38. cross sectional.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
39. case control.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
40. 33 or 34 or 35 or 36 or 37 or 38 or 39
41. 32 and 40

Table 1.2 Characteristics of countries included in review

Continent	Country	Type of healthcare system Immunization program characteristics
South America	Argentina	Mixed[90, 91] • Immunization schedule contains 13 immunogens until 24 months • 2009 Immunization became required and offered free of charge • High vaccination rates (93-99%)
Australia	Australia	Mainly public[92] • Immunization schedule contains 12 immunogens until 24 months • Coverage for 2 year olds 92% to 93% until 2013. The rate has fallen to 89% in 2015 • Vaccination registry for <7 years of age
Europe	Belgium	Mainly public[77, 93] • Immunization schedule contains 12 immunogens until 24 months • Mandatory Polio vaccination • Child immunization against diphtheria, tetanus, pertussis and poliomyelitis have been stable at ~95% for last 30 years
	Germany	Mainly public[94, 95] • Immunization schedule contains 12 immunogens by 24 months • Nationwide monitoring of vaccination coverage at school entry
	Greece	Mainly public[96] • Immunization schedule contains 13 immunogens by 24 months • 3rd dose DTap 99.2% and MCV 98.9%
	Ireland	Mainly public[97] • Immunization schedule contains 13 immunogens by 24 months • Immunization programme for infants provided free of charge from birth to 13 months •
	United Kingdom	Mainly public[98] • Immunization schedule contains 13 immunogens by 24 months • Coverage >90% by 24 months
Asia	Japan	Mixed[50, 99] • 5 recommended immunogens covered free of charge 1993-2008
North America	Canada	Mainly public[6, 100] • Immunization schedule contains 12-13 immunogens by 24 months • Provincial and territorial ministries of health are responsible for a number of immunization and screening programmes • National survey conducted every 2 years to estimate coverage at ages 2, 7 and 17 years
	USA	Mainly private[101] • Immunization schedule contains 13 immunogens by 24 months • Preventive services (immunizations) offered free of charge to high risk groups • National Immunization Survey (NIS) provides annual estimates of immunization coverage for children 19-35 months

Table 3.3 summary of study finding and quality assessment by study type

Case control studies	**Country**	**Year(s) of data collection**	**Sample size**	**Statistical analysis**	**Age at outcome (vaccines)**	**RESULTS**	**Newcastle Ottawa Quality Assessment Scale**		
							Selection	**Comparability**	**Exposure**
Boulianne, N et. 2003	Canada	1998	696	Logistic regression	24 months(4 DTaP-Hib, 2 MMR)	**Incomplete immunization:** non-simultaneous immunization with 2nd MMR and 4th DTaP-Hib (aOR: 11.8, 95% CI 7.3-19.2); single parenthood (aOR: 3.8, 95% CI 2.0-7.2); 2 or more children (aOR: 2.3, 95% CI 1.5-3.7); age at first vaccine > 3 months (aOR: 3.9, 95% CI 2.0-7.6); responding parent works outside the home (aOR: 1.8, 95% CI 1.1-2.9)[2]	****	**	***
Gust, A.et al. 2004	USA	2001-2002	2,302	Logistic regression	19-35 months(≥2 of DTP/DTaP, HBV, and/or MCV)	**Incomplete immunization:** lower income bracket, $0-$30,000(aOR: 2.7, 95% CI 1.5-4.6); 4 or more children(aOR: 3.1, 95% CI 1.5-6.3)	****	**	**
MacDonald, E. et al. 2014	Canada	2008-2009	444	Logistic regression	2 years (4 DTaP-Hib 1 MMR, 1 varicella, 3 Men-C-C, 4 PCV 7)	**Delayed immunization:** moved in past 2 years(aOR: 3.91, 95% CI 2.08-7.36); regular family doctor or pediatrician(aOR: 0.22, 95% CI 0.06-0.85)	**	*	*
Cohort studies	**Country**	**Year(s) of data collection**	**Sample size**	**Statistical analysis**	**Age at outcome (vaccines)**	**RESULTS**	**Selection**	**Comparability**	**Outcome**

[2] Mothers were the responding parent 91% of the time

Alessandrini, E.A et al. 2001	USA	1994 -1997	513	Logistic regression	24 months (4 DTaP, 3 IPV, 4 Hib, 3 HBV, 1 MMR)	**UTD immunization:** first born (aOR: 2.28, 95% CI 1.45-3.60); adequate prenatal care (aOR: 2.24, 95% CI 1.44-3.48); private office based primary care (aOR:0.39, 95% CI 0.23-0.63)	****	*	***
Bell, C.A et al. 2015	Canada	2008-2010	43, 965	Logistic regression	2 years (4 DTaP-IPV-Hib, 4 PCV, 3 MennC, 1 MMR)	**Incomplete immunization:** not married (aOR: 1.58, 95% CI 1.49-1.67); highest income quintile (aOR: 0.91, 95% CI 0.84-0.98); maternal age is >40 compared to <21 years (aOR: 0.44, 95% CI 0.35-0.55); 4 or more children (aOR: 3.24, 95% CI2.95-3.54); 3 or more household moves (aOR: 1.69, 95% CI 1.35-2.10); rural dwelling (aOR: 1.16, 95% CI 1.09-1.24)	****	**	***
Feemster, K,A et al. 2009	USA	2002 - 2004	54,429	Logistic regression	90 days (≥1 DTaP, IPV, Hib, PCV)	**Delayed immunization**: maternal education vs some college or higher(< high school: aOR: 1.23, 95% CI 1.08-1.38); high school equivalent: aOR: 1.10, 95% CI 1.01-1.20); maternal age compared to ≥35(<17: aOR: 1.79, 95% CI 1.46-2.20; 18-24: aOR: 1.54, 95% CI 1.31-1.81; 25-29: aOR: 1.26, 95% CI 1.07-1.50); prenatal visits compared to ≥10 visits(no prenatal care: aOR:2.31, 95% CI 1.95-2.73; 1-4 visits: aOR: 2.11, 95% CI 1.89-2.40; 5-9 visits: aOR: 1.43, 95% CI 1.32-1.54); prenatal cigarette smoking(aOR: 1.25, 95% CI 1.15-1.36); birth order(2nd child: aOR: 1.57, 95% CI 1.43-1.72; ≥3rd: aOR: 2.08, 95% CI 1.90-2.28); healthcare service vs private pediatrician(hospital clinic: aOR: 1.54, 95% CI 1.12-2.12; family practice: aOR: 1.32, 95% CI 1.03-1.68; public health clinic: aOR: 2.02, 95% CI 1.42-2.88); identifies as Black compared to Caucasian(aOR: 1.22, 95% CI 1.07-1.40); is other/unknown compared to Caucasian(aOR: 1.37, 95% CI 1.16-1.63)	****	**	***
Fiks, A.G et al 2006	USA	2002- 2003	5,464	Logistic regression	24 months (4 DTaP, 3 IPV, 1 MMR, 3 Hib, 3 HBV)	**Delayed immunization:** delayed initiation of immunization(aOR: 4.54, 95% CI 3.98-5.19); prematurity(aOR: 0.40, 95% CI 0.23-0.68); uninsured(self-pay)(aOR:1.53, 95% CI 1.14-2.05); primary caregiver is nonparent(aOR: 1.39, 95% CI 1.10-1.76); other race compared to Caucasian(aOR: 1.50, 95% CI 1.03-2.16)	****	*	***
Guttmann, A et al. 2006	Canada	1997-2000	101,570	Logistic regression	2 years (4 DTaP-Hib, 1 MMR)	**UTD immunization:** neighborhood income quintile(lowest: aOR: 0.80, 95% CI 0.75-0.84; 2nd: aOR: 0.85, 95% CI 0.75-0.90; 4th: aOR: 1.05, 95% CI 1.00-1.10)	****	*	***

Hambidge, S.J et al 2006	USA	1998 - 1999	1,160	Logistic regression	12 months (3 DTaP, 3 IPV, 2 Hib, 3HBV)	**Incomplete immunization:** maternal smoking (aOR: 2.1, 95% CI 1.2-3.4); uninsured(aOR: 2.7, 95% CI 1.3-5.9); late prenatal care (aOR: 1.9, 95% CI 1.2-3.2); born <38 or > 42 WGA(aOR: 1.9, 95% CI 1.2-3.1); late starters-first vaccines at >2 months(aOR: 8.9, 95% CI 3.6-21.9)	****	*	***
Jessop, L. J et al. 2010	Ireland	2001-2007	749	Logistic regression	4-6 years (3 DTaP-Hib-IPV, 1 Men-C-C)	**Incomplete immunization:** prematurity <37 WGA (aRR: 4.63, 95% CI 1.23 to 17.3)	****	**	**
Koller, D et al 2009	Germany	2004	9,353	Logistic regression	6 years (9 vaccines consisting of MMR, DTaP, HBV, Men-C-C)	**Incomplete immunization:** <12 months kindergarten attendance (aOR: 1.34, 95% CI 1.09-1.63); high percent of low-education households by school district(aOR: 0.78, 95% CI 0.66-0.92)	****	**	**
Minkovitz, C.S et al. 2005	USA	1996 - 1997	4,874	Logistic regression	24 months (4 DTaP, 3 Polio, 1 MMR)	**UTD immunization:** maternal depressive symptoms at 2-4 months (aOR: 0.72, 95% CI 0.59-0.89)	***	**	**
Pati, S et al. 2011	USA	2006	506	Logistic regression	7 months (3 HBV, 2 polio, 2Hib, 3 PCV7, 3 DTaP)	**UTD immunization:** increasing maternal age(aOR:1.07, 95% CI 1.01-1.12); birth order compared to ≥3rd child(1st born:aOR:2.91, 95% CI 1.63-5.19; 2nd born:aOR:1.88, 95% CI 1.09-3.26); UTD immunization at 3 months(aOR:11.32,95% CI 6.04-21.21)	****	*	***

Pati, S et al 2017	USA	2007-2008	744	Logistic regression	24 months (4 DTaP, 3 polio, 1 MMR, 3 Hib, 1 Var, 4 PCV)	**UTD immunization:** prenatal care some or none of the time(aOR: 0.48, 95% CI 0.25-0.95); no usual health care location(aOR:0.17, 95% CI 0.08-0.37); UTD at 7 months(aOR:3.84, 95% CI 2.50-5.89); not UTD at 3 or 7 months(aOR: 0.31, 95% CI 0.20-0.47)	****	*	**
Pearce, A et al 2008	UK	2000 - 2003	18,261	Poisson regression	9 months (3 DTaP, 1 Men-C-C)	**Incomplete immunization:** moved more than twice(aRR: 1.53, 95% CI 1.07-2.19)	****	**	**
Samad, L et al. 2006	UK	2000-2002	18,488	Poisson regression	9 months (primary vaccines)	**Incomplete immunization:** maternal age vs 20-29 years (14-19:aRR:1.7, 95% CI 1.3-2.1; 30-39:aRR: 0.70, 95% CI 0.60-0.80; 40 or greater:aRR:0.40, 95% CI 0.20-0.80); number of children(2-3:aRR:2.3, 95% CI 1.9-2.8; 4 or more: aRR: 5.0, 95% CI 3.80-6.40); single parent(aRR:1.50, 95% CI 1.30-1.80); employed since birth(aRR: 0.7, 95% CI 0.60-0.80); maternal smoking(aRR: 1.60, 95% CI 1.40-1.90)	***	*	*
Turner, C et al. 2003	Australia	1997-1998	159	Logistic regression	6 months (age-appropriate 2, 4, 6 months vaccines)	**Incomplete immunization:** ≥3rd child (aOR: 4.01, 95% CI 1.09-14.78);	****	*	***
Cross-sectional studies	**Country**	**Year(s) of data collection**	**Sample size**	**Statistical analysis**	**Age at outcome (vaccines)**	**RESULTS**	**Selection**	**Comparability**	**Outcome**

Allred, N.J et al 2007	USA	2003-2004	5,400	Logistic regression	19-35 months (4 DTaP, 3 OIPV, 1 MMR, 3 Hib 3 HBV)	**UTD immunization:** never married (aOR:0.63, 95% CI 0.44-0.90)	***	**	***
Bond, L. et al. 1999	Australia	1997	1,779	Logistic regression	<48 months (4 DTP, 3 Hib, 3 OIPV, 1 MMR)	**Incomplete immunization:** low income (aOR: 1.77, 95% CI 1.3-2.4); ≥2 children (aOR: 1.83, 95% CI 1.2-2.7); doctor as immuniser (aOR: 1.32, 95% CI 1.0-1.8); **Delayed immunization:** low income (aOR: 1.47, 95% CI 1.2-1.9); ≥2 children (aOR: 2.92, 95% CI 2.1-4.1); doctor as immuniser (aOR: 1.54, 95% CI 1.2-1.96)	****	**	**
Boulianne, N et al. 2015	Canada	2014	986	Logistic regression	24 months (4 DTaP-Hib, 2 MMR, 3 PCV, 1 Men-C-C, 1 Varicella, 1 RV)	**Incomplete immunization:** first vaccines > 2month (15 mo: aOR: 3.0, 95% CI 1.4-6.6 ; 24 mo: aOR: 3.0, 95% CI 1.7-5.2); ≥ 3rd child(15 mo: aOR: 2.0, 95% CI 1.0-4.3; 24 mo: aOR: 2.0, 95% CI 1.2-3.5); immunization at medical of hospital clinic at 15 mo(aOR: 2.1, 95% CI 1.0-4.3); received first vaccines elsewhere than CLSC at 24 mo(aOR: 1.86, 95% CI 1.1-3.2)	*****	**	***
Chen, W et al. 2016	USA	2008	4,160	Logistic regression	19-35 months (4 DTaP, 3 OIPV, 1 MMR, 3 Hib 3 HBV, 1 Var, 4 PCV7	**UTD immunization**: ≥4 children(aPR: 0.8, 95% CI 0.71-0.95); maternal education <high school (aPR: 0.9, 95% CI 0.7-1.0); uninsured (aPR: 0.8, 95% CI 0.7-1.0); family mobility (out of state move: aPR: 0.8, 95% CI 0.7-1.0: in-state move: aPR: 0.9, 95% CI 0.8-1.0)	***	*	***
Crouch, E et al. 2015	USA	2007	14,951	Logistic regression	preschool age (age appropriate vaccines)	**Complete immunization:** maternal education vs college graduate(<12 years of school: aOR: 0.73, 95% CI 0.63-0.84; 12 years of school: aOR, 0.77, 95% CI 0.69-0.86; >12 years of school: aOR: 0.81, 95% CI 0.74-0.89); first born child(aOR:0.82, 95% CI 0.76-0.88); maternal age <30 years (aOR: 0.87, 95% CI 0.79-0.94)	****	**	***

Daniels, D et al. 2001	USA	1999	3,467	Logistic regression	19-35 months (4 DTaP, 3 OIPV, 1 MCV, 3 Hib)	**Incomplete immunization:** maternal age vs ≥35 years (24 year or less; aOR: 2.75, 95% CI 1.70-4.47; 25-34 years: aOR 1.76, 95% CI 1.08-2.87);	*****	**	***
Danis, K et al. 2010	Greece	2004-2005	3,434	Logistic regression	6 years (5 DTaP, 4 Hib, 4 IPV, 2 MMR, 3 HBV, 3 MCV, 4 PCV, 1 Var)	**Complete immunization:** ≥3 children (aRR: 0., 95% CI 0.59-0.85); maternal age at birth 25 years or more (aRR: 1.26, 95% CI 1.03-1.54); immigrant status vs non-minority population(aRR: 0.50, 95% CI 0.36–0.93); Roma vs non-minority population(aRR: 0.45, 95% CI 0.36–0.57); **Timely immunization:** number of children(1-2: aRR: 0.89, 95% CI 0.81-0.98; ≥3 children: aRR: 0.67, 95% CI 0.53-0.84); paternal education vs < 9 years(12 years: aRR: 1.18, 95% CI 1.02-1.35; college/university graduate: aRR: 1.23, 95% CI 1.07-1.42); immigrant status vs non-minority population(aRR: 0.38, 95% CI 0.28–0.51); Greek Muslim vs non-minority population(aRR: 0.66, 95% CI 0.50–0.88); Roma vs non-minority population(aRR: 0.13, 95% CI 0.06–0.52)	****	**	*
Dayan, G.H et al. 2004	Argentina	2002	1,391	Logistic regression	13-59 months (1 BCG, 3 polio, 3 DTP, 3 Hib, 1 MMR, 3 HBV)	**Incomplete immunization:** birth order(2nd child: aOR: 1.58, 95% CI 1.14-2.19; 3rd or later child: aOR: 1.87, 95% CI 1.33-2.63)	*****	*	**
Dempsey, A.F et al 2011	USA	2010	748	Logisitic regression	6 months to 6 years (CDC immunization schedule)	**Incomplete immunization:** no regular health care provider(aOR: 18.66, 95% CI 6.13-56.80); identifies as Black compared to Caucasian(aOR: 0.21, 95% CI 0.06-0.78)	**	**	**
Doherty, E et al. 2014	Ireland	2008-2009	9,851	Logistic regression	6 months (3 DTaP-Hib-HBV, 2 PCV, 2 Men-C-C)	**Incomplete immunization:** private health insurance(aOR:0.67, 95% CI 0.52-0.86); child currently breastfed(aOR:1.95, 95% CI 1.47-2.59); mother self-employed(aOR: 2.09, 95% CI 1.47-2.98); mother unemployed or on disability(aOR: 0.51, 95% CI 0.29-0.91); mother smokes(aOR:1.53, 95% CI 1.25-1.87); Mother's ethnicity is African Irish(aOR: 0.33, 95% CI 0.14-0.77); Mother's ethnicity is Asian vs Irish(aOR: 0.32, 95% CI 0.12-0.86)	****	**	***

Dunn, A.C et al. 2015	USA	2007-2012	103,807	Logistic regression	19-35 months (4 DTaP, 3 IPV, 3 Hib, 3 HBV, 1 MCV, 1 var)	**Incomplete immunization:** maternal education vs college graduate(12 or less years: aOR: 1.2, 95% CI 1.1-1.3; >12 years: aOR: 1.1, 95% CI 1.1-1.2); maternal age group 20-29 years vs ≥ 30 years (aOR: 1.2, 95% CI 1.1-1.3); never married/widowed/divorced/separated(aOR:1.1, 95% CI 1.0-1.2); number of children(2-3: aOR: 1.3, 95% CI 1.2-1.4; 4 or more: aOR: 1.9, 95% CI 1.7-2.1); living in a state other than birth state(aOR: 1.5, 95% CI 1.3-1.7); identifies as Hispanic compared to Caucasian non-Hispanic(aOR: 0.80, 95% CI 0.80-0.90); identifies as other compared to Caucasian non-Hispanic(aOR: 0.80, 95% CI 0.80-0.90)	*****	**	***
Kim, S.S et al. 2007	USA	2003	11,860	Cox proportional hazard regression	19-35 months (4 DTaP, 3 IPV, 1 MCV, 3 Hib)	**Complete immunization:** maternal education < high school vs college(aHR: 1.16, 95% CI 1.01-1.33); number of children(2-3: aHR: 0.85, 95% CI 0.79-0.91; 4 or more: aHR: 0.68, 95% CI 0.59-0.78); mother divorced/separated/widowed (aHR: 0.83, 95% CI 0.73-0.96); never married: aHR: 0.86, 95% CI 0.76-0.96); identifies as Hispanic compared to Caucasian non-Hispanic(aHR: 1.11 95% CI 1.01, 1.22)	*****	**	***
Luman, E.T et al. 2003	USA	2000 - 2001	21,212	Logistic regression	19-35 months (4 DTaP, 3 IPV, 1 MCV, 3 Hib, 3 HBV)	**UTD immunization:** divorced/separated/widowed(aOR:0.80, 95% CI 0.70-0.90); maternal education vs college graduate(< high school: aOR: 0.60, 95% CI 0.50-0.80; high school: aOR: 0.70, 95% CI 0.60-0.80; > high school: aOR: 0.80, 95% CI 0.70-0.90); number of children(2-3: aOR: 0.80, 95% CI 0.70-0.90; 4 or more: aOR: 0.60, 95% CI 0.50-0.70); identifies as Black non-Hispanic compared to Caucasian non-Hispanic(aOR: 0.80, 95% CI 0.70-0.90)	****	**	***
Luman, E.T et al. 2005	USA	2003	14,810	Logistic regression	24 months ((4 DTaP, 3 IPV, 1 MCV, 3 Hib, 3 HBV)	**Delayed immunization:** not married(aOR: 1.3, 95% CI 1.1-1.6); maternal education vs college graduate(< high school: aOR: 2.3, 95% CI 1.9-3.0; high school: aOR: 1.7, 95% CI 1.4-2.1); > high school: aOR: 1.5, 95% CI 1.2-1.8); ≥2 children(aOR: 1.8, 95% CI 1.5-2.2); public immunization provider vs private(aOR: 1.6, 95% CI 1.3-1.9); identifies as Black non-Hispanic compared to Caucasian non-Hispanic(aOR: 1.3, 95% CI 1.1-1.6)	*****	**	***
Pavlopoulou, I.D et al. 2013	Greece	2010-2011	731	Logistic regression	12 months (3 DTaP, 3 IPV, 2-3 Hib, 3 HBV, 2-3 Men-C-C, 3 PCV7)	**Timely immunization:**2 children vs 1(aOR:1.64, 95% CI 1.03-2.62)	****	*	***

Pearce, A et al. 2015	Australia	2004	3,241	Poisson regression	7-11 months (2,4 6 month primary vaccines)	**Incomplete immunization:**7-11 months: maternal education vs a degree(< 10 years:aRR:2.22, 95% CI 1.22-4.04; certificate:aRR:1.62, 95% CI 1.07-2.45); Aboriginal and Torres Strait Islander(aRR: 1.73, 95% CI 1.03, 2.91)	***	**	**
Robert, E et al. 2014	Belgium	2012	1,057	Logistic regression	18-24 months (4 DTaP, 3 PCV, 1 MMR, 1 Men-C-C)	**Complete immunization:** parity of 1 in Wallonia(aOR 2.0, 95% CI 1.1-3.6); attendance at maternal and child clinic in Wallonia and Brussels(aOR:3.2, 95% CI 1.9-5.4 and aOR: 4.6, 95% CI 2.7-7.8); maternal employment full time, self-employed in Brussels(aOR: 2.3, 95% CI 1.2-4.6)	****	**	***
Santoli, J.M et al 2004	USA	2000	735	Logistic regression	19-35 months (4 DTaP, 3 IPV, 1 MCV, 3 Hib, 3 HBV)	**UTD immunization:** maternal education less than high school compared to > high school(aOR: 0.40, 95% CI 0.20-0.90); usual setting for healthcare is hospital clinic compared to private practice(aOR: 0.30, 95% CI 0.10-0.80)	****	**	***
Santoli, J.M et al 1999	USA	1997	21,522	Logistic regression	19-35 months (4 DTaP, 3 polio, 1 MMR, 3 Hib)	**UTD immunization**: vaccinated by pediatricians vs family physician(aOR: 1.63, 95% CI 1.46-1.82)	****	**	***
Shefer, A et al. 2004	USA	1999 - 2000	23,065	Logistic regression	19-35 months (4 DTaP, 3 polio, 1 MMR, 3 Hib)	**UTD immunization:** maternal education <12 years vs college graduate(aRR: 0.90, 95% CI 0.82-0.98); number of children(2-3:aRR: 0.90, 95% CI 0.86-0.95; 4 or more: aRR: 0.92, 95% CI 0.86-0.99); moved from different state(aRR: 0.77, 95% CI 0.68-0.88); compared to Caucasian non-Hispanic(Black non-Hispanic: aRR: 0.91, 95% CI 0.86-0.97; Asian: aRR: 0.78, 95% CI 0.61-0.98)	****	**	***

Smith, P.J et al. 2004	USA	2001	21,163	Logistic regression	19-35 months (4 DTaP, 3 polio, 1 MMR, 3 Hib, 1 Var)	**incomplete immunization:** marital status vs married (widowed/divorced/seperated:aOR:1.4, 95% CI 1.2-1.6; never married: aOR: 1.3, 95% CI 1.1-1.5); maternal education vs college graduate(<12 years:aOR:1.4, 95% CI 1.3-1.7; 12 years: aOR: 1.5, 95% CI 1.3-1.6; >12 years: aOR: 1.3, 95% CI 1.2-1.5); maternal age group 20-29years vs ≥ 30 years or (aOR: 1.3, 95% CI 1.2-1.4); annual income <$75,000(aOR:1.4, 95% CI 1.3-1.6); number of children(2-3: aOR: 1.3, 95% CI 1.1-1.4; 4 or more: aOR: 1.8, 95% CI 1.5-2.1); moved from a different state(aOR: 1.3, 95% CI 1.1-1.5)	*****	**	***
Steyer, T.E et al. 2005	USA	1993-2001	~12,000	Logistic regression	3-71 months (age appropriate DTaP, IPV, MMR, Var, Hib, HBV)	**Delayed immunization:** uninsured(aOR: 1.83, 95% CI 1.13-2.96)	***	**	**
Stockwell, M.S et al. 2011	USA	2007 - 2008	392	Logistic regression	2-36 months (age appropriate DTaP, IPV, MMR, Var, Hib, HBV)	**Incomplete immunization:** maternal education ≤high school vs >high school(aOR: 1.77, 95% CI 1.05-2.98)	***	*	***
Theeten, H et al. 2007	Belgium	2005	1,354	Logistic regression	18-24 months (4 IPV, DTP and Hib, 3 HBV, 1 MMR, 1 Men-C-C	**Complete immunization:** main vaccinating practitioner vs pediatrician(well-baby clinic: aOR: 3.0, 95% CI 2.00-4.70; family physician: aOR: 0.30, 95% CI 0.20-0.60); **Timely immunization:** main vaccinating practitioner vs pediatrician(well-baby clinic: aOR: 2.4, 95% CI 1.70-3.40; family physician: aOR: 0.30, 95% CI 0.20-0.60); maternal employment full time(aOR: 1.80, 95% CI 1.30-2.40)	****	**	**
Ueda, M. et al 2014	Japan	2011	1727	Logistic regression	36 months (1 BCG, 2 OIPV, 4 DTaP)	**Incomplete immunization:** maternal education vs college degree(<high school: aOR: 2.20, 95% CI 1.38-3.50; 2 year college: aOR: 0.63, 95% CI 0.50-0.80); maternal age <25 years vs 30-34(aOR: 2.29, 95% CI 1.43-3.67); worked after birth with and without maternity leave(aOR: 1.89, 95% CI 1.45-2.45 and aOR:2.89, 95% CI 2.49-3.31); not first born child(aOR: 1.42, 95% CI 1.17-1.73)	***	**	**

Wooten, K.G 2007	USA	1999-2003	43,730	Logistic regression	19-35 months (4 DTaP, 3 polio, 1 MMR, 3 Hib, 1 Var)	**UTD immunization:** >12 years of school(aOR: 1.27, 95% CI 1.19-1.35); income vs low middle income(middle income: aOR: 1.29, 95% CI 1.20-1.39; upper income: aOR: 1.36, 95% CI 1.22-1.52); rural dwelling(aOR: 1.14, 95% CI 1.06-1.23); married(aOR: 1.23, 95% CI 1.14-1.32); number of children(2-3: aOR: 0.81, 95% CI 0.76-0.85; 4 or more: aOR: 0.56, 95% CI 0.51-0.61)	*****	**	***

Chapter 4 Bridge

The first manuscript, a systematic review, revealed several core determinants that are associated with vaccine uptake and the immunization status of children in high-income countries. An increasing number of children in the home, single motherhood, maternal age, high mobility, late initiation of immunization, and smoking were the most common determinants associated with a child's immunization status. The study also revealed several determinants that were not conclusive and can most likely be attributed to being highly localized such as belonging to a minority group, healthcare service type and education levels. I was able to assure that when available, the same variables in the cohort dataset were assessed as associated factors of immunization in this secondary analysis. Most important was to identify where these core determinants converged as important in our cohort, and where they diverged to help to define factors unique to our population. Combined, these two manuscripts built an understanding of locally relevant determinants of immunization in metropolitan Quebec and a broader understanding of the most common determinants of immunization in high-income countries.

Chapter 5 Methods and foreword

Chapter 6 is the manuscript associated with a secondary analysis of a database created for the original study by M.K. Doll, observing temporal changes in pediatric gastroenteritis after the implementation of provincially funded rotavirus vaccination in Quebec [102-104]. Conducting a secondary analysis of this dataset represented a unique opportunity to assess vaccine coverage

and uptake practices in a cohort of Quebec pre-schooler that otherwise would not have been captured.

In this analysis, I used all available variables that were collected in the original study that are also found to be important in the broader literature and those identified in my systematic review. See Annex B for the variable coding scheme. See Annex C for additional model results graphics and model fit using C-statistic Area under the Curve analysis.

The following is the description of the study setting, ethic approval, patient recruitment, and data collection in the original study.

Study Setting and Ethics

Prospective, active surveillance for acute Rotavirus gastroenteritis (AGE) among children aged 8 weeks to less than 3 years was conducted at 3 teaching hospitals in Quebec: The Montreal Children's Hospital and Centre Hospitalier Universitaire Sainte-Justine, located in Montreal, and Centre Hospitalier Universitaire de Sherbrooke, located in Sherbrooke. The active surveillance protocol was approved by Research Ethics Boards at each hospital.

Patient Recruitment and Eligibility

Patients were eligible for inclusion if hospitalized or seeking emergency care for acute GE at a study location and their parent or legal guardian consented to be contacted for research purposes. Acute GE was defined as either (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 (for participants meeting any criteria) occurred ≤7 days of hospital presentation. Patients were

excluded from study participation if Rota virus (RV) vaccination was contraindicated, in accordance with the Quebec Immunization Protocol. Written consent to participate in active surveillance was obtained from a parent or legal guardian of all participants

Data Collection

Participant demographics, medical information, vaccination history and history of present illness were systematically collected via phone interview with the child's caretaker and review of medical records. Vaccination history, including vaccine type and date, was collected in reference to the participant's immunization booklet. Symptoms were ascertained as of the time of interview and included fever and duration of febrile illness; diarrhea, duration of diarrheal illness, and the maximum number of stools produced in a 24-hour period at the height of diarrheal illness; and vomiting, duration of vomiting illness and the maximum number of vomiting episodes in a 24-hour period at the height of vomiting illness. Medical records were used to ascertain information regarding hospitalization, a clinical history of dehydration, seizures, hematemesis, hematochezia, prematurity and presence of underlying conditions. Prematurity was defined as gestational age of less than 37 weeks at birth; underlying conditions were defined as documentation of any of the following underlying disorders: cardiovascular, respiratory, non-malignant hematologic, neurological, developmental, genitourinary, renal, gastrointestinal, hepatic, endocrine, nutritional, metabolic, inherited immunodeficiency, bone, joint, connective tissue or severe skin disorders. Stool samples from participants were collected ≤14 days after symptoms onset from specimens collected at home by the participant's parent/guardian or from stool retrieved during routine emergency or hospital care.

Chapter 6 manuscript 2: as published in Vaccine

Determinants of under-immunization and cumulative time spent under-immunized in a Quebec cohort

At the time of submission of this thesis, the following manuscript was published in Vaccine and cited as follows:

O'Donnell S, Dube E, Tapiero B, Gagneur A, Doll MK, Quach C. Determinants of under-immunization and cumulative time spent under-immunized in a Quebec cohort. Vaccine. 2017; 35:5924-31. doi.10.1016/j.vaccine.2017.08.072

Abstract

Background: Under-immunization refers to a state of sub-optimal protection against vaccine preventable diseases. Vaccine coverage for age may not capture intentional or non-intentional spacing of vaccines in the recommended provincial immunization guidelines. We aim to identify factors associated with coverage and under-immunization and to determine the number of days during which children were under-immunized during their first 24 months of life.

Methods: Secondary analysis of children ≤ 3 years recruited through active surveillance for gastroenteritis from three Quebec pediatric emergency departments from 2012-2014. Vaccination status for children at least 24 months of age was determined using provincial immunization guidelines. Cumulative days under-immunized were calculated for DTaP-VPI-Hib, PCV, MMR, and Men-C-C. Factors associated with up-to-date (UTD) status at 24 months of life and for under-immunization ≥6 months were analyzed using logistic regression.

Results: Of 246 eligible children, 180 (73%) were UTD by 24 months of life. The mean cumulative days under-immunized for MMR was 107 days, for PCV 209 days, for Men-C-C 145 days, and for DTaP-VPI-Hib 227 days. Overall, 149 children (60%) experienced delay for at least 1 vaccine. Factors associated with both an UTD status at 24 months and concurrently associated with being under-immunized ≥6 months, include timely initiation of the immunization (OR=5.85; 95% CI: 2.80-12.22) and (OR=0.13; 95% CI: 0.07-0.24), failure to co-administer 18-month vaccines (OR =0.15; 95% CI: 0.10-0.21) and (OR=3.29; 95% CI: 2.47-4.39), and having a household with ≥3 children under 18 years ((OR= 0.50; 0.28-0.86) and (OR=2.99; 1.45-6.22).

Conclusion: Paired with an unexpected low level of coverage at 24 months of life the majority of our cohort also experienced a state of under-immunization for a least one of the vaccines. Estimates of coverage do not capture intentional or non-intentional gaps in protection from vaccine preventable illness. Timely preventive care should be prioritized among this population.

Introduction

Evaluation of vaccination coverage is a key health indicator that is crucial to ensure that vaccination programs are reaching their objectives. In jurisdictions lacking a regional vaccine registry, studies that evaluate changes in coverage and timeliness, provide valuable information for targeted immunization strategies among specific groups [104]. Under the provincial immunization program, all recommended childhood vaccines are offered free of charge in public health clinics (CLSC), hospitals, and in physicians' offices. More than 75% of vaccinated children 0-4 years are vaccinated by public health nurses [24, 105]. Proof of vaccination or vaccination exemption is not required in Quebec to enter the education system. When looking

at the most recent Canadian childhood National Immunization Coverage Survey (cNICS), vaccination uptake by vaccine type at age 2 years in 2013 varied from 72%-91%. A 2014 proportionally representative survey study from Québec estimated full coverage at 24 months to be between 71%-85% [24].

Vaccination coverage is the standard measure to assess if recommended threshold for herd immunity has been met, by vaccine type. Coverage often does not consider the timeliness of doses and may underestimate periods of sub-optimal protection or absence of protection against vaccine preventable diseases, leaving children susceptible to illness in the event of an outbreak [23, 106-110]. Age-appropriate vaccination can be assessed by determining the age at vaccine dose, while the measure of delay may be categorized by cumulative time under-immunized [111]. Finally,coverage seldom distinguishes unvaccinated from undervaccinated children. This lack of distinction ignores the refusal of all vaccines, having received some, but not all, age-appropriate vaccines, and those who are fully vaccinated for age, but experienced serious delays [112]. Arguably, children who are not up-to-date (UTD) when coverage is assessed or who are under-immunized by spacing vaccines beyond recommended timing, represent a more important group to target than those who receive no immunization at all, and likely represent entirely different population [24, 65].

Several factors have been found to influence an UTD immunization status. Maternal age, marital status, low level of education, and large family size have been associated with a delay in complete vaccine coverage [40, 42, 43, 45, 47, 48, 50-52, 54, 55, 58-64, 113-118]. In contrast, higher levels of education and daycare attendance have been positively associated with complete immunization for age [113, 119]. Additionally, variables that relate to parental choice

or the parents' ability to organize, such as timely initiation of immunization and failure to co-administer 18 months vaccines (2nd dose MMR and 4th dose DTaP-IPV-Hib) are associated with a future immunization status [24, 63, 68, 72, 120, 121].

The behaviour of individuals or communities who delay vaccination is complex and determinants of these choices, context specific [8]. Without a vaccine registry, the unique opportunity to analyse the localized determinants of UTD immunization status and describe vaccination coverage at 24 months of age in pre-schoolers in two metropolitan areas in the province of Quebec, will provide valuable information to regional public health decision makers [8, 28]. To challenge the standard measure of vaccine coverage, our secondary objective was to evaluate the average number of days under-immunized for four vaccines: diphtheria and tetanus toxoids, acellular pertussis vaccine, poliovirus vaccine and *Haemophilus influenzae* type b vaccine (DTap-IPV-Hib), pneumococcal conjugate vaccine (PCV-7, 10 or 13), Measles, Mumps, and Rubella with one containing varicella (MMR (v)), and Meningococcal type C vaccine (Men-C-C). Finally, we determined factors associated with a cumulative delay of more than 6 months for one or more vaccines.

Methods

Study design:

This was a secondary analysis of a prospective, active surveillance study of children 8 weeks to 3 years of age, presenting to the emergency department for acute gastroenteritis (AGE) at 3 tertiary pediatric hospitals in the province of Quebec [102-104]. The aim of the original study in which the data was collected, was to examine the relative burden of pediatric gastroenteritis by

etiology and compare the clinical severity of rotavirus and norovirus cases after the 2011 implementation of publicly funded rotavirus vaccination program in Quebec. Recruitment and data collection took place between February 2012 and December 2014 with a total of 937 patients recruited. All recruited patients with immunization records were included in the current study. .

Data collection and variables

Participant demographics, medical information and vaccination history were systematically collected via phone interview with the child's caretaker. Vaccination history (vaccine type and date) was collected from the participant's immunization booklet. If the booklet was not available, parental permission was sought to contact vaccination provider to review records. History of prematurity (<37 weeks gestation) and presence of underlying conditions were coded as binary variables. The number of children in the home under the age of 18 years, in addition to the index child, was categorized as only index child, 2 children (index + 1) and, ≥2 (at least 2 + index). The age of parents at index child's birth was categorized into three groups, based on distribution, <26, 26-39, and >39 years as the reference. Parents' highest level of education was coded as <12 years of education, college, university and, graduate degree, the latter was used as the reference category.

We selected covariates for our model based on factors found in the literature to be associated with immunization practice in high-income countries. The first three characters (forward sortation area, FSA) of the residential postal code were used to determine the median household income using 2006 census data. Two hospitals were located in the Montreal Census

Metropolitan Area (CMA) with a population ~4 million and in the Sherbrooke CMA, with a population of >200,000. Two binary variables were created to assess initiation of vaccination at 2 months (with one month grace period) and to assess whether co-administration of the two recommended 18-month vaccines were associated with an UTD status at 24 months in accordance with the Quebec Immunization Protocol (PIQ) [24, 63, 67, 68, 79, 114, 122-125]. To allow all children equal time to receive vaccinations, only children 24 months and older were included. Patient's age was determined at phone call date, when immunization data was collected or if missing, at consent date. Patients were excluded if they reported underlying inherited immunodeficiency and neoplasm of any kind past or present, as this population's immunization needs differs from those of the healthy preschool population. We also excluded children with complete vaccination refusal, as they were likely to represent a different population.

Outcome ascertainment

The two outcome variables were UTD for age for all recommended vaccines at 24 months of life and delay of ≥6 months for one or more vaccines [106]. We examined the UTD status regardless of timeliness of 4 vaccines during the first 24 months of life. Children were defined as being UTD by 24 months if they received the recommended number of vaccine doses, as per the PIQ during the study time frame (4 doses of DTap-IPV-Hib, 3 doses PCV 13, 2 doses MMR(v), and 1 dose Men-C-C). The Hepatitis B vaccine was not included in our analysis, as newborn vaccination was added to the PIQ after our study time frame. Rotavirus vaccine was not included, as it was introduced during our study. Results of uptake from this cohort have been previously described [102]. The influenza vaccine was also excluded due to its nonspecific

timing in the recommended series. Children with missing immunization dates were considered unvaccinated for that vaccine.

To determine days under-immunized as per PIQ guidelines, we considered a valid schedule where all 4 recommended vaccines were administered, with a 30-day grace period. Cumulative days under vaccinated were calculated according to the recommended schedule. Therefore, if vaccination was initiated late, e.g. at 4 months instead of 2, the child would be 30 days under-immunized. The next expected immunizations would be within 2 months + 30 days grace and if late for the next immunization, those days would be added to the initial 30 days for a final cumulative number days sub-optimally immunized by vaccine type. If vaccination was initiated after 12 months of age, the PIQ catch-up calendar for 1 to 3 years of age was used where the minimal acceptable intervals between vaccines was applied and the first year counted as time under-immunized [126]. Required minimum intervals between doses were not counted as days under-immunized. We reported the mean number of days that children were under-immunized during the first 24 months of life, by vaccine type. We further categorized duration of under-immunization as less than 6 vs. 6 months or more, for at least one vaccine to determine the importance of timeliness to contrast with the standard measures of vaccination status.

Statistical Analysis:

Descriptive statistics were performed by first examining the summary of the data covariates. A chi-square test was run for all categorical variables. Covariates with a p-value of ≤0.20 in univariate logistic regression or recognized as an important variable, as drawn from the literature, were considered for inclusion in the final logistic model. Interaction was assessed

based on what the literature identifies as plausible two-way interactions; no significant interaction was found [127, 128].

Three multivariable logistic models were generated for each outcome, including sensitivity analysis: factors associated with incomplete immunization at 24 months and factors associated with cumulative delay ≥6 months. Model 1 included all independent variables related to the outcome. Model 2 included all variables from Model 1 with the addition of the variables "initiating vaccination on time" and "simultaneous vaccination at 18 months". Model 3 included all variables in Model 2 and adjusted for recruitment site using random effects. Model fit was assessed by calculating the index of concordance, or c-index, which in logistic regression models is equivalent to the area under the receiver operator curve (AUC) [129]. The population attributable fraction (PAF), accounting for missed vaccination opportunity in the source population, was calculated using the formula, $PAF = pe+ * (OR - 1) / OR$ where *pe+* is the exposed population[130]. All analyses were done with Stata v.14 software (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Results

Population characteristics

A total of 246 subjects were included in the analysis. We excluded subjects <24 months of age, non-vaccinated children (n=20) and immunocompromised children (n=3). The distribution of parental age at child's birth was consistent with that of Montreal's fertility rate by age group for 2014 [131]. Mean age of mothers and fathers at the index child's birth was 30.5 (±5.62) and 30 (±6.16) years respectively.

Determinants for UTD status at 24 months of age

The overall UTD status was 73%. Subjects from hospitals A and B had an UTD status of 75% compared to only 61% of subjects at hospital C, indicating a different source population. Subjects who were UTD in their immunization schedules at 24 months of life differed from those not UTD (Table 1*)*. Those who received simultaneous 18-month immunizations had the overall greatest vaccination coverage at 81%. Families with ≥3 children represented 36% of families where the index child was not UTD, compared to 24% of families where the index child was UTD. Groups with the lowest UTD status were children who were ever breastfed (58%), whose fathers had a graduate degree (58%), and whose parents were divorced (62.5%), although no statistical significance was found.

In the multivariable analysis, factors that were negatively associated with being UTD at 24 months were: having 3 or more siblings (OR=0.50; 95% CI: 0.28-0.86) and not receiving the 18-month vaccines simultaneously (OR= 0.15; 95% CI: 0.11-0.21). Low maternal education, high school equivalent or less, was associated with an UTD immunization status, (OR=1.70; 95% CI: 1.09-2.65). Timely initiation of the immunization schedule at 2 months of age was highly associated with an UTD status at 24 months of life (OR= 5.85; 95% CI: 2.80-12.22). The final model had a c-index of 0.76 (Table 2*)*. The etiological fraction was 0.35: indicating that 35% of our cohort who were not UTD could be attributed to missed opportunities to co-administer vaccines at 18 months.

Table 2 Population characteristics and variables associated with vaccination status in the first 24 months of life

VARIABLE[3]	UTD BY AGE 24 MO, NO. (%)	NOT UTD BY AGE 24 MO, NO. (%)	STUDY POPULATION, NO. (%)	P-VALUE
TOTAL	180(73.17 %)	66(26.83%)	246	
SOURCE HOSPITAL				
A	82(45.5%)	27(41%)	109(44%)	
B (REF)	76(42%)	25(38%)	101(41%)	0.20
C	22(12%)	14(21%)	36(15%)	
FEMALE (REF)	85(47%)	31(47%)	116(52%)	0.99
HEALTHY[4]	162(90%)	60(91%)	222(90%)	0.92
PREMATURITY[5]	9(5%)	4(6%)	13(5%)	0.73
WAS EVER BREASTFED	143(79%)	54(81%)	197(80%)	0.57
DAYCARE >4 HRS PER DAY	159(88%)	53(80%)	212(86%)	0.08
AGE OF FATHER AT BIRTH				0.58
<39	149(83%)	56(85%)	205(73%)	
≥39	27(15%)	8(12%)	35(77%)	
AGE OF MOTHER AT BIRTH				
<39	166(92%)	61(92%)	227(92%)	
≥39	14(8%)	4(8%)	18(7%)	0.67
MOTHER'S EDUCATION LEVEL				
ELEMENTARY/ HIGH SCHOOL	53(29%)	16(24%)	69(28%)	
CEGEP/COLLEGE	47(26%)	18(27%)	65(26%)	0.71
UNIVERSITY	59(33%)	21(32%)	80(32.5%)	
GRADUATE (REF)	21(12%)	11(17%)	32(13%)	
FATHER'S EDUCATION LEVEL				
ELEMENTARY/HIGH SCHOOL	66(37%)	17(26%)	83(34%)	
CEGEP/COLLEGE	43(24%)	16(24%)	59(24%)	0.16
UNIVERSITY (REF)	46(25.5%)	18(27%)	64(26%)	
GRADUATE	18(10%)	13(20%)	31(13%)	
MEDIAN FAMILY INCOME[6]				
<55,000	68(38%)	29(44%)	97(39%)	
55,000-64,999	49(27%)	14(21%)	63(26%)	0.75
65,000-75,000	45(25%)	16(24%)	61(25%)	
>75,000 (REF)	18(10%)	6(9%)	24(10%)	
MARITAL STATUS				
COMMON-LAW/MARRIED (REF)	165(92%)	57(86%)	222(90%)	
DIVORCED	5(3%)	3(4.5%)	8(3%)	0.57
SINGLE	9(5%)	5(7.5%)	14(6%)	
PRINCIPAL CAREGIVER AT HOME				
MOTHER (REF)	156(87%)	57(86%)	213(87%)	
FATHER	22(12%)	8(12%)	30(12%)	0.97
GRANDPARENT	2(1%)	1(1.5%)	3(1%)	

[3] Percent of missing data per variable ranges between 0.2%-2.5%
[4] Child had only minor ailments and no serious underlying medical condition
[5] GA of less than 37 weeks
[6] Median household census 2006 linked to the first 3 characters of the FSA

NUMBER OF CHILDREN <18 IN HOUSEHOLD				
ONLY CHILD (REF)	57(32%)	20(30%)	77(31%)	0.13
2	80(44%)	22(33%)	102(41%)	
≥3	43(24%)	24(36%)	67(27%)	
HEALTH SERVICE SOUGHT WHEN CHILD IS SICK				
FAMILY DOCTOR	41(23%)	14(21%)	55(22%)	0.90
PAEDIATRICIAN (REF)	31(17%)	10(15%)	41(17%)	
CLSC	9(5%)	5(7.5%)	14(6%)	
WALK IN CLINIC	44(24%)	18(27%)	62(25%)	
ED	53(29%)	17(26%)	70(28%)	
TIMELY IMMUNIZATION AT 2 MONTHS[7]	169(94%)	47(71%)	216(88%)	***<0.001***
SIMULTANEOUS AND TIMELY 18TH MONTH IMMUNIZATION[8]	165(92%)	39(59%)	204(83%)	***<0.001***

[1] 1st dose of DCaT-VPI-Hib and Pneu-C-13
[1] 4th dose of DCaT-VPI-Hib and 2nd dose MMR

Table 3 Unadjusted and adjusted logistic regression derived odds ratios and corresponding 95% CI of factors associated with complete immunization at 24 months[9]

DETERMINANT	**OR 95%CI**		**AOR 95%CI**[10]	
NUMBER OF CHILDREN <18 IN HOUSEHOLD				
ONLY CHILD (REF)	1.00	-----	1.00	-----
2	1.28	0.64-2.55	1.05	0.46-2.39
≥3	0.63	0.31-1.28	0.50	0.28-0.86*
AGE OF MOTHER AT BIRTH				
<26	0.62	0.18-2.17	0.52	0.18-1.48
26-39	0.84	0.26-2.68	0.81	0.51-1.29
>39 (REF)	1.00	-----	1.00	-----
MOTHER'S EDUCATION LEVEL				
≤ 12 YRS	1.73	0.69-4.35	2.01	1.39-2.90***
COLLEGE	1.37	0.55-3.40	1.33	0.62-2.87
UNIVERSITY	1.47	0.61-3.56	1.53	0.77-3.07
GRADUATE (REF)	1.00	-----	1.00	-----
MEDIAN HOUSEHOLD INCOME[11]				
<55,000	0.78	0.28-2.17	0.99	0.40-2.48
55,000-64,999	1.17	0.39-3.50	1.43	0.53-3.88
65,000-75,000	0.94	0.32-2.78	0.98	0.48-1.99
>75,000 (REF)	1.00	-----	1.00	----

[7] 1st dose of DCaT-VPI-Hib and Pneu-C-13
[8] 4th dose of DCaT-VPI-Hib and 2nd dose MMR

[9] Adjusted for all variables in table and for hospital and health status of child
[10] Cluster analysis to account for hospital
[11] Median household census 2006 linked to the first 3 characters of the FSA

TIMELY IMMUNIZATION AT 2 MONTHS	6.21	2.76-13.96***	5.85	2.80-12.22***
NON-SIMULTANEOUS OR TIMELY 18TH MONTH IMMUNIZATION[12]	0.13	0.06-0.27***	0.15	0.11-0.21***

Individual vaccines

Children were more likely to be UTD for each individual vaccine than for the series as a whole (Table 3*)*. The percentage of children in the cohort with any delay ranged from 54% for the recommended doses of MMR vaccine and 35% for pneumococcal conjugate vaccine, to 27% for the meningococcal type C vaccine and to less than 25% for the DTap-IPV-Hib vaccines. However, a number of children remained under vaccinated for each vaccine for a substantial portion of their first 24 months of life. Of the mean cumulative number of days under-immunized, children spent the largest amount under-immunized for the antigen components of the pentavalent DTap-IPV-Hib vaccine (mean duration of 227 days) for 34% of 22 months of expected coverage. The mean cumulative days under-immunized was 209 days for PCV, 145

[12] 4th dose of DCaT-VPI-Hib and 2nd dose MMR
*P<0.05

**P<0.01

***P<0.001

days for Men-C-C, and 107 days for MMR. Almost 50% of children with vaccination delay were under vaccinated for 6 months or more for DTap-IPV-Hib and PCV-13 vaccines. For MMR and meningococcal type C vaccine, the total possible delay was considerably shorter. Nevertheless, 17% were delayed for at least 6 of the possible 11 months for MMR and almost 32% for Men-C-C. Approximately 12% of our cohort was late to initiate their immunization schedule at 2 months of age. Of those who were late to initiate DTap-IPV-Hib, the median start time was 106 days (IQR 102-155) and for PCV (7, 10 or 13) median start time was 113 days (IQR 102-300).

Table 4 Days Under-immunized during first 24 months of life

	DcaT-VPI-Hib	Pneu-C-13	Men-C-C	MMR
	Complete schedule by vaccine n (%)			
	209 (85%)	212 (86%)	227 (92%)	200 (81%)
	Timely completion of schedule by vaccine n (%)			
	190 (77%)	161 (65%)	180 (73%)	114 (46%)
	Children with delay n (%)			
	56 (23%)	85 (35%)	66 (27%)	132 (54%)
	Cumulative no. days under-immunized Mean (SE)			
Cumulative time under-immunized	227.43 (24.5)	209.44 (23.0)	144.77 (17.70)	106.81 (9.7)
	Children with delay % (SE)			
1 day-2 mo	33.93 (0.06)	43.53 (0.05)	53.03 (0.06)	56.82 (0.04)
3 – 6 mo	17.86 (0.05)	11.76 (0.04)	15.15 (0.04)	25.76 (0.04)
7 – 12 mo	19.64 (0.05)	27.06 (0.05)	31.82 (0.06)	17.42 (0.03)
> 12 mo	28.57 (0.06)	17.65 (0.04)	NA	NA
n (%) ≥6 months delayed	27(48%)	38(45%)	21(32%)	22(17%)
Total possible delay, mo[13]	21	21	11	11

[13] DCaT-VPI-Hib and Pneu-C-13 are considered late >93 days and therefore assessed at 24 months have a maximum possible delay of 21 months. Men-C-C and MMR are administered at 12 months with a 31 day grace period and can have a maximum possible delay of 11 months.

Determinants for delay ≥6 months under-immunized

In multivariable analysis, subjects with 2 or more siblings were 3 times more likely to be under-immunized for ≥ 6 months (OR= 2.99; 95% CI: 1.45-6.22) (Table 4). Having a mother younger than 39 years at subject's birth was also associated with a delay of ≥ 6 months (OR= 2.13-2.77; 95% CI: 1.73-3.60). Location where subjects were usually seen when ill was associated with a vaccination delay of ≥ 6 months: subjects who attended a walk-in clinic (OR= 1.69; 95% CI: 1.13-2.52) or an emergency department (OR=1.39; 95% CI: 1.02-1.90) when ill were more likely to present with delay. Non-simultaneous vaccination at 18 months represented an almost 4-fold increased odds of having a delay ≥ 6 months for one or more vaccines (OR =3.61; 95% CI: 2.47-4.39). Factors associated with an absence of delay or delays < 6 months included mothers and fathers with a high school education or less compared to a graduate degree (OR= 0.43; 95% CI: 0.22-0.83 and OR=0.50; 95% CI: 0.35-0.70, respectively). Having a household income < $75,000 annually was associated with less delay compared to high-income earners. Having access to a family physician, with the possibility for urgent consultation when ill was also associated with a delay of < 6 months (OR= 0.63; 95% CI: 0.44-0.91). Timely initiation of the immunization schedule was found to be protective against delays in immunization by 24 months of age (OR= 0.13; 95% CI: 0.07-0.24). The final model had a c-index of 0.76.

Table 5 Unadjusted and adjusted logistic regression derived odds ratios and corresponding 95% CI of factors associated with being ≥ 6 months late for one or more vaccines at age 24 months[14]

	OR 95%CI		**AOR 95%CI**[15]	
NUMBER OF CHILDREN <18 YEARS IN HOUSEHOLD				
ONLY CHILD (REF)				
2	1.00	-----	1.00	-----
≥3	0.86	0.41-1.78	1.12	0.55-2.31
	1.97	0.95-4.11	2.99	1.45-6.22*

[14] Adjusted for all variables in table and for hospital site and health status of child
[15] Cluster analysis to account for hospital

AGE OF MOTHER AT BIRTH OF INDEX CHILD				
<26				
26-39	1.75	0.44-6.96	2.77	2.13-3.30***
>39 (REF)	1.71	0.47-6.17	2.13	1.73-2.61***
	1.00	-----	1.00	-----
MOTHER'S HIGHEST EDUCATION LEVEL				
≤ 12 YRS	0.39	0.15-0.99*	0.43	0.22-0.83*
COLLEGE	0.59	0.24-1.46	0.71	0.31-1.65
UNIVERSITY	0.52	0.21-1.25	0.75	0.42-1.33
GRADUATE (REF)	1.00	-----	1.00	-----
FATHER'S HIGHEST EDUCATION LEVEL				
≤ 12 YRS	0.35	0.15-0.94*	0.50	0.35-0.70***
COLLEGE	0.64	0.26-1.60	0.64	0.53-0.76***
UNIVERSITY	0.44	0.17-1.13	0.39	0.06-2.61
GRADUATE (REF)	1.00	-----	1.00	-----
MEDIAN HOUSEHOLD INCOME[16]				
<55,000	1.22	0.45-3.39	0.80	0.67-0.97*
55,000-64,999	0.71	0.23-2.16	0.42	0.22-0.78**
65,000-75,000	0.99	0.33-2.92	0.68	0.47-0.98*
>75,000 (REF)	1.00	-----	1.00	-----
HEALTH SERVICE SOUGHT WHEN CHILD IS SICK				
PAEDIATRICIAN (REF)	1.00	-----	1.00	-----
FAMILY DOCTOR	0.78	0.29-2.05	0.63	0.44-0.91*
CLSC	1.72	0.47-6.35	2.34	0.52-10.58
WALK IN CLINIC	1.08	0.43-2.68	1.69	1.13-2.52*
ED	0.99	0.41-2.44	1.39	1.02-1.90*
TIMELY IMMUNIZATION AT 2 MONTH	0.12	0.05-0.27***	0.13	0.07-0.24***
NON-SIMULTANEOUS OR TIMELY 18TH MONTH IMMUNIZATION[17]	3.61	1.80-7.25***	3.29	2.47-4.39***

Discussion

[16] Median household census 2006 linked to the first 3 characters of the FSA

[17] 4th dose of DCaT-VPI-Hib and 2nd dose MMR

*P<0.05

**P<0.01

***P<0.001

Immunization coverage is not yet optimal in the province of Quebec. Yet, children in our study cohort seemed to have higher coverage, by vaccine type, compared to the Canadian average, with the exception of the MMR vaccine (81% coverage compared to 89%, respectively), but comparable to the 2014 Quebec survey [24] [132], in particular when compared to data stratified by region (65.8% for the Greater Metropolitan Montreal and 73.8% for regions with >100,000 inhabitants). The proportion of non-vaccinated children in our cohort was comparable to results from previously described Canadian studies [24, 133].

A recent globally inclusive systematic review by Larson et al. suggests that to be most efficient, vaccination programs must be tailored at the community level with adapted, targeted strategies that will improve immunization among specific groups [8, 28]. Between 2004 and 2013, five new vaccines were introduced in the Quebec pediatric schedule, which may have led to scheduling constraints for some parents and may have placed a higher demand on healthcare services resulting in unintentional delays in immunization [119].

Several factors were associated with immunization status. Children from families in the lower income categories and with parents with the lowest levels of education spent less time under-immunized were more likely to be UTD with their immunizations at 24 months of life. These findings were consistent with results from Dummer et al., a Canadian study that showed higher immunization rates in poorer, less educated families but contrast largely with findings in many American studies [42, 45, 54, 55, 58, 60, 61, 107, 113, 114]. The distribution of parental education levels in our population was similar to provincial statistics, with a slighter higher proportion of parents with graduate degrees, as compared to the rest of the province [134].

Maternal age at child's birth influenced vaccination uptake: mothers 39 years of age and older

were more likely to have children that were UTD with their immunizations, although this was not significant at 24 months; while mothers younger than 39 years had a higher risk of having children with ≥ 6 months delays for specific vaccines. Keeping with findings in several similar studies, this could suggest that older parents may experience less constraint for timely vaccination, such a smaller family size[40, 42, 46, 48, 50, 55, 58, 64].

The impact of non-simultaneous immunization of the two recommended vaccines at 18 months and timely initiation of the immunization schedule were important findings. Missed opportunity at 18 months represented 35% of the population attributable fraction. This percentage was smaller than estimated by Boulianne et al. in 2003 (46%), hopefully demonstrating an improvement in this area. In this study, the estimation of time spent under-immunized cannot definitely be attributed to intentional vaccine spacing or simple logistic barriers but nevertheless, uncover important gaps in preventive care. We observed that 70% of our cohort who were not UTD at 24 months still received 3 doses of the DTap-IPV-Hib vaccine and 1 dose of MMR; very little was missing for these children to complete their vaccination schedule. More precisely, 31 (12%) children did not receive their 4^{th} dose of the DTap-IPV-Hib vaccine. Several studies, including the cNICS 2013 survey, have identified dose 4 of DTaP as the most frequently missed vaccine for children not adequately immunized [32, 107, 135-138]. For a majority of our study population, the time interval between 19 and 24 months represented an important catch-up period: the overall completion rate at 18 months was 46% compared to 73% by 24 months, for the same cohort, representing a 60% increase in coverage. Most children in our study were immunized on time: 77% to 87% of children had between none to 2 months delay by vaccine type. However, half of the children under-immunized had significant delay of ≥ 6

months during their first 24 months of life. Finally, 12% of our study cohort was late to start their immunization schedule, an important predictor of UTD status as previously reported [24, 63, 67, 68, 79].

Children in large families were not UTD for age, but also experienced important time under-immunized [40, 43, 49, 56, 63, 89, 106]. Efforts to schedule children in the same family simultaneously and emphasis on the importance of multiple vaccine co-administration will reduce the under immunized status of the majority of our target population. Furthermore, providing families with access to family practice care seemed associated with a better immunization status [77]. Initiatives in some regions, which offer scheduling of childhood vaccinations through a web application as well as a tool to determine immunization needs, help families proactively schedule immunizations into their busy lives [139]. A recent Cochrane review of patient-reminder studies in the US, Australia, Canada, Denmark, New Zealand, and the UK found that reminder and recall interventions increased the number of children who were vaccinated or UTD with their immunizations. A reminder during a vaccination visit remains a low cost and easy way to effectively encourage parents to present to their next vaccination appointment [140, 141].

The main study strength was reduced selection bias. Unlike studies where the primary aim is to determine coverage, our subjects were enrolled based on their presentation to the ED or hospitalization with acute gastroenteritis and were thus less likely to self-select based on immunization status, improving external validity. To further address selection bias, we estimated the uptake of the Rota virus vaccine, introduced during the study period and found it to fall between rates estimated in 2012 and 2014 provincial immunization survey[24, 102, 104].

Similar uptake rates of a newly introduced vaccine leads us to be confident that our population's vaccination behavior is similar to that of the greater urban Quebec population. All immunizations were verified against booklet or provider, reducing chances of misclassification and increased study precision. This study also had several limitations. Our sample was not proportionately representative of the provincial population in terms of cultural background and locality (mostly metropolitan). As this was a secondary analysis, we were not able to collect all relevant variables associated with immunization such as employment, health, and mobility status of recruited families. Finally, we cannot rule out selection bias associated with health seeking behaviours.

Risk of disease due to spacing in the immunization schedule varies by disease circulation, transmissibility and likelihood of importation and severity of outcome. Vaccination timeliness is important for diseases that have the potential to cause large outbreaks and for diseases currently circulating such as measles, mumps and pertussis. In this study, we illustrated that children spent non-insignificant time under-immunized whether through intentional vaccine spacing or logistical constraints. This finding strongly suggests that the standard measure of coverage does not capture these important lapses in preventive care. Timely initiation of the immunization schedule, close follow-up and simultaneous vaccination at 18 months will bridge a large gap between completeness for age and appropriate coverage at all ages.

Chapter 7: Conclusion

Restatement of objectives and findings

The principal aims of this thesis were to address gaps in the literature pertaining to factors associated with incomplete immunization and under-immunization. The primary objectives was to determine the factors associated with vaccine coverage in Quebec pre-schoolers and the amount of time they spent under immunized in their first 24 months of life. The secondary objective was to determine through a systematic review, the core determinants of incomplete immunization in high income countries.

In the first manuscript, I summarized peer reviewed literature on the factors associated with incomplete immunization of children in high-income countries. A few systematic reviews have attempted to identify common global determinants of immunization status but found few cohesive results at this scale. In the studies reviewed, I collected descriptive information and effect measures for the following variables: socio-economic status (i.e. neighbourhood wealth index, family income, families receiving government aid), maternal employment, birth order or number of children, maternal and paternal education, racial or linguistic minority status, indigenous status, rural dwelling, high mobility before or after birth, parental smoking, maternal depression, maternal age and marital status, and prematurity. I additionally looked at factors associated with the following caregiver behaviors: breastfeeding, pre-natal care, preventive care for premature infants, delay in initiating immunization, and failure to co-administer vaccines. Almost half the studies reviewed found that an increasing number of children per household under the age of 18 was a significant barrier to complete immunization

status. Other significant factors in order of occurrence were, single motherhood, younger maternal age, high mobility, and parental smoking. Late initiation of immunization was identified as an important factor associated with subsequent incomplete immunization. Consequently, several inconclusive factors were identified through this review. By referencing back to SAGE's model of determinants of vaccine hesitancy, these inconclusive factors fit into several spheres of influences such as, belonging to a linguistic or racial minority group, type of healthcare or immunization provider and, maternal employment and level of education.

In Chapter 6, I conducted a cohort analysis of the immunization status of Quebec pre-schooler and the amount of time they spent under-immunized. In the absence of a vaccine registry, the opportunity to analyze a cohort with exhaustive vaccine records, can provide valuable information for local public health organizations. I found that coverage for age was unexpectedly low in our cohort with only 73% of pre-schoolers considered up-to-date with immunization at 24 months of life. While children in the cohort had adequate coverage overall for the individual vaccines assessed in the study, children spent a significant amount of time under-immunized where overall, 149 children (60%) experienced delay for at least one vaccine. Half the children who experienced any delay were under-immunized for ≥6 months for these preventable diseases.

Results from the cohort analysis underlined that several factors found to be common barriers to complete immunization in high-income countries were equally barriers to urban Quebec children. An increasing number of children in the home represented a three-fold increased risk for under-immunization at 24 months of life, whereas timely initiation of vaccination resulted in a six-fold increased chance of being up-to-date with immunization. I found that approximately

12% of our cohort were late to initiate their immunization schedule before the age of three months. Low maternal education was represented by a two-fold increased chance with being up-to-date by 24 months of age. Maternal education was found to be important in 25% of articles reviewed in Chapter 3, although it remains inconclusive as a barrier or promoter of immunization status.

The second objective of the cohort study was to identify factors associated with under-immunization for ≥6 months for at least one of the vaccines studied. I found that an increasing number of children per household under the age of 18, mothers under the age of 39, consulting at a walk-in clinic or emergency room when the child was ill, and failing to co-administer 18 months vaccines were independently associated with a ≥6 months of time spent under-immunized for one or more childhood vaccine. Lower parental education and income, consulting a pediatrician for urgent care, and timely initiation of immunization appeared to be associated with low incidence of vaccine spacing and thus protection against vaccine preventive illness.

Limitations and strengths

There were several limitations in the cohort analysis. As a secondary analysis, a priori sample size calculation was not possible. Our population sample was limited to subjects presenting to emergency department for acute gastroenteritis. Additionally, I was unable to collect important data such as parental employment, self-reported income as compared to ecological data, mobility, and parental smoking. Lacking these data, I was unable to compare their importance

against the findings in the systematic review. Race of child was collected but not those of both parents, making it impossible to infer race as associated with immunization in this cohort. Secondly, our sample size was underpowered to detect difference between racial groups. In summary, inclusion of race in the main analysis would not be informative. Nevertheless it would seem through evidence uncovered in the systematic review, that if there is an assumption that this data would be useful and can be collected and analyzed, it would be highly informative at the local level. Lastly, my review and cohort analysis only assessed caregiver characteristics and not attitudes and beliefs and therefore the results of this thesis should be interpreted with these limitations in mind.

While the overall cohort comprised 937 children, ages 8 weeks to 3 years, I chose to analyze the up-to-date status at 24 months of life to allow for temporal behaviors within the cohort. This decision resulted in a much smaller cohort of 246 subjects that nevertheless resulted in reasonable 95% confidence intervals in the multivariable logistic regression models. I initially thought that spatial analysis with the objective to identify clusters of under-immunized children in Quebec would be interesting. Regrettably, this small sample size precluded any conclusive results. Further limitation was the use of the FSA to extrapolate neighbourhood income; this could lead to ecological fallacy, assigning neighbourhood characteristic to the individual.

Limitations associated with the systematic review were largely related to the heterogeneity of the study designs. In the hierarchy of study designs, randomized controlled trials notwithstanding, a large number of cohort and case-control studies would have been preferable. Despite this, the large sample sizes of the cross-sectional studies make for robust

results that enriched the scope of aggregate findings and allowed for a large number of determinants of under-immunization to be examined.

Keeping this work's limitations in mind, there were several strengths associated with each study. To our knowledge, there is no systematic review that covers the determinants of immunization in high-income countries. This systemic review summarized a large number of studies in a comprehensive manner, identifying several core determinants of immunization in high-income countries that can drive further research. The cohort analysis benefits from reduced selection bias as a secondary analysis; caregivers of subjects were less likely to self-select based on immunization status, rendering the study generalizable to the population from which the cohort originated. Taken together, the two manuscripts are complementary and add to the body of literature on the drivers of current immunization uptake practices.

Implications and recommendations for future research

The findings in the cohort study are generalizable to the broader urban, Quebec population. Given that 75% of Quebec children are vaccinated by a Centre de Santé et Service Sociaux (CSSS) nurse, the barriers to complete immunization can and should be addressed at all levels of the provincial government and specifically within health regions. Historical and locally relevant characteristics such as belonging to a racial or linguistic group, healthcare model, healthcare provider, and parental education should be prioritized alongside the factors shown to be conclusive barriers to immunization when developing public health strategies to increase coverage.

Principal recommendations:

1. Identify locally relevant factors associated with incomplete or severely delayed immunization and develop actionable strategies to increase timely uptake and coverage.
2. This study has identified important gaps in vaccine uptake between 18 and 24 months of age. Given provincial healthcare cost constraints, focussing on an immunization reminder service for 18 and 24 months vaccines may be a worthy investment to limit the state of under-immunization and vulnerability in an outbreak event.
3. Complete the implementation of the provincial vaccine registry. A registry offers several benefits such as easing the complexity of scheduling for parents, generation of reminders, provides proof of vaccination, and prevents over-vaccination. For public health officials, a registry can help identify populations at risk and target appropriate education and early interventions. Importantly, a registry provides a means of identification and contact for children who are not routinely immunized so as to advise on extra precaution measures in case of outbreak[7].

Incomplete immunization may jeopardize or reduce the effect of new and established vaccines on the burden of disease. A provincial vaccination registry will capture temporal gaps in immunization (intentional or not) that coverage estimates cannot. Systematic analysis of a vaccine registry database will guide strategies such as enhanced geographic access to vaccination services. Trust building strategies such as improved dialogue with healthcare providers will ensure timely and complete immunization of Quebecers of all life stages.

Appendix

Annex A : PIQ

Regular Québec vaccine schedule : Protocol d'Immunisation de Québec[126]

Immunization Schedule for Young Children

Vaccine to prevent:	At 2 months	At 4 months	At 6 months	At 12 months	At 18 months
Diphtheria-whooping cough-tetanus-hepatitis B-polio-Hib	X	X			X
Diphtheria-whooping cough-tetanus-polio-Hib			X		
Pneumococcus	X	X		X	
Rotavirus	X	X			
Flu (fall/winter)			X[1]		
Meningococcal C				X	
Measles-mumps-rubella				X	X
Chicken pox					X

[1] Your child must receive the flu vaccine as of 6 months or as soon as the vaccine becomes available (fall/winter) after the child is 6 months old. This vaccine must be administered every year until the age of 2. In some cases, it may also be recommended after the age of 2.

Annex B: variable code

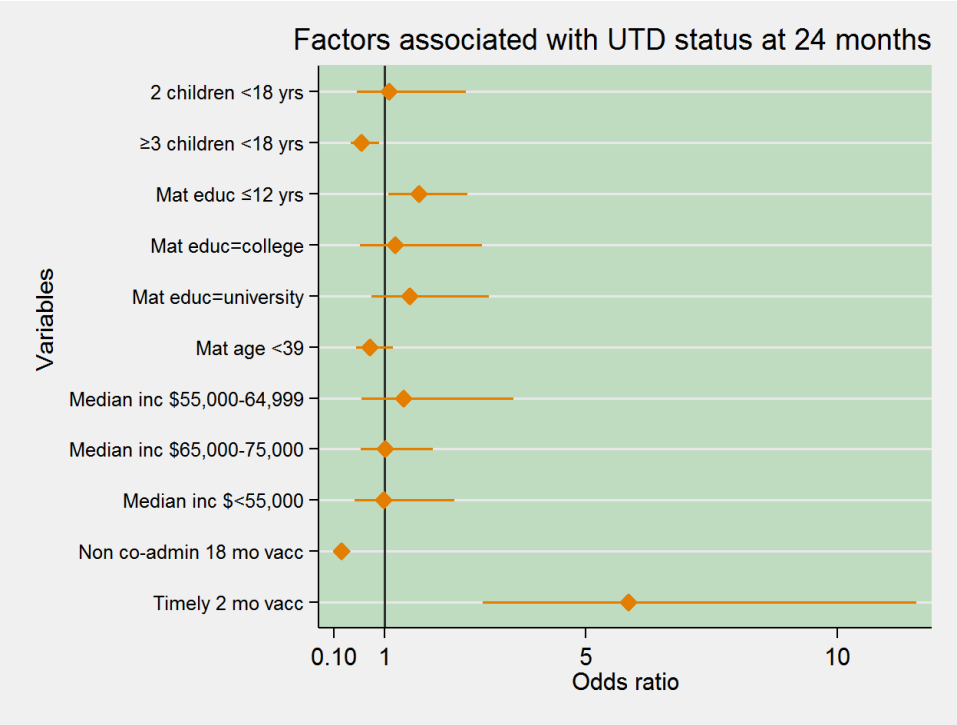
	Coding	Variable Name
Hospital at which the child presented at the emergency department and was recruited into the study	A=0 B=1 C=2	HOSP_N
Child has a significant health condition (listed below) ❒ Healthy (Minor ailments only) ❒ Neoplasm of any kind, past or present ❒ Underlying cardiovascular disorder ❒ Underlying respiratory disorder	0 = no health condition 1 = health condition	HEALTH

❒ Underlying hematologic disorder, non-malignant ❒ Underlying neurological or developmental disorder ❒ Underlying genitourinary or renal disorder ❒ Underlying gastrointestinal or hepatic disorder ❒ Underlying endocrine, nutritional or metabolic disorder ❒ Underlying inherited immunodeficiency ❒ Underlying bone, joint, or connective tissue disorder ❒ Underlying skin disorder (severe only) ❒ Sequelae from an injury ❒ Multi-system disorder or syndrome ❒ Chronic infection present ❒ Relevant concurrent acute infection		
Prematurity (<37 weeks of gestation)	0=no 1=yes	prem
Sex of the child	0=female 1=male	sex
Age of the child	Months	age
Race of the child	0=Caucasian 1=black 2=asian 3=latin american 4=middle eastern 5=multiracial (child is two or more of the previous races)	race
Has the child ever been breastfed	0=no 1=yes	breast_fed
Child attends any type of daycare or preschool for more than 4 hours/week	0=no 1=yes	daycare
Age of the father of the subject categorized <26 26-39 ≥39	<26=0 26-39=1 ≥39=2	dadcat
Age of the mother of the subject categorized <26 26-39 ≥39	<26=0 26-39=1 ≥39=2	momcat
Father's highest degree or diploma completed	≤ 12 elementary/high school=1 college/CEGEP=2 university=3 graduate level education=4	educ_dad
Mother's highest degree or diploma completed	≤ 12 elementary/high school=1 college/CEGEP=2	educ_mom

	university=3 graduate level education=4	
Marital status of the child's parents	married/common law=0 single=1 divorced=2	married_cat
Median family income by first 3 postal code Categorical <55,000 55,000-64,999 65,000-75,000 >75,000	<55,000=0 55,000-64,999=1 65,000-75,000=2 >75,000=3	incomecat
Number of children aged 0-18 years lived in child's household in the last week excluding the index child	none=0 one=1 two or more=2	all_kidscat
Place where child is usually taken to receive health services when they are sick	0=family doctor 1=paediatrician 2=CLSC 3=walk in clinic 4=emergency department	health_hype
Person who takes care of the child most of the time at home	mother=0 father=1 grandparent=3	CARE
Received all two month vaccines on time within 3 months of age	no=0 yes=1	two_mo
Received 18 month vaccines simultaneously (4th dose DTaP-Hib and 2nd dose MMR(v)	no=0 yes=1	both_18
Received all first year vaccines within 24 months of age + 30 days (395 days) (outcome) • Diptheria-tetanus-pertussis (DTaP-Hib): 2, 4, 6, 18 months • Pneumococcus: 2, 4, 12 months • Meningoccus C: 12 months • Measles-Mumps-Rubella (MMR): 12 months	no=0 yes=1	UTD2
Was cumulatively under-immunized for at least 1 vaccine ≥6 months	no=0 yes=1	under_6

Annex C: Model results and fit plots

Annex C Figure 1 Factors associated with UTD status at 24 months



Annex C Figure 2 Factors associated with cumulative time spent under-immunized

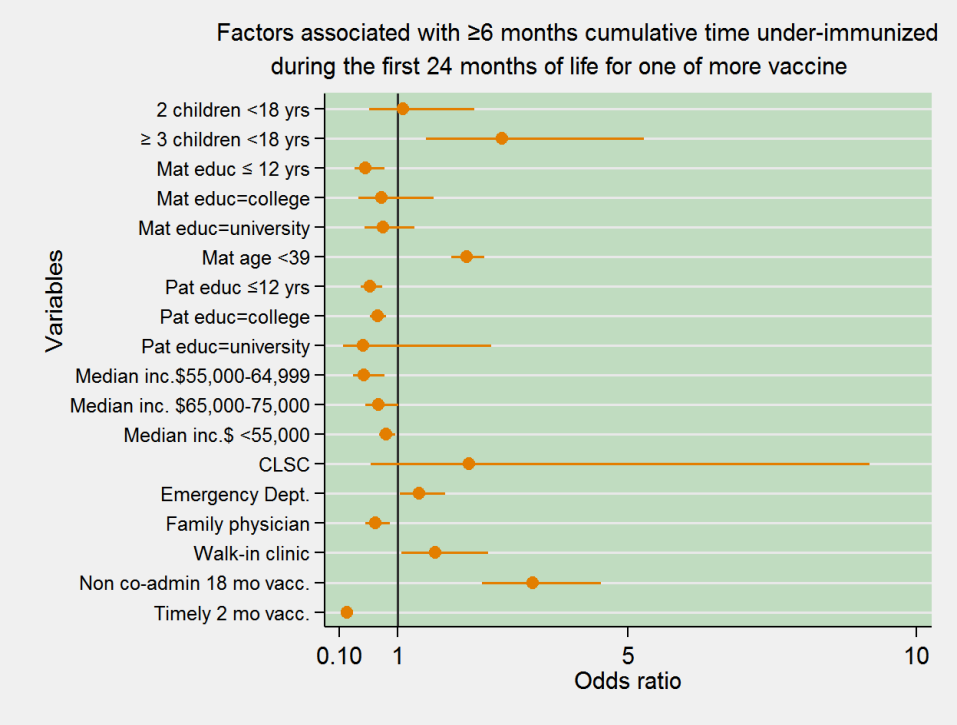
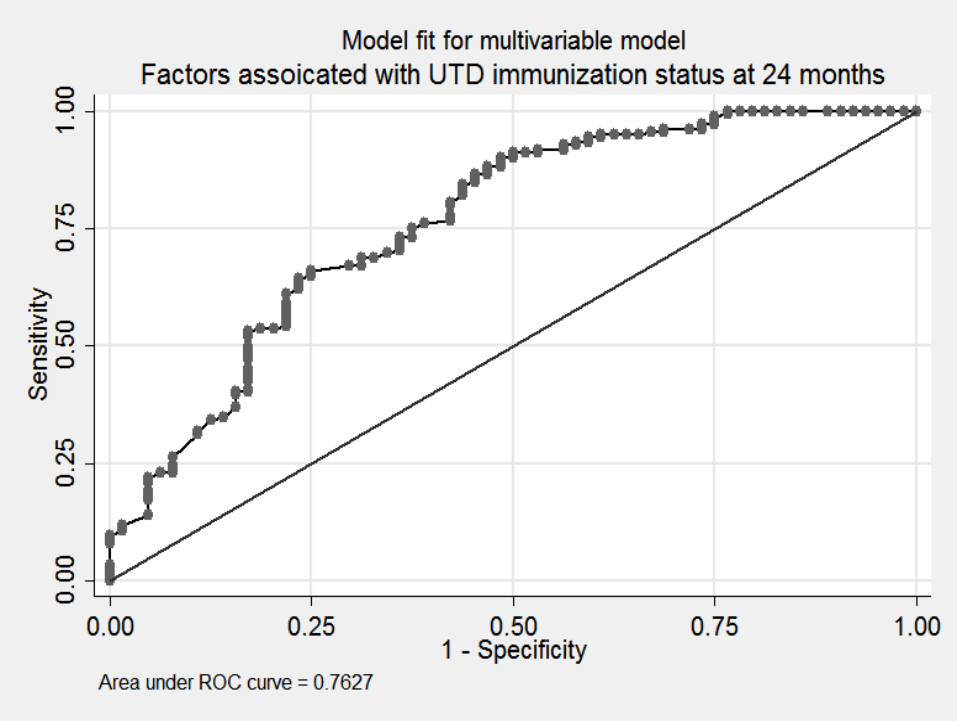
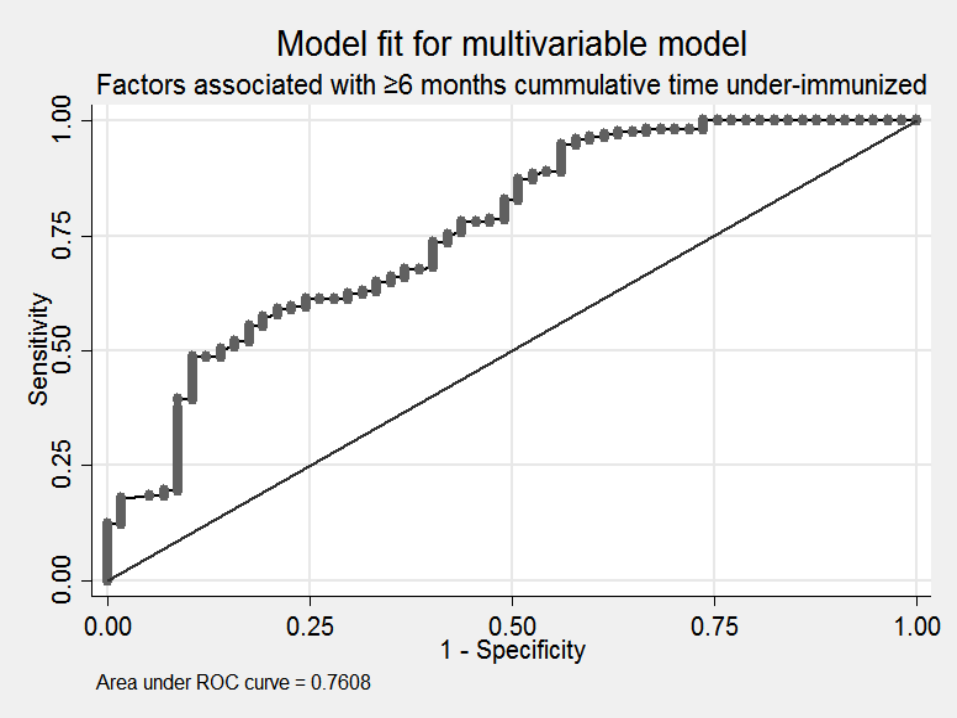


Figure: C statistic presented as AUC ROC

Annex C Figure 3 Model fit for UTD status at 24 months



Annex C Figure 4 Model fit for factors associated with under-immunization



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