Preparing for a Safety Evaluation of Rotavirus Vaccine Using Health Services Data in Ontario: The Development of a Diagnostic Algorithm for Intussusception, an Estimation of Baseline Incidence and an Evaluation of Methods

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ABSTRACT

In view of the recent implementation of a publicly funded rotavirus vaccination program in Ontario, we undertook studies to help guide the design of a safety evaluation of the vaccine with respect to intussusception. We used administrative data to develop and validate an algorithm for intussusception, and quantified its incidence in Ontario. We also conducted a systematic review of study designs used to evaluate post-licensure vaccine safety, and discussed each design's strengths and weaknesses.

The validated algorithm for intussusception was sensitive (89.3%) and highly specific (>99.9%). We observed the highest mean incidence (34 / 100,000) in males <1 year of age. While other designs are more robust, the inability to ascertain individual vaccination status from Ontario's administrative data dictated our selection of an ecological design for safety evaluation of rotavirus vaccine.

Data assimilated from this thesis represent a critical step toward the timely evaluation of rotavirus vaccine safety in Ontario.

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CONTRIBUTIONS OF AUTHORS

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Robin Ducharme: contributed to the study design, coordinated the study, drafted Research Ethics Board applications, maintained all study documentation, designed the data collection tool, acquired and compiled the study data, completed the data analyses, wrote the first draft of the manuscript, edited the manuscript, submitted the manuscript for publication and completed revisions as requested by the journal.

Dr. Eric Benchimol: contributed to the conception and design of the study, provided guidance on clinical and methodological issues, provided feedback on Research Ethics Board applications, contributed to data acquisition, edited the manuscript for important intellectual content.

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Robin Ducharme: conceptualized the study, wrote the review protocol, created the data abstraction form, maintained all study documentation, acquired and compiled the study data, summarized study results, drafted the manuscript.

Steven Hawken: provided guidance on methodological issues, reviewed the manuscript and gave feedback on important intellectual content.

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Robin Ducharme wrote the remainder of the Thesis, with guidance, feedback and revisions from **Dr. Dean Fergusson** and **Dr. Kumanan Wilson**.

STATEMENT OF ORIGINALITY

This Thesis represents original work undertaken by me (Robin Ducharme) as part of the requirements for the M.Sc. degree in Epidemiology. As outlined by the Contributions of Authors, I took the lead of every aspect of the work encompassed in this Thesis.

CHAPTER 1: Introduction and Background

1.1 Project Rationale

Pediatric vaccines are administered to a vast number of healthy children every year. In population-wide exposures, even very rare adverse events can have important implications in relation to the public's confidence in vaccination. Post-marketing surveillance (PMS) of pediatric vaccine safety is prioritized in order to monitor for such rare adverse events that are hard to detect in pre-licensure studies.

The Government of Ontario introduced a publicly funded rotavirus vaccination program in August 2011 (1). In view of the anticipated increase in vaccine uptake, this project was initiated in consultation with Public Health Ontario with the goal of informing and facilitating the design and implementation of a post-marketing safety surveillance system for rotavirus vaccine in Ontario. In conducting this project, we assembled and assimilated the key information required to conduct rotavirus vaccine safety studies in Ontario.

1.2 Rotavirus Disease

Rotavirus is a common gastrointestinal infection which almost all children experience by their fifth year of life (2). The virus is spread from person-to-person via the fecal-oral route, or via contaminated fomites (3). Factors aiding rotavirus transmission include a high degree and duration of viral shedding in the stool, and a low infectious dose threshold (4). A wide spectrum of symptom severity has been reported with rotavirus, ranging from asymptomatic infection to severe illness resulting in hospitalization or even death, although

death is quite rare in high-income countries such as Canada (4). The highest severity of illness is often seen in children between 3 and 24 months of age, while children under 3 months typically experience a milder version of the illness as a result of acquiring maternal antibodies through the placenta(4).

A substantial number of pediatric hospitalizations for severe gastroenteritis are related to rotavirus infection (5). The clinical presentation of hospitalized cases typically involves vomiting, diarrhea and fever (6). As compared to cases of gastroenteritis from other causes, rotavirus-related cases of gastroenteritis tend to be more severe, and have a higher probability of hospitalization and of requiring intravenous rehydration (7). As a result, rotavirus gastroenteritis results in a significant use of health care resources (7).

It is estimated that worldwide, there are nearly 25 million outpatient visits, and 2 million hospitalizations for rotavirus-related diarrhea each year, in children under 5 years (2). Global estimates have suggested that rotavirus-related diarrhea accounts for 5% of all deaths in children under 5 years of age (8). This translates to approximately 453,000 deaths per year (8). While most deaths related to rotavirus infection occur in developing nations (2), the burden associated with the virus is experienced by countries worldwide (9, 10). In turn, the public health community has recognized the importance of rotavirus vaccine development (11).

1.3 The Safety of Rotavirus Vaccines

1.3.1 RotaShield ™

Wyeth developed the first oral tetravalent rotavirus vaccine (intended to immunize against four strains of rotavirus), which was marketed as RotaShield™ (11). Pre-licensure trials of RotaShield™ demonstrated the vaccine's efficacy, safety and tolerability (12-15). Following the Food and Drug Administration (FDA)'s licensure of RotaShield ™ in the US in 1998, a passive adverse event reporting system capturing reported events from vaccine manufacturers and health service providers identified an association between the administration of the RotaShield ™ vaccine and an increased risk of a relatively rare condition, intussusception (16). The increased risk of intussusception associated with RotaShield ™ had not been identified in pre-licensure studies. A review of 11 placebo-controlled trials of RotaShield™ vaccine found the rates of intussusception in vaccine recipients to be higher as compared to placebo, but this difference was not statistically significant (17). Intussusception is the occurrence of one section of the intestine sliding inside an adjacent section, causing an obstruction and cutting off blood supply which may lead to vomiting, abdominal distension and rectal bleeding (18). While most cases of intussusception can be effectively treated with air enema or surgery, the condition can be fatal if untreated (19).

Several subsequent post-licensure studies confirmed the temporal association between administration of RotaShield ™ and intussusception (20). Although mesenteric lymphadenitis has been identified in patients with intussusception, the pathological mechanism and possible organism underlying the association between RotaShield ™ and

intussusception has not been confirmed (19, 20). A follow-up study was conducted by Murphy et al. using case-control and case-series methods to evaluate the association between RotaShield ™ and intussusception (21). In the case-control analysis, Murphy and colleagues found that vaccination with RotaShield ™ was associated with an adjusted odds ratio for intussusception of 21.7 (95% CI: 9.6 to 48.9) within 3-14 days of the first vaccine dose (21). The population-attributable risk of intussusception in RotaShield ™ recipients was estimated to be 1 in 9474 from the case-control analysis, and 1 in 4670 from the case-series analysis (21). Conversely, in an ecological study using hospital discharge information from ten US States, Simonsen and colleagues estimated the population-attributable risk of intussusception admissions to be 1 in 66,000 to 302,000 vaccinees (22). Upon reviewing the body of evidence from various sources, an expert panel estimated the population-attributable risk of intussusception to be approximately 1 in 10,000 infants vaccinated with RotaShield ™, with the highest risk occurring within 7 days of receiving the vaccine's first dose (23). In view of the evidence collected post-licensure, the US Center for Disease Control and Prevention (CDC) recommended a halt on rotavirus vaccine administration in August 1999 (16). Wyeth withdrew RotaShield ™ from the United States market in 1999 as a result of safety concerns (11). This vaccine was never licensed in Canada.

1.3.2 RotaTeq ™ and Rotarix ™

The development of new rotavirus vaccines continued despite RotaShield™'s demise. Two live attenuated vaccines are currently approved for use by Health Canada (24). RotaTeq ™ (Merck Sharp & Dohme Corp.) is a pentavalent human-animal reassortant

vaccine made from a combination of proteins from human and animal rotaviruses and is designed to protect against five strains of rotavirus (20). Rotarix™ (GlaxoSmithKline) is a monovalent human-based vaccine, designed to immunize against the most common rotavirus strain in humans (20). Clinical trials have established the efficacy of both vaccines in the prevention of acute rotavirus gastroenteritis (25, 26). Furthermore, both vaccines were shown to lead to a reduction in gastroenteritis-related health care utilization (25, 26). In consideration of the history with RotaShield™, pre-licensure clinical trials evaluating RotaTeq ™ and Rotarix ™ were powered to detect an increase in intussusception risk of the magnitude which led to RotaShield ™'s withdrawal (25, 26). Although these trials found no significantly increased risk of intussusception within 31 days of administering the first or second dose of Rotarix ™ (RR and 95% CI for Rotarix ™ vaccine vs. placebo = 0.85 (0.30 to 2.42)) or within 42 days of either dose of RotaTeq ™ (Adjusted RR and 95% CI for RotaTeq ™ vaccine vs. placebo = 1.6 (0.4 to 6.4)), safety in routine clinical practice remained to be confirmed (25, 26). As a result, the World Health Organization (WHO) recommended that ongoing post-licensure safety surveillance be implemented in any country planning to introduce a new rotavirus vaccine (27).

Several post-licensure safety evaluations have been conducted since RotaTeq ™ and Rotarix ™ were licensed for routine use. Early post-licensure studies conducted in the United States examining data from the Vaccine Safety Datalink (VSD) and the Vaccine Adverse Events Reporting System (VAERS) concluded that the risk of intussusception following vaccination with RotaTeq ™ was not elevated above the background risk in the periods studied between 2006 and 2008 (28, 29). Similarly, another study using the VSD found no increased risk of intussusception within 1-7 or 1-30 days of vaccination with RotaTeq ™

between 2006 and 2010 (30). A study using active surveillance to identify cases of intussusception following Rotarix™ administration in Mexico and Brazil between 2008 and 2010 reported an increased risk of intussusception within 1-7 days of the first dose of vaccine compared to a control period in children from Mexico (Incidence Ratio and 95% CI = 5.3 (3.0 to 9.3)), but no increase was observed in children from Brazil (31). An Australian study which also used active surveillance found no overall increase in risk of intussusception in infants aged 1-9 months after receipt of all doses of RotaTeq™ or Rotarix™ (32). In younger infants (aged 1-3 months) however, the risk of intussusception was slightly elevated 1-7 days after receiving the first dose of either vaccine (RR and 95% CI for RotaTeq™ = 5.3 (1.1 to 15.4); RR and 95% CI for Rotarix™ = 3.5 (0.7 to 10.1) (32). Most recently, a study conducted in the United States evaluated cases of intussusception reported to the VAERS following administration of RotaTeq™ or Rotarix™ (33). A self-controlled risk-interval analysis revealed an grouping of intussusception cases 3-6 days after receipt of only the first dose of RotaTeq™ (Daily Reporting Ratio and 95% CI for days 3-6 vs. 0-2 =3.75 (1.90 to 7.39)) (33). The study also reported an apparent clustering of intussusception cases 4-7 days after administration of the first dose of Rotarix™, although the risk could not be quantified due to an insufficient sample size (33). Given the possibility of an association between vaccination with RotaTeq™ or Rotarix™ and intussusception found in some of the post-licensure studies conducted to date, further methods and analyses are required to confirm or refute the safety of these vaccines in routine immunization programs.

1.4 Intussusception

Intussusception is a type of intestinal obstruction most common in infants (<1 year) that can lead to restricted blood flow to the intestine (18). In infants, intussusception is primarily idiopathic (18). In older children, it is more frequently associated with a pathological lead point such as a tumor or polyp (20). Symptoms of intussusception may include abdominal pain, vomiting and rectal bleeding (18). Signs reported at presentation have included abdominal distension, palpable abdominal mass, and abnormal or absent bowel sounds (18, 20, 34). Clinical investigations are typically comprised of abdominal ultrasound and / or x-ray, and confirmation of diagnosis requires radiologic studies including air-contrast or liquid-contrast enema, or surgical investigation (20). Intussusception can be treated by reduction using air or hydrostatic enema, or by laparotomy (20). The proportion of cases treated surgically is higher in developing countries, whereas in developed countries, more cases are treated by air or hydrostatic enema (18). Untreated intussusception can lead to complications such as intestinal infarction and perforation (20). Mortality from intussusception is much more common in developing nations as cases have generally further progressed and are more severe by the time of treatment (18).

Given the differences in resources available to diagnose and treat intussusception in various health care setting around the world, it is impracticable to apply a single case definition requiring specific clinical investigations to all settings (35). To facilitate data collection on cases of intussusception for rotavirus vaccine safety evaluations across health care settings, the Brighton Collaboration Intussusception Working Group developed a standardized case definition for Acute Intussusception (35). The case definition combines clinical, radiographic and surgical criteria to identify true cases of intussusception and allows

cases to be identified even when confirmation by radiologic or surgical means is not possible (see Table 2.2-1).

Accurate, population-based estimates of intussusception incidence are not available for many countries as the majority of available data have been generated from hospital-based studies (34, 36-40). A review of European studies indicated that hospital-based estimates of incidence ranged from 0.7 to 2.2 cases per 1000 young children of various age groups in inpatient or emergency departments (40). In a study utilizing a database of hospital discharges, the annual incidence of hospitalizations for intussusception among infants ranged from 33 to 44 per 100,000 between the years of 1993 and 2004 (36). In a US study, the incidence rate for 1994-1996 obtained from the National Hospital Discharge Survey was 56 per 100,000 (37).

Reported population estimates of incidence in infants and young children from various countries have ranged widely from 18 to 56 per 100,000 in North America, 56 to 72 per 100,000 in Europe, 81 to 131 per 100,000 in Australia, 75 to 219 per 100,000 in Israel, 18 per 100,000 in India, 185 per 100,000 in Japan and 236 per 100,000 in South Korea (36-39, 41-46) (47) (48).

The wide range of reported incidence rates from different countries may be partly attributable to variation in intussusception risk by ethnicity. The effect of ethnicity on intussusception risk has been observed previously in a study reporting a significantly increased risk in black infants (RR 1.8, 95% CI 1.2–2.9) and infants of other races (RR 8.0, 95% CI 4.6 –14.1) as compared to Caucasian infants in Indiana, as well as a significantly increased risk in infants of other races as compared to Caucasian infants in California and Georgia (California: RR 3.2, 95% CI 2.7-3.7; Georgia: RR 9.3, 95% CI 5.0-17.0) (37).

Further, an Australian study reported a significantly decreased risk of intussusception in indigenous infants as compared to non-indigenous infants (RR 0.32; 95% CI 0.19–0.49) (45).

1.5 Post-Marketing Surveillance for Vaccines in Canada

Several countries have established diverse types of post-marketing surveillance systems for vaccine safety (27). In Canada, there are two national vaccine safety surveillance systems: the Immunization Monitoring Program ACTive (IMPACT) and the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS). IMPACT is a pediatric hospital-based active sentinel surveillance system in which designated monitors seek and report cases of adverse events following vaccine administration (49)**.** CAEFISS is a voluntary reporting system capturing adverse events believed to be temporally related to vaccination and reported to public health by health care providers or individuals (50). The current surveillance systems are complementary to each other with each having different strengths and weaknesses. A system based on health administrative data, although not currently in position, would allow for a broader range of safety analyses with high statistical power. This type of system would allow for analyses requiring baseline rates of adverse events (such as time-series analyses) in addition to estimates of the population's vaccine uptake.

1.6 Objectives of the Thesis

In order to design and implement an optimal safety surveillance system for rotavirus vaccine in Ontario using health administrative data, an accurate method of identifying cases of intussusception in administrative data needed to be established. Further, in order to have the ability to detect a change in intussusception incidence after vaccine introduction, the baseline incidence of intussusception in Ontario needed to be ascertained. Thus for the first part of my thesis, my aim was to develop and validate a method of identifying cases of intussusception from within health administrative data, and use this method to ascertain the baseline incidence of intussusception in the pediatric population of Ontario.

For the second part of my thesis, my aim was to conduct a systematic methodological review of the existing observational study designs used for post-marketing vaccine safety. In the context of the information assimilated through the review, I then discussed the specific applicability of the identified methods for evaluating rotavirus vaccine safety. Ultimately, the aim of my thesis was to establish the foundation required for the creation and implementation of infrastructure for ongoing vaccine safety monitoring related to the rotavirus vaccine in the future.

Therefore, the **four main objectives** to meet my thesis aims were:

1) To develop and validate an algorithm to accurately identify cases of intussusception in Ontario's health administrative data;

2) To use the validated algorithm to describe the baseline incidence of intussusception in Ontario prior to introduction of the publicly funded vaccine program;

3) To conduct a systematic review of the literature to identify and evaluate the existing observational study designs for post-marketing vaccine safety;

4) To identify an optimal study design and analysis method to assess the risk of intussusception associated with the rotavirus vaccine, during post-marketing administration in Ontario.

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CHAPTER 2

2.1 Preface to Manuscript 1

The following manuscript demonstrates the fulfillment of my first two thesis objectives: 1) to develop and validate an algorithm to accurately identify cases of intussusception in Ontario's health administrative data, and 2) to use the validated algorithm to describe the baseline incidence of intussusception in Ontario prior to introduction of the publicly funded vaccine program. The study presented in this manuscript received approval from the research ethics boards of The Ottawa Hospital and of the Children's Hospital of Eastern Ontario (CHEO), and from the Institute of Clinical Evaluative Sciences (see Appendix 2-4). The manuscript titled "Validation of Diagnostic Codes for Intussusception and Quantification of Childhood Intussusception Incidence in Ontario, Canada: A Population-Based Study" has been published in the *Journal of Pediatrics* (2013 Jun 25. pii: S0022-3476(13)00583-0. doi: 10.1016/j.jpeds.2013.05.034 [Epub ahead of print]).

In the context of identifying cases of disease in health administrative data, an algorithm is a combination of health services utilization and diagnostic codes, including physician billing, hospital discharge, procedural, and/or laboratory contact codes. The validity of incidence data derived from studies using health administrative data depends entirely on the accuracy of the algorithms used to define cases, and they must therefore be carefully evaluated before being applied.

In order to accomplish the objective of developing and validating an algorithm to identify cases of intussusception, the following steps were taken (see also Figures 2.1.1 and 2.1.2). Further details can be found in the manuscript.

1) We identified true cases of intussusception by reviewing the clinical charts of intussusception patients seen at the Children's Hospital of Eastern Ontario (CHEO). Cases of intussusception confirmed by chart review served as the true-positive reference standard;
2) We linked each patient selected for chart review to their health administrative data at ICES;
3) Using Ontario's health administrative data, we identified all children living in Ottawa during the study period but not presenting to CHEO for intussusception. These children, as well as those deemed true negative cases by chart review, comprised the true-negative reference standard.
4) We used the true-positive and true-negative reference standards to validate an algorithm to accurately identify intussusception in Ontario's health administrative data.
5) We applied the validated algorithm to quantify the baseline incidence of IS in Ontario prior to the launch of the publicly funded rotavirus vaccination program.

Supplementary information about the study including the list of postal codes used to define the Ottawa area, and the data extraction form used for the chart review, are presented in Appendices 5 and 6. In addition to the results summarized in the final manuscript, supplementary results of subgroup and sensitivity analyses are presented in Appendix 7.

Figure 2.1-1: Flow diagram of algorithm project methods (part 1)

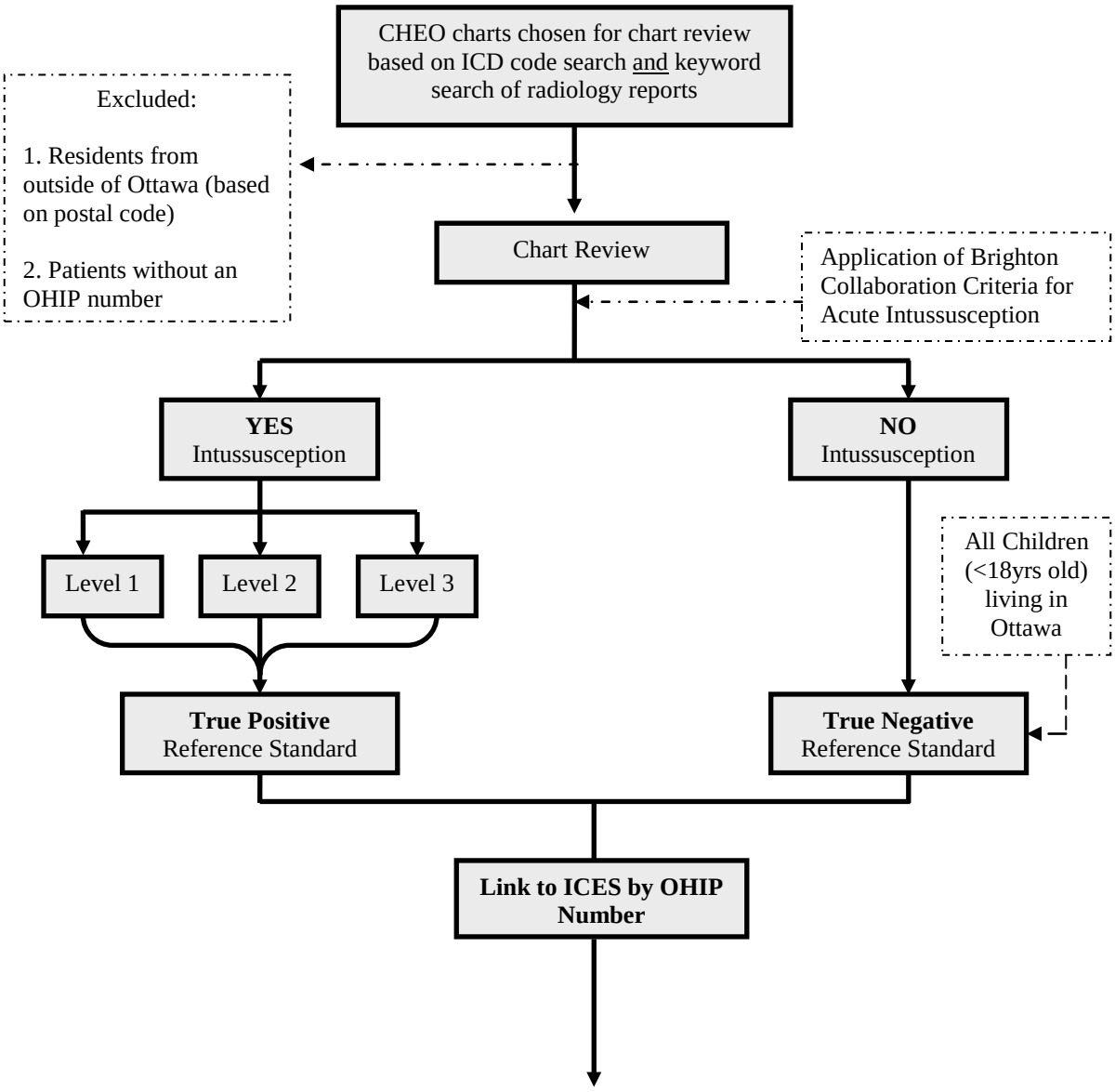
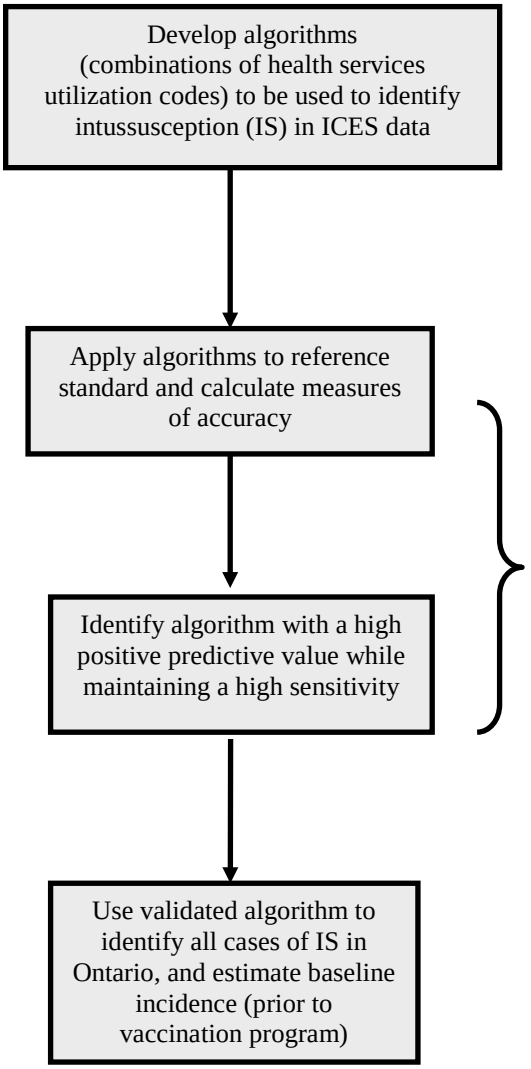


Figure 2.1-2: Flow diagram of algorithm project methods (part 2)



Algorithm	Reference Standard (Chart Review)	
	IS	**No IS**
IS (Algorithm+)	True Positive (TP)	False Positive (FP)
No IS (Algorithm –)	False Negative (FN)	True Negative (TN)

2.2 Manuscript 1

Validation of Diagnostic Codes for Intussusception and Quantification of Childhood Intussusception Incidence in Ontario, Canada: A Population-Based Study

(Adapted from the manuscript published in the Journal of Pediatrics)

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Short title: A Validation Study for Intussusception in Ontario, Canada.

Abbreviations:

PPV: positive predictive value

ICD: International Classification of Disease

CHEO: Children's Hospital of Eastern Ontario

ICES: Institute for Clinical Evaluative Sciences

CIHI-DAD: Canadian Institute for Health Information Discharge Abstract Database

OHIP: Ontario Health Insurance Plan

NACRS: National Ambulatory Care Reporting System

ED: emergency department

FYs: fiscal years

NPV: negative predictive value

RR: relative risk

95% CI: 95% confidence intervals

Keywords:

Intestinal obstruction; Validation; Health administrative data; Diagnostic accuracy; Sensitivity and specificity; Predictive values; Health services research; Epidemiology

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Financial Disclosure Statement: Robin Ducharme was supported by an Ontario Graduate Scholarship from the Ontario Ministry of Training, Colleges and Universities. Eric Benchimol is supported by a Career Development Award from the Canadian Child Health Clinician Scientist Program. Steven Hawken is supported by a doctoral scholarship from the Canadian Institutes of Health Research (CIHR). Dean Fergusson holds a New Investigator award from CIHR. Kumanan Wilson is supported by the Canada Research Chair in Public Health policy.

Conflict of Interest Statement: The authors declare no conflicts of interest.

ABSTRACT

Objectives: To validate an algorithm to identify cases of intussusception using Ontario, Canada's health administrative data, and to apply the algorithm to estimate provincial incidence of intussusception, preceding the introduction of the universal rotavirus vaccination program.

Study Design: We determined the accuracy of various combinations of diagnostic, procedural and billing codes using the chart abstracted diagnosis of patients of the Children's Hospital of Eastern Ontario (CHEO) as the reference standard. We selected an algorithm which maximized positive predictive value (PPV) while maintaining a high sensitivity, and utilized it to ascertain annual incidence of intussusception for fiscal years 1995 to 2010. We explored temporal trends in incidence using Poisson regression.

Results: The selected algorithm included only the International Classification of Disease (ICD)-9 or ICD-10 code for intussusception in the hospitalization database, and was sensitive (89.3%) and highly specific (>99.9%). The PPV of the ICD code was 72.4%, and the negative predictive value was >99.9%.

We observed the highest mean incidence (34 per 100,000) in males <1 year of age. Temporal trends in incidence varied by age group. There was a significant mean decrease in incidence of 4% per year in infants (<1 year) until 2004 and rates stabilized thereafter.

Conclusions: We have demonstrated that intussusception can be accurately identified within health administrative data using validated algorithms. We have described changes in

temporal trends in intussusception incidence in Ontario and established a baseline to allow ongoing monitoring as part of vaccine safety surveillance.

INTRODUCTION

Intussusception is the most common type of acute intestinal obstruction seen in infants (1). Males under 1 year of age are at highest risk, with peak risk occurring between 4 and 8 months of age (1). Clinical presentation varies by age, however commonly reported signs or symptoms include abdominal pain, vomiting, rectal bleeding, abdominal distension, abdominal mass, and abnormal or absent bowel sounds (1-3). While abdominal ultrasound and x-ray are used for assessment, confirmation of a diagnosis of intussusception requires laparotomy or radiologic studies including air-contrast or liquid-contrast enema (4). Estimates of intussusception rates from regions around the world vary widely. Although genetic, environmental and dietary factors may play roles in the level of susceptibility, the variation in incidence observed between geographic regions and temporal periods may also represent disparities between studies in diagnostic and ascertainment methods and rigor (1, 5-7).

This study was conducted in response to the World Health Organization's recommendation that countries introducing rotavirus vaccination programs also implement post-licensure safety surveillance in order to monitor for increased incidence of intussusception (8). In this study we developed and validated an algorithm to identify cases of intussusception from within health administrative data. Based on our validated algorithm, we estimated incidence of intussusception in the pediatric population of Ontario, Canada prior to the introduction of the universal Rotarix^{TM} vaccination program in August 2011.

METHODS

This study was approved by the Research Ethics Boards of the Children's Hospital of Eastern Ontario (CHEO) and The Ottawa Hospital.

Data Sources

Ontario, Canada has approximately 13.5 million residents as of 2011, of whom 20% are under the age of 18 (9). Data for all individuals enrolled in the Ontario Health Insurance (OHIP) plan (virtually all residents of Ontario), are individually linked and housed at the Institute for Clinical Evaluative Sciences (ICES; Toronto, Ontario, Canada).

We identified hospital admissions to acute care hospitals using the Discharge Abstract Database (DAD), physician claims data from OHIP, emergency department (ED) visits from the National Ambulatory Care Reporting System (NACRS), and demographic data from the Registered Persons Database. Canada Census area profiles from the 1996, 2001, and 2006 Canadian Censuses were used. All patient-level data were linked across the multiple databases using the encrypted ICES unique identifier (IKN), to ensure the privacy and confidentiality of health information. Hospitalizations before April 1, 2002 were assigned diagnostic codes from the International Classification of Disease (ICD)-9, and those after April 1, 2002 used ICD-10. NACRS used ICD-10 classification, while OHIP data contained an abbreviated three-digit ICD-9 classification for diagnosis. Patient data collected through chart review were linked to ICES databases by health card number and then de-identified.

Algorithm Validation Sample

CHEO is the sole tertiary pediatric health care centre serving the Census Metropolitan Area of Ottawa, Canada (population 883,000 in 2011). The vast majority of children <18 years requiring admission to hospital or surgical intervention are treated at CHEO. While other Ottawa EDs may treat a limited number of children <18 years, all identified cases of suspected or confirmed intussusception are transferred to CHEO.

For our true positive reference standard population, we identified all incident cases of intussusception in children <18 years seen in the ED or admitted to hospital at CHEO between fiscal years (FYs) 1995 and 2010 (April 1, 1995 to March 31, 2011). Patients were excluded if they did not reside within the Census Metropolitan Area of Ottawa, did not have a valid OHIP number, or did not have a complete medical chart available. We identified patients using an electronic search of CHEO's health records database using intussusception-related ICD codes (ICD-9: 560.0, 543.9, 751.5; ICD-10: K56.1, K38.8, and Q43.8). To supplement the ICD search, an electronic keyword search for "intussusception" was conducted on all dictated air-contrast enema, barium enema and abdominal ultrasound reports beginning on February 1, 2006 (earliest date available in the database).

We reviewed the hospital charts of identified patients and applied diagnostic criteria from the Brighton Collaboration Intussusception Working Group (10) (Table 1). For patients with multiple visits for intussusception, we reviewed only the index visit. To ensure consistency, both the main reviewer (RD) and clinical expert (EIB) conducted a blinded review of a 10% sample of charts. After discussion and reconciliation, the agreement rate was 100%. In addition, the clinical expert completed an independent review of all cases of

Level 3 diagnostic certainty, and of Level 2 diagnostic certainty with a possible alternative cause for symptoms, as determined by the main reviewer.

On the assumption that CHEO treats all children with intussusception living in Ottawa, our negative reference standard comprised all children < 18 years living in the Census Metropolitan Area of Ottawa between FYs 1995 and 2010 and not identified as cases of intussusception by our chart review. We assembled the true negative reference standard population by identifying children who had not reached the age of 18 years by the last day of each fiscal year, and then combining these groups into an overall cohort.

Algorithm Selection

We calculated measures of diagnostic accuracy including sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for various algorithms incorporating ICD diagnostic codes in the DAD and/or NACRS databases, relevant procedural codes in the DAD, and physician billing codes in the OHIP database (Table 2; online). We calculated 95% confidence intervals (95% CI) for the algorithm properties using the binomial distribution. We performed pre-specified subgroup analyses by age group, sex and level of diagnostic certainty. We also explored the effect of the supplemental radiology database search (beginning in 2006) and compared ICD-9 and ICD-10 codes with subgroup analyses by incidence date. We aimed to select an algorithm with a high PPV (to minimize false positives), while maintaining a high sensitivity (of approximately 90%).

Estimates of Intussusception Incidence

We applied the selected algorithm in the health administrative data to obtain estimates of the annual incidences of intussusception in Ontario from FYs 1995 to 2010. Crude overall and stratified incidence rates (by age group and sex) were calculated per 100,000 children <18 years of age. Denominators were based on inter-censal population estimates from Statistics Canada. We standardized incidence rates by sex and age group to the 2001 Canadian Census population structure using the direct standardization method (11). Confidence intervals were calculated based on the Gamma distribution (12). We used multivariable Poisson regression to model the relationship between year of diagnosis and incidence while controlling for age group and sex. Due to significant interactions between age group and year of incidence as well as age group and sex, we stratified the regression analysis by age group.

RESULTS

Reference Standard Sample

A total of 1448 patient records were identified by electronic diagnostic code search and keyword search of radiology reports. Of the 565 patient charts meeting inclusion and exclusion criteria, 150 were classified as cases of intussusception according to the Brighton Collaboration Criteria for Acute Intussusception (10): 125 cases of Level 1 diagnostic certainty and 25 cases of Level 2 and Level 3 diagnostic certainty (Figure 1). The median age of the 150 cases at diagnosis was 1.3 years (IQR: 0.7 to 2.8; range: 2 days to 16.7 years) and 134 (68.7%) were male.

Algorithm Properties

Of the 565 patient charts included in the chart review, 100% of the records were successfully linked to their health administrative data. The accuracies of various algorithms for classifying Ottawa children according to true diagnosis are presented in Table 3. Of the algorithms tested, we selected the algorithm including only the ICD-9 or ICD-10 code for intussusception in the CIHI-DAD as it had the highest PPV while maintaining a high sensitivity.

Subgroup and sensitivity analyses

The ICD codes were more accurate in identifying cases of intussusception in infants <1 year as compared to cases in children between 1 and 18 years of age (PPV (95% CI) = 77.1% (65.6 to 86.3) vs. 70.9% (61.5 to 79.2), respectively). The algorithm captured 96% of the true cases of Level 1 diagnostic certainty, and 44% of the true cases of Level 2 or Level 3 diagnostic certainty. In a post-hoc sensitivity analysis, we excluded children who attended a hospital outside Ottawa for intussusception based on provincial administrative data. These patients would not have been ascertained with chart selection methods, and therefore would have been considered false positives based on incomplete reference standard. After excluding these cases, the PPV improved to 82.6%.

Comparing test properties of the ICD-9 and ICD-10 codes for intussusception in the CIHI-DAD, sensitivity of the ICD-9 code for intussusception was higher than that of the ICD-10 code, however the PPV of the ICD-10 code was improved over the ICD-9 code (Table 4; online).

Cohort Creation and Annual Incidence Estimates

Applying our algorithm of CIHI-DAD ICD-9 and ICD-10 codes to the entire province, we identified 1629 children <18 years as having intussusception in Ontario between April 1, 1995 and March 31, 2011. Of these, 1042 were male (64.0%). The proportion of male patients varied between age groups, ranging from 60.4% in infants <1 year, to 69.6% in children over 8 years. The median age was 1.6 years (IQR: 0.7 to 3.3; range: 0 days to 16.8 years).

The standardized incidences of intussusception in Ontario between FYs 1995 and 2010 are displayed in Table 5. Age- and sex-stratified crude incidences for Ontario in FYs 1995 to 2010 are presented in Table 6 (Table 6; online). We observed the highest incidence in infants <1 year of age, and rates were higher in males than in females within each age category.

Sex and age group were both significant predictors of incidence in regression analysis (male vs. female incidence ratio 1.74 (95% CI 1.57, 1.92); <1 year vs. 8-17 years incidence ratio 63.35 (95% CI 51.93, 77.29)). In infants <1 year, there was a significant decrease in incidence over time (Table 7; online). Decreasing incidence occurred prior to 2004, and rates stabilized after that time (Figure 2). In children aged 3-7 years, incidence significantly increased over time, whereas there were no significant trends over time in children aged 1-2 years or 8 years or older (Table 7; online). Male sex was significantly associated with increased rates of intussusception in all age groups.

DISCUSSION

In this study, we validated an algorithm based on ICD-9 and ICD-10 codes for intussusception, and found them to be sensitive and highly specific in identifying patients with intussusception from within Ontario health administrative data. We used this validated algorithm to estimate annual incidence between FYs 1995 and 2010 and demonstrate changing demographics.

To our knowledge, our study is the first to focus on the validation of intussusception codes to identify patients using health administrative data and to report the accuracy of these codes. Several other studies have used chart abstraction to validate cases of intussusception identified from electronic diagnostic code searches but the majority of these studies did not quantitatively report on the accuracy of the codes (13-18). A German study reported that identification of cases using an ICD-10 code in addition to a procedural code for desinvagination resulted in improved specificity by eliminating suspected and unconfirmed intussusception cases, while maintaining an acceptable sensitivity (14). Contrary to these findings, our results indicate that the addition of a procedural code for identification of patients with intussusception did not improve the accuracy of the algorithm. As could be expected, the addition of a procedural code improved the predictive values significantly, but the sensitivity was dramatically reduced.

Our estimates of annual intussusception incidences for infants < 1 year in Ontario were comparable to the results from two studies conducted in the United States (6, 19). In contrast, reported incidences in South Korea (18), Japan (20), Southern Germany (14), and Denmark (15) were substantially higher than our Ontario rates. Some of this variation could be explained by the lack of case validation and/or standardized case definitions for chart

abstraction, admission practice variations, or ethnic/geographic variation in risk. Ethnic variations in intussusception risk have been observed previously in an American study comparing Caucasians to non-Caucasians (19) and in a study comparing indigenous and non-indigenous Australians (5).

As compared to our study, higher estimates of incidence in infants were reported in two population-based prospective studies conducted in Switzerland (17) and in Germany (16) which also employed the Brighton Collaboration Criteria for Acute Intussusception. The rate discrepancies may be explained by the case ascertainment methods, as both studies involved prospective surveillance for intussusception in addition to retrospective data collection to capture any missed cases. As both studies inflated their estimates to reflect the degree of surveillance system underreporting measured in a select number of units, over-adjustment is a possibility if all units did not have similar degrees of underreporting. The variation in incidence between geographic regions and between studies highlights the necessity for investigators to ascertain rates that are specific to the population of interest.

The decrease in rates in Ontario infants over time may be due in part to decreased sensitivity of the ICD-10 code as compared to the ICD-9 code for intussusception. While this explanation can partially account for a decrease in rates after the transition, it cannot account for the downward trend observed over the study years from 1995 to 2004. Reduction in incidence in young children over time has been noted previously in studies conducted in Denmark (15), in Australia (5), and in the United States (6). These studies also showed that trends over time can vary by the levels of patient factors such as age (5, 15) and ethnicity (6).

The strengths of this study include its population-based design and the use of a validated case definition for acute intussusception. Validation of the ICD code for

intussusception will allow for further cost-effective epidemiological and health services research in Ontario using data that is routinely collected as part of the health care system. The ICD-9 and ICD-10 codes for intussusception can now be used prospectively to study trends over time in incidence and health services utilization, and to monitor changes in incidence since a publicly-funded rotavirus vaccination program was introduced for infants in 2011. Our study also has important limitations. Our reference standard data was collected retrospectively, which increases susceptibility to misclassification of disease status. As we were limited to the data documented in the health record, the accuracy of our diagnoses are reliant on the accuracy and completeness of the data in the patient health records. However, we used the validated Brighton Collaboration Case Definition which was proposed specifically for retrospective surveillance of intussusception. While our algorithm identified the vast majority of true cases of Level 1 diagnostic certainty, it disproportionately missed cases of Level 2 or Level 3 certainty. While the difference in misclassification between levels of diagnostic certainty can be viewed as a weakness of our algorithm, the high proportion of Level 1 cases captured is a noteworthy strength. Another important limitation is that our selected algorithm is applicable to identifying hospitalized cases of intussusception which were contained within the CIHI-DAD. Practice variation in hospitalization of cases would result in variation of accuracy of the algorithm across jurisdictions.

The results of our study represent a critical step toward the timely evaluation of rotavirus vaccine safety, as recommended by the World Health Organization. Accurate estimates of intussusception rates are essential as jurisdictions introduce post-marketing surveillance programs to monitor for changes in rates with introduction of mass rotavirus

vaccination programs. We believe that the validation of ICD codes for identifying cases of intussusception resulting from our study will improve the efficiency and accuracy of these post-marketing surveillance efforts.

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Table 2.2-1: Brighton Collaboration Case Definition for the Diagnosis of Acute Intussusception (reproduced with permission from Bines et al., 2004) (10)

Level 1 of Diagnostic Certainty

***Surgical criteria*:**
Demonstration of invagination of the intestine at surgery; and/or

***Radiologic criteria*:**
Demonstration of invagination of the intestine by either air or liquid contrast enema; *or*

Demonstration of an intra-abdominal mass by abdominal ultrasound with specific characteristic features that is proven to be *reduced* by hydrostatic enema on *postreduction ultrasound*;

and/or

***Autopsy criteria*:**
Demonstration of invagination of the intestine.

Level 2 of Diagnostic Certainty

***Clinical criteria*:**
Two major criteria;
or

One major criterion and three minor criteria

Level 3 of Diagnostic Certainty

***Clinical criteria*:**
Four or more minor criteria.

****All Levels of Diagnostic Certainty**

Only in the absence of surgical criteria with the definitive demonstration of an alternative cause of bowel obstruction or intestinal infarction at surgery (i.e. volvulus or congenital pyloric stenosis).

Major and Minor Criteria

Major criteria

1. *Evidence of intestinal obstruction*:
- History of bile-stained vomiting; *and*
- Examination findings of acute abdominal distension and abnormal / absent bowel sounds;
or
- Plain abdominal radiograph showing fluid levels *and* dilated bowel loops.

2. *Features of intestinal invagination*:
One or more of the following:
1. abdominal mass;
2. rectal mass;
3. intestinal prolapse;
4. plain abdominal radiograph showing a visible intussusceptum or soft tissue mass;
5. abdominal ultrasound showing a visible intussusceptum or soft tissue mass;
6. abdominal CT scan showing a visible intussusceptum or soft tissue mass.

3. *Evidence of intestinal vascular compromise or venous congestion*:
- Passage of blood per rectum; *or*
- Passage of a stool containing "red currant jelly" material; *or*
- Blood detected on rectal examination.

Minor criteria
- Predisposing factors: <1 year old and male;
- Abdominal pain;
- Vomiting;
- Lethargy;
- Pallor;
- Hypovolemic shock;
- Plain abdominal radiograph showing an abnormal but non-specific bowel gas pattern

Table 2.2-2: List of diagnostic, procedural and physician billing codes included in the various algorithms tested.

ICD Diagnostic Codes		
Diagnosis	**ICD-9 (up to 31-Mar-02)**	**ICD-10 (since 01-Apr-02)**
Intussusception	560.0	K56.1
Procedures in CIHI-DAD		
Type of Procedure	**Codes used up to 31-Mar-02**	**Codes used since 01-Apr-02**
Abdominal x-ray	239	3.NM.10.VN 3.NK.10.VN
	259	3.NK.10.WG
Upper GI tract x-ray	n/a	3.NL.10.VN
Abdominal CT scan	251	3.NM.20.WC 3.NM.20.WA
Abdominal ultrasound	284	3.OT.30.DA 3.OT.30.DD
	286	3.OT.30.DB 3.OT.3O.DG
	289	3.OT.30.DC 3.OT.30.HA
Enema	1039	n/a
Laparotomy / Laparoscopy	6611	1.NP.73.BA 2.OT.70.DA
	6619	1.NP.73.DA 2.OT.70.LA
	6683	1.NP.73.LA
Intestinal reduction without laparotomy	n/a	1.NP.73.BA-PK 1.NP.73.JH
		1.NP.73.CC
Physician Services in OHIP		
Type of Service	**Billing Codes**	
Abdominal x-ray	X100	X110
	X101	X111
	X103	X126
	X104	X197
	X108	X409
	X109	X410
Abdominal ultrasound	J135	J128
	J162	
Reduction of intussusception by enema	J068	
Diagnostic enema (barium or air-contrast)	X112	
	X113	
Laparotomy	E733	S150
	E734	S154
	E736	S156
	S155	S164
	S170	S165
	S175	S166
	S176	S167

	S177 S188 S199 S312 Z538	S169 S172 S171 S188

Figure 2.2-1: Flow diagram of chart review process at CHEO and results following review by a clinical expert, April 1, 1995 to March 31, 2011

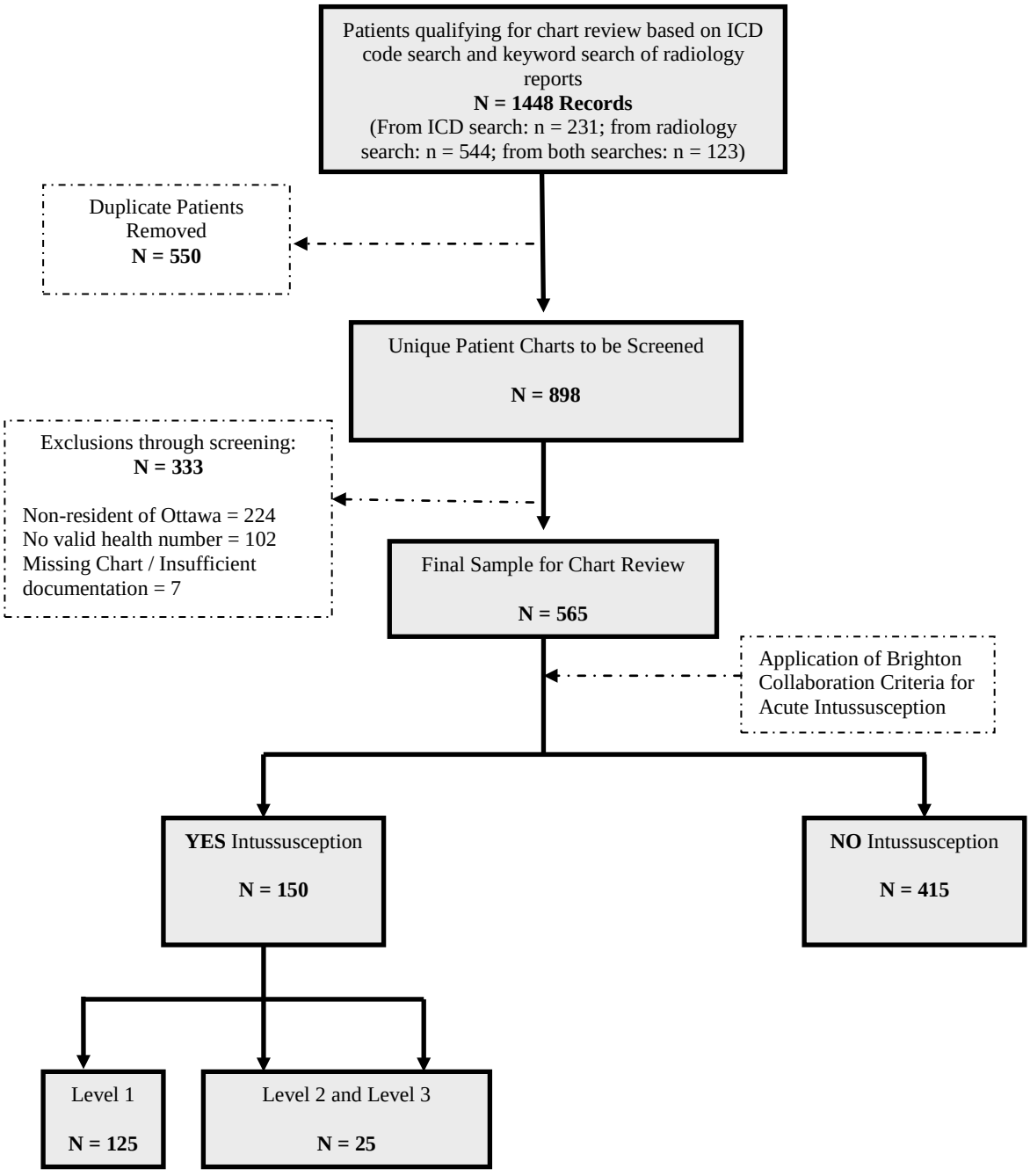


Table 2.2-3: Test properties of various algorithms in identifying true cases of intussusception between 1-Apr-95 and 31-Mar-2011 in children (<18 years old) living in Ottawa.

<table>
<tr><th>Algorithm</th><th>Sensitivity % (95%CI†)</th><th>Specificity % (95% CI†)</th><th>PPV % (95% CI†)</th><th>NPV % (95% CI†)</th></tr>
<tr><td>Algorithms Using CIHI-DAD
N (cases) = 150; N (controls) = 417,847
ICD-9 or ICD-10 code for intussusception in CIHI DAD
<table><tr><th>Algorithm</th><th colspan="2">Chart Review</th><th></th></tr><tr><th></th><th>Yes (n)</th><th>No (n)</th><th>Total</th></tr><tr><td>Yes (n)</td><td>134</td><td>51</td><td>185</td></tr><tr><td>No (n)</td><td>16</td><td>417796</td><td>417812</td></tr><tr><td>Total</td><td>150</td><td>417847</td><td>417997</td></tr></table></td><td>89.3
(83.3, 93.8)</td><td>>99.9
(>99.9, 100.0)</td><td>72.4
(65.4, 78.7)</td><td>>99.9
(>99.9, 100.0)</td></tr>
<tr><td>ICD-9 or ICD-10 code for intussusception in CIHI-DAD
+
CIHI procedure code for intestinal reduction or laparotomy during hospitalization
<table><tr><th>Algorithm</th><th colspan="2">Chart Review</th><th></th></tr><tr><th></th><th>Yes (n)</th><th>No (n)</th><th>Total</th></tr><tr><td>Yes (n)</td><td>31</td><td>7</td><td>38</td></tr><tr><td>No (n)</td><td>119</td><td>417840</td><td>417959</td></tr><tr><td>Total</td><td>150</td><td>417847</td><td>417997</td></tr></table></td><td>20.7
(14.5, 28.0)</td><td>>99.9
(>99.9, 100.0)</td><td>81.6
(65.7, 92.3)</td><td>>99.9
(>99.9, 100.0)</td></tr>
<tr><td>Algorithm Using NACRS (post-2002 only)
N (cases) = 103; N (controls) = 398,468
ICD-10 code for intussusception in NACRS
<table><tr><th>Algorithm</th><th colspan="2">Chart Review</th><th></th></tr><tr><th></th><th>Yes (n)</th><th>No (n)</th><th>Total</th></tr><tr><td>Yes (n)</td><td>67</td><td>60</td><td>127</td></tr><tr><td>No (n)</td><td>36</td><td>398,408</td><td>398444</td></tr><tr><td>Total</td><td>103</td><td>398468</td><td>398,571</td></tr></table></td><td>65.1
(55.0, 74.2)</td><td>>99.9
(>99.9, >99.9)</td><td>52.8
(43.7, 61.7)</td><td>>99.9
(>99.9, >99.9)</td></tr>
<tr><td>Algorithm Using OHIP: Level 1 diagnostic certainty
N (cases) = 125; N (controls) = 417,872
ICD-9 or ICD-10 code for intussusception
+
OHIP billing code for diagnostic enema or enema reduction within 2 weeks
<table><tr><th>Algorithm</th><th colspan="2">Chart Review</th><th></th></tr><tr><th></th><th>Yes (n)</th><th>No (n)</th><th>Total</th></tr><tr><td>Yes (n)</td><td>89</td><td>20</td><td>109</td></tr><tr><td>No (n)</td><td>36</td><td>417852</td><td>417888</td></tr><tr><td>Total</td><td>125</td><td>417872</td><td>417997</td></tr></table></td><td>71.2
(62.4, 79.0)</td><td>>99.9
(>99.9, 100.0)</td><td>81.7
(73.1, 88.4)</td><td>>99.9
(>99.9, 100.0)</td></tr>
</table>

† Exact confidence intervals were calculated using the binomial distribution.

Table 2.2-4: Comparison of test properties between ICD-9 and ICD-10 codes in identifying true cases of intussusception in Ottawa.

Measures of Accuracy	ICD-9 Code for Intussusception in CIHI-DAD (1-Apr-95 to 31-Mar-02) N (cases) = 47; N (controls) = 281,467	ICD-10 Code for Intussusception in CIHI-DAD (1-Apr-02 to 31-Mar-11) N (cases) = 103; N (controls) = 377,671
Sensitivity, % (95% CI†)	**97.9** (88.7, 100.0)	**84.5** (76.0, 90.9)
Specificity, % (95% CI†)	**>99.9** (>99.9, 100.0)	**>99.9** (>99.9, 100.0)
Positive predictive value, % (95% CI†)	**63.0** (50.9, 74.0)	**79.82** (71.0, 86.9)
Negative predictive value, % (95% CI†)	**>99.9** (>99.9, 100.0)	**>99.9** (>99.9, 100.0)

† Exact confidence intervals were calculated using the Binomial distribution.

Table 2.2-5: Annual incidence rates of intussusception in Ontario children (<18 years of age), standardized to the 2001 Canadian Census population structure by age-group and sex.

FYs	Number of incident cases in Ontario	Ontario rate per 100,000 person-years (95% CI)
1995	129	4.2 (3.5, 5.0)
1996	100	3.3 (2.7, 4.0)
1997	89	3.0 (2.4, 3.7)
1998	112	3.9 (3.2, 4.7)
1999	105	3.7 (3.0, 4.5)
2000	95	3.4 (2.7, 4.1)
2001	90	3.2 (2.5, 3.9)
2002	120	4.3 (3.6, 5.2)
2003	90	3.3 (2.6, 4.0)
2004	87	3.1 (2.5, 3.9)
2005	94	3.4 (2.7, 4.1)
2006	86	3.1 (2.4, 3.8)
2007	96	3.4 (2.8, 4.2)
2008	113	4.0 (3.3, 4.8)
2009	106	3.7 (3.0, 4.5)
2010	117	4.1 (3.4, 4.9)

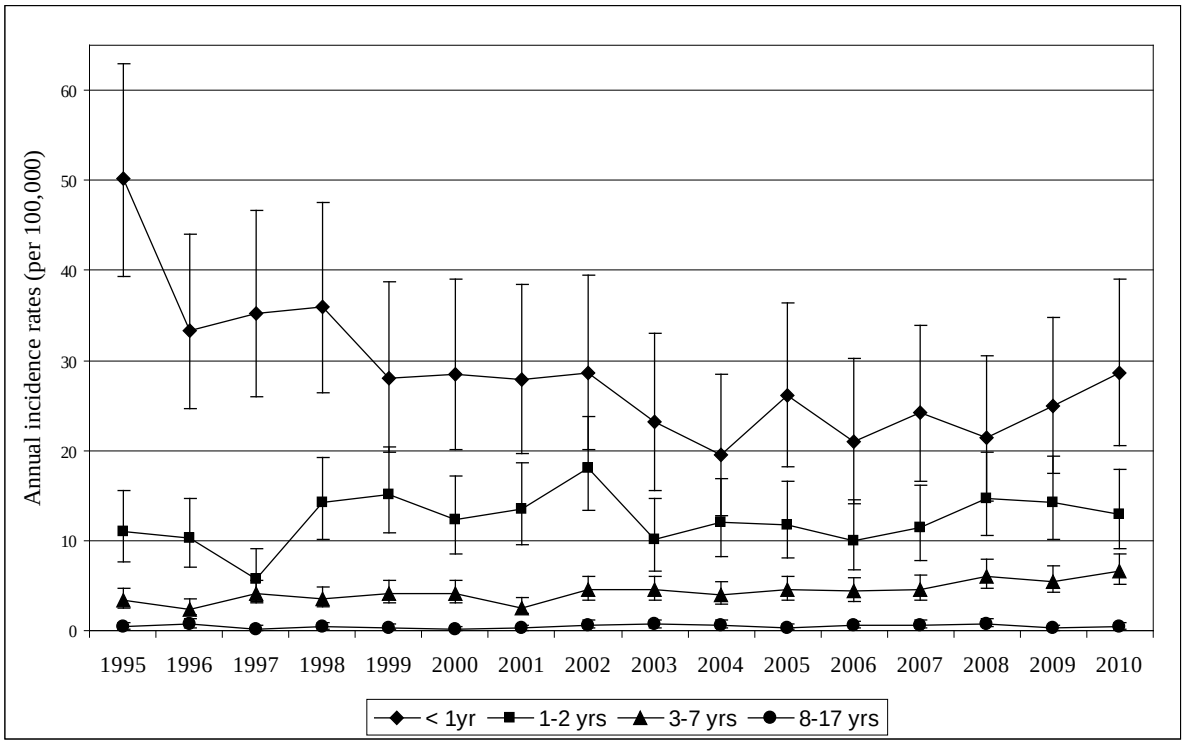
Table 2.2-6: Stratified crude annual incidence rates of intussusception in Ontario

FYs	Sex	Incidence per 100,000 population (95% CI)			
		< 1 year	1-2 years	3-7 years	8-17 years
1995	M	52.7 (37.6, 71.7)	14.7 (9.2, 22.3)	3.4 (1.8, 5.8)	0.7 (0.2, 1.6)
	F	47.5 (32.9, 66.4)	7.3 (3.7, 13.1)	0.8 (0.2, 2.3)	0.1 (0.0, 0.8)
1996	M	38.5 (25.8, 55.3)	15.3 (9.7, 23)	1.0 (0.3, 2.6)	0.9 (0.4, 1.9)
	F	27.9 (17, 43.1)	5.4 (2.3, 10.5)	1.6 (0.6, 3.4)	0.4 (0.1, 1.2)
1997	M	43.0 (29.0, 61.4)	8.0 (4.2, 14.0)	3.6 (1.9, 6)	0.3 (0.0, 1.0)
	F	27.1 (16, 42.8)	3.3 (1.1, 7.8)	1.8 (0.7, 3.8)	0.1 (0.0, 0.8)
1998	M	46.8 (32, 66.1)	20.1 (13.5, 28.8)	2.5 (1.2, 4.7)	0.5 (0.1, 1.3)
	F	24.5 (14, 39.8)	8.3 (4.3, 14.5)	1.8 (0.7, 3.8)	0.3 (0.0, 1.0)
1999	M	25.3 (14.7, 40.5)	16.5 (10.5, 24.8)	4.1 (2.3, 6.6)	0.4 (0.1, 1.1)
	F	31 (18.9, 47.9)	13.7 (8.2, 21.3)	1.3 (0.4, 3.1)	0.3 (0.0, 0.9)
2000	M	36.6 (23.7, 54.1)	21 (14, 30.1)	3.3 (1.8, 5.7)	0.3 (0.0, 0.9)
	F	20.0 (10.6, 34.1)	3.6 (1.2, 8.4)	2.1 (0.9, 4.2)	0.0 (0.0, 0.0)
2001	M	26.5 (15.7, 41.9)	14.9 (9.3, 22.8)	1.8 (0.7, 3.7)	0.5 (0.1, 1.3)
	F	29.2 (17.6, 45.7)	12.1 (7.1, 19.4)	1.1 (0.3, 2.7)	0.0 (0.0, 0.0)
2002	M	31.7 (19.6, 48.5)	23.1 (15.8, 32.6)	4.4 (2.6, 7.1)	1.0 (0.4, 1.9)
	F	25.4 (14.5, 41.3)	13 (7.7, 20.6)	1.6 (0.6, 3.5)	0.3 (0.0, 0.9)
2003	M	31.6 (19.6, 48.3)	14.2 (8.5, 22.1)	4.5 (2.6, 7.3)	1 (0.4, 1.9)
	F	14.3 (6.5, 27.1)	6 (2.6, 11.7)	1.4 (0.4, 3.2)	0.4 (0.1, 1.1)
2004	M	27.6 (16.6, 43.1)	16.5 (10.3, 25)	2.5 (1.1, 4.7)	0.6 (0.2, 1.4)
	F	10.8 (4.4, 22.3)	7.5 (3.6, 13.8)	2.5 (1.2, 4.8)	0.7 (0.3, 1.6)
2005	M	30.5 (18.9, 46.6)	16.8 (10.6, 25.2)	3.9 (2.1, 6.5)	0.4 (0.1, 1)
	F	21.5 (11.8, 36.1)	6.6 (3.0, 12.5)	2.0 (0.8, 4.1)	0.4 (0.1, 1.1)
2006	M	26.7 (16.1, 41.7)	11.5 (6.6, 18.7)	3.1 (1.5, 5.5)	0.5 (0.1, 1.2)
	F	14.9 (7.2, 27.5)	8.6 (4.5, 15)	2.6 (1.2, 4.9)	0.6 (0.2, 1.4)
2007	M	32.9 (20.9, 49.4)	13.6 (8.2, 21.2)	4.2 (2.3, 6.9)	0.8 (0.3, 1.7)
	F	15.0 (7.2, 27.5)	9.3 (5, 15.9)	1.7 (0.6, 3.8)	0.4 (0.1, 1.1)
2008	M	23.7 (13.8, 37.9)	18.6 (12.2, 27.3)	5.8 (3.6, 8.9)	1.4 (0.7, 2.4)
	F	19.0 (10.1, 32.5)	10.7 (6.0, 17.6)	2.6 (1.2, 4.9)	0.1 (0.0, 0.7)
2009	M	26.4 (15.9, 41.3)	21.9 (14.9, 31.2)	4.4 (2.5, 7.2)	0.3 (0.0, 0.9)
	F	23.5 (13.4, 38.1)	6.4 (2.9, 12.1)	3.1 (1.6, 5.6)	0.3 (0.0, 0.9)
2010	M	37.7 (24.8, 54.8)	13.3 (8.0, 20.8)	5.7 (3.5, 8.8)	0.6 (0.2, 1.5)
	F	19.2 (10.2, 32.7)	12.6 (7.5, 19.9)	3.7 (2.0, 6.3)	0.1 (0.0, 0.7)

Table 2.2-7: The effects of diagnosis year on incidence of intussusception, controlled for sex and stratified by age group

Age group	Estimated percent change in incidence for each one year increase (95% CI)	p value
< 1 year	-4.0% (- 2.4 %, - 5.6 %)	< 0.0001
1 – 2 years	1.3% (- 0.5 %, 3.1 %)	0.1604
3 – 7 years	5.4% (3.0 %, 7.9 %)	< 0.0001
8 – 17 years	2.0% (- 2.0 %, 6.2 %)	0.3310

Figure 2.2-2: Trends in crude intussusception incidence rates over time, stratified by age group



CHAPTER 3

3.1 Preface to Manuscript #2

The following manuscript demonstrates the fulfillment of my third thesis objective: 3) to conduct a systematic review of the literature to identify and evaluate the existing observational study designs for post-marketing vaccine safety. To date, the manuscript has not yet been submitted for publication in a peer-reviewed journal.

In addition to the results presented in the following manuscript, additional relevant study materials are presented in Appendices 11 and 12, including the data extraction form and the Reviewer's Guide outlining review procedures.

3.2 Manuscript #2

Epidemiologic Study Designs for Post-Licensure Vaccine Safety: A Qualitative Methodological Review

Robin Ducharme [a, b, c], HBSc, MSc (candidate), Dean A Fergusson [a, b, d, e], MHA, PhD, Steven Hawken [a, b, c], MSc and Kumanan Wilson [a, c, d] MD, FRCPC, MSc.

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b) Department of Epidemiology and Community Medicine, University of Ottawa, Ottawa, Ontario, Canada
c) Institute for Clinical Evaluative Sciences, University of Ottawa, Ottawa, Ontario, Canada
d) Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada
e) Department of Surgery, University of Ottawa, Ottawa, Ontario, Canada.

INTRODUCTION

As the vast majority of the population receive pediatric vaccines, there is a much lower tolerance for vaccine associated adverse events compared to those associated with other health interventions (1). Given that so many healthy people get vaccinated, even extremely rare adverse events are relevant in the appraisal of a vaccine's overall safety (1). While common and uncommon adverse events can be detected in Phase I-III vaccine studies, these studies are not powered to detect rare adverse events occurring at a frequency below 1 in 10,000 (2). Further, pre-licensure clinical trials have stringent inclusion criteria that often result in the exclusion of patients who are at higher risk of adverse events (1). The risk of rare adverse events in the general population, in the presence of complex treatment regimens and other important factors can only be appraised in post-marketing studies (1).

In Canada, there are two national post-marketing vaccine safety surveillance systems: the Immunization Monitoring Program ACTive (IMPACT) and the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS). Epidemiological studies can be implemented to complement these systems, confirming and quantifying associations between vaccines and adverse events. In post-marketing surveillance, researchers rely on observational data to conduct safety analyses of licensed and marketed vaccines. We have the unique ability in Ontario to conduct powerful observational analyses using the population-based datasets housed at the Institute for Clinical Evaluative Sciences (ICES; Toronto, Ontario). Hospitalization, emergency department visits, outpatient care and physician billing data for each resident of Ontario with a valid health card number are housed at ICES, which facilitates the evaluation of health interventions provided to Ontarians, including pediatric vaccines.

Our objective was to identify, describe and evaluate the existing observational epidemiological study designs for post-marketing vaccine safety surveillance. The identification and evaluation of methods and the characterization of their suitability will provide an overview of each study design's strengths and limitations. The results of this study will guide our future work in post-marketing pediatric vaccine safety evaluation, specifically with the use of ICES data.

METHODS

Data Sources

In collaboration with a Librarian at The Ottawa Hospital, we developed a comprehensive search strategy using Medical Subject Heading (MeSH) terms and relevant key words (Appendix 1). References were identified using MEDLINE and EMBASE (OvidSP Interface). Search outputs were exported into Reference Manager® (version 12).

Eligibility Criteria

We included articles that evaluated or discussed at least one study design for assessing potential adverse events as part of post-licensure vaccine safety evaluations. We excluded articles that evaluated or discussed methods for pre-licensure vaccine assessment (i.e. placebo-controlled Randomized Trials). We also excluded articles that focused on vaccine effectiveness, or that focused on safety surveillance systems (i.e. spontaneous reporting systems, passive surveillance and active surveillance).

Study Selection

Titles and abstracts were independently screened by two trained reviewers (RD and RF) for eligibility. All disagreements regarding eligibility were resolved by consensus and discussion of the established eligibility criteria. Following reconciliation, we retrieved the full text of all eligible articles. The two reviewers then independently screened each full-text article for eligibility and disagreements were resolved by consensus. Eligible articles were retained for data extraction. Reasons for exclusion were recorded and classified into common categories.

Data Collection

One trained reviewer (RD) reviewed the included articles and collected the data items of interest using a standardized form, which was designed and pilot-tested *a priori.* We collected data on the methodological features of each study design including: situations suitable for use, methodological strengths and weaknesses, susceptibility to sources of bias and confounding and statistical power. All data collected for this review were entered and maintained in Microsoft Office Excel spreadsheets (Microsoft Inc.). We managed and maintained citations using Reference Manager® (version 12).

RESULTS

Article Selection

We identified a total of 2058 records from our Medline and Embase searches, of which 325 were found to be duplicates. Therefore, a total of 1733 titles and abstracts remained and were screened by both reviewers for inclusion. Of these, we screened 85

potentially eligible articles in full text and retained 14 for data extraction. The reasons for exclusion of articles at the full text screening stage are summarized in Figure 3.2-1.

Article Characteristics

The included articles were published between 1996 and 2012 (Table 3.2-1). Article types included reviews (n=11), simulation studies (n=2) and a re-analysis for a specific study (n=1). Study designs discussed in the included articles ranged from traditional comparative observational designs such as the cohort (3-9) and case-control (3-11) to non-traditional designs such as the case-coverage (12) and risk-interval designs (7, 8), to ecological designs (12), and self-controlled designs such as the self-controlled case series (3-5, 7-9, 11-16) and case-crossover (12, 16) (Figure 3.2- 2). A description of the general study population, exposure of interest, outcomes and comparators for each design is presented in Table 3.2-2. A summary of each study design's characteristics including a general description, information on suitability and strengths and weaknesses are presented in Table 3.2-3 (Appendix).

OVERVIEW OF STUDY DESIGNS IN CONTEXT OF EVALUATING VACCINE SAFETY

Cohort, Case-Control, Case-Coverage and Risk-Interval Designs

The traditional comparative observational designs used for evaluating vaccine safety include the cohort and case-control. Non-traditional designs that have evolved from these include the case-coverage and risk-interval.

In this context, the traditional **cohort design** begins with ascertainment of vaccination and compares the incidence rates of the outcomes of interest between vaccinated and unvaccinated individuals. Utilizing this design allows the calculation of absolute incidence and risk of outcomes. The cohort design is most suitable for vaccinations for which coverage does not approach 100%, as a group of unvaccinated controls is required. For a given number of cases (individuals experiencing the outcome of interest), the cohort design has the highest statistical power of the identified observational designs (8). Studying rare events following vaccination or events occurring long after vaccination using the cohort design is not economical as a very large sample size is required to achieve adequate statistical power and follow-up of subjects over long periods of time can be challenging. These limitations can be overcome when the cohort design is implemented using existing health administrative databases, as the cost and human resources associated with primary data collection and follow-up of subjects can be avoided. The most important limitations of the cohort design is the susceptibility to information and selection bias and confounding associated with comparing vaccinated and unvaccinated individuals. While adjustment for confounders of the association between vaccination and the outcome of interest is possible when such variables are measured (such as socioeconomic status and ethnicity), bias due to unmeasured risk factors is still likely to confound the risk estimates obtained from the cohort study.

The **case-control design** begins with ascertainment of cases and controls and looks back retrospectively to identify vaccination status in each group. Cases are typically matched to controls (sampled from the population from which the cases arose) with respect to known

confounders of the association between vaccination and the outcome of interest in order to control for the confounding effect of these variables. Care must be taken in choosing factors upon which to match cases and controls in order to avoid overmatching. Odds ratios are calculated to estimate association of exposure and disease status. Although absolute measures of risk cannot be obtained using a case-control design, the odds ratio approximates the relative risk when the outcome is rare (10, 17). Since this design begins with the ascertainment of outcomes, it is well-suited to studying rare events and events that occur long after vaccination, and can be used to study multiple vaccinations. Case-control studies generally require fewer subjects than cohort studies, making them more efficient, particularly for rare outcomes. This design can also be used to study multiple exposures. Identification of suitable controls that arise from the same population as the cases is a challenging aspect of employing this design. When implemented using existing health administrative databases, the identification of multiple controls per case is possible, which increases statistical power. The validity of the case-control design is limited by its susceptibility to differential exposure misclassification between cases and controls, in addition to the issues associated with comparing vaccinated to unvaccinated individuals, as with the cohort design. The analysis must be adjusted for confounding factors upon which cases and controls were not matched.

The **case-coverage design** (12) is similar to the case-control design except the vaccine coverage for cases is compared to the vaccine coverage in the entire population, typically obtained from population-based coverage statistics collected for other purposes. Accordingly, this design is only suited to circumstances in which the vaccine coverage data is accurate and reliable. Limitations of this design stem from the inability to control for

confounding factors due to the aggregate nature of the control data. Important individual characteristics are unlikely to be measured and/or available. Bias can also result if the control population for which there is coverage data is inconsistent with the population from which the cases arose.

The **risk-interval design** (7, 8) is a modification of the traditional cohort design, and compares the risk of the event of interest in a 'risk' interval to the risk in the 'control' interval in vaccinated individuals. Time periods before and after vaccination are typically included in the design. The period immediately following vaccination usually comprises the 'risk' interval, and time periods outside of this interval are deemed the 'control' interval. Events occurring within the 'risk' interval are considered exposed cases whereas those occurring in the 'control' interval are deemed unexposed cases. This design is most suitable for acute and self-limiting events since the 'control' interval includes time from before and after vaccination (7). The risk-interval design has advantages over the traditional cohort design in terms of cost and resources as only vaccinated individuals are included. This design also eliminates bias associated with comparing vaccinated and unvaccinated individuals. Limitations of this design include the requirement to explicitly control for time-varying confounders in the analysis, and its susceptibility to the 'healthy vaccinee bias' – which can be controlled for by censoring the affected period from the analysis, or by beginning follow-up after vaccination (7). The 'healthy vaccinee bias' relates to the period immediately preceding vaccination being a particularly healthy time for individuals as many physicians choose to defer vaccination when signs of illness are present, resulting in underestimation of the true background incidence of events (18-20). This bias affects all study designs but is

most evident in designs that compare the risk of events between two periods in time. Misclassification of exposure status and timing can occur in the risk-interval design when implemented using existing databases if vaccination dates are not well-documented or are unreliable.

Ecological Design

An **ecological study** of vaccine safety is undertaken at a group-level with the group defined by place such as a geographical area or by time. Rates of events of interest can be compared between sub-groups with varying vaccination rates, or between time periods within the same population. This design is suited to studying rates of safety outcomes following vaccination campaigns or new vaccination programs. Existing health administrative databases can be used to conduct ecological studies, rendering them relatively inexpensive and quick to complete. The power of the ecological design is increased with a greater difference in coverage of the vaccine studied between groups, geographical areas or time periods. While this design can provide insight into associations between vaccination and events at a population-level, these associations are not necessarily the same at an individual level; a limitation noted in the epidemiological literature as the ‘ecological fallacy’ (12, 21). Seasonal confounding is also an important issue with this design, particularly when rates of outcomes are compared between time periods. Data on individual-level confounders that affect the association between vaccination and the outcome may not be available from aggregate group-level data and may result in distortion of the associations observed in ecological studies.

Self-Controlled Case Series and Case-Crossover Designs

Self-controlled designs used for evaluating vaccine safety, in which the case serves as their own control, include the self-controlled case series and case-crossover designs. In this context, the **self-controlled case series (SCCS) design** (13) is focused on the risk of events within specified periods of time following vaccination (deemed the 'risk' period). The analysis only includes individuals who had the event of interest within the specified period of interest (i.e. cases). Rather than including a separate control group, cases act as their own controls within time periods further removed from the time of vaccination (named the 'control' period). The relative incidence of events in the 'risk' vs. 'control' periods is determined, which characterizes the risk of events with respect to time since vaccination. By excluding separate controls, this design requires fewer subjects than cohort or case-control designs, rendering it more efficient in terms of cost and computational resources. This design is suitable for studying rare acute events following immunization with short latency periods. It can also be used to study recurrent events, provided that each event is independent of one another within the individual or if not independent, clustered events are classified into episodes and only the index episode constitutes the outcome in the analysis. Use of the SCCS requires accurate date of vaccination, as the 'risk' and 'control' periods are based on this date. An assumption of the design is that vaccination exposure must not be affected by previously occurring events. If vaccination is contraindicated or inhibited by previously occurring events, the model must be adjusted to account for this by including only vaccinated cases and beginning follow-up at the time of vaccination. When only vaccinated cases are included in the design, it can be considered a self-controlled risk-interval design (22). While the design implicitly controls for measured and unmeasured fixed confounders (i.e. that do

not change over time), time-varying confounders such as age and seasonal effects must be explicitly controlled for in the analysis. The effect of the 'healthy vaccinee bias' is particularly evident in the SCCS design. Adjustment for this bias can be made either by excluding the period immediately preceding vaccination from the analysis, or by beginning follow-up time only after vaccination occurs. Absolute risk estimates can be obtained from this design when the analysis is conducted at a population-level, or when the exact proportion of the population sampled is known.

The **case-crossover design** (16) is restricted to cases who cross between levels of exposure. Vaccination status is ascertained in a period immediately prior to the event (deemed the 'event' period) and in at least one separate prior period (deemed the 'control' period). The resulting 'event' and 'control' exposure data is similar to that obtained in a matched case-control study. This design is suitable for studying the transient effects of vaccinations on the risk of acute events that occur very close to the time of vaccination. In order to implement the design, dates of vaccination must be well-documented and accurate. An assumption of the design is that the probability of vaccination must be the same in each of the study periods. This limits the applicability of the design and makes in unsuitable for seasonal vaccines and for scheduled pediatric vaccines. As with other self-controlled designs, the case-crossover design has advantages in terms of cost and resources as separate controls are not required. Further, analyzing data within individuals allows for implicit control of fixed measured and unmeasured confounding. Loss of data due to incomplete matching (which can be an issue with the traditional case-control design) is unlikely to occur in the case-crossover design. The typical unidirectional case-crossover design avoids reverse causality bias by excluding any observation time after the outcome occurs. Other sources of

bias may affect the unidirectional case-crossover design such as confounding by contraindication when early signs of disease prevent the use of a vaccine, or exposure-trend bias when the background rate of exposure is changing over time which may occur shortly after the introduction of a new vaccination program (16). The effect of exposure-trend bias can be reduced by using a bidirectional case-crossover design, in which control periods occur both before and after the event of interest.

DISCUSSION

In this methodological review, we have identified 7 observational study designs which have been described in the literature for use in evaluating post-licensure vaccine safety. We have described the suitability, strengths and weaknesses of each design.

We now discuss special considerations in evaluating vaccine safety in each of the following four scenarios: 1) routine pediatric vaccinations, 2) adult vaccinations, 3) new vaccination programs, and 4) seasonal vaccination campaigns.

Routine Pediatric Vaccinations and Adult Vaccinations

For routine pediatric vaccinations such as the Measles, Mumps and Rubella (MMR) vaccine and for adult vaccination such as the Herpes Zoster vaccine, the effect of bias related to the comparison of vaccinated and unvaccinated individuals is evident. In these scenarios, the SCCS is a strong option to study adverse events that occur shortly after vaccination, and implicitly adjusts for individual –level fixed confounding. Our research team has implemented the SCCS method to study adverse events following routine pediatric

vaccinations (19, 23-28). While not suitable for pediatric vaccinations because the probability of vaccination must be equal in all intervals observed, the case-crossover could be used for adult immunizations. The case-crossover design has been used previously to study the association between adult vaccinations and relapse in patients with Multiple Sclerosis (29) (Table 3.2-4 (Appendix)). The risk-interval design is another strong choice, because sources of bias are reduced by only including vaccinated individuals. If long-term effects of pediatric or adult vaccines or outcomes with long latencies are of interest, a case-control or retrospective cohort study can be implemented using existing databases, although care must be taken to limit the effect of confounding either by matching and / or adjustment for important covariates in the analysis. For example, a previous cohort study investigated the risk of Type I Diabetes within the 10 years following Haemophilus influenzae type B vaccination (30). The assessment of causality is generally more challenging for pediatric vaccines because multiple vaccinations are often given within short periods of time, making it difficult to attribute long-term adverse events to any specific vaccine.

New Vaccination Programs

For new vaccination programs such as that for rotavirus in Ontario, the priority may be to obtain a measure of the vaccine's safety at a population level, which can be accomplished using an ecological design such as a time-series analysis. A previous study used an ecological design to evaluate the effect of a mass measles vaccination campaign on population rates of Guillain-Barre Syndrome in children (31) (Table 3.2-4 (Appendix)). This type of design can be used to provide a group-level estimate of the effect of the new vaccination campaign on the rate of adverse events of interest to guide further analyses using individual-level designs such as the SCCS.

Seasonal Vaccination Programs

For seasonal vaccination programs such as those for influenza, it is extremely important to adjust for seasonal effects in whichever study design is implemented. This can be done in a SCCS design by explicitly controlling for calendar time in the Poisson regression model. The risk-interval design with adjustment for seasonality is another suitable option. This design was used previously in a study evaluating the risk of Guillain-Barre Syndrome following influenza immunization (32) (Table 3.2-4 (Appendix)). The case-crossover design is not a suitable option for seasonal vaccines due to the assumption of equal vaccination risk between intervals.

CONCLUSIONS

In the study of very rare outcomes post-vaccination, existing population-level databases, such as those housed at ICES in Ontario, provide an opportunity to conduct robust analyses in an economical and efficient manner. Instrumental to the success of such evaluations is an understanding of the methodological strengths and limitations of the study designs used. For future studies of vaccines by our research team and others, this methodological review will provide insight into the available study designs and will help guide the design and implementation of future safety studies.

ACKNOWLEDGEMENTS

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Figure 3.2-1: Article selection flow diagram

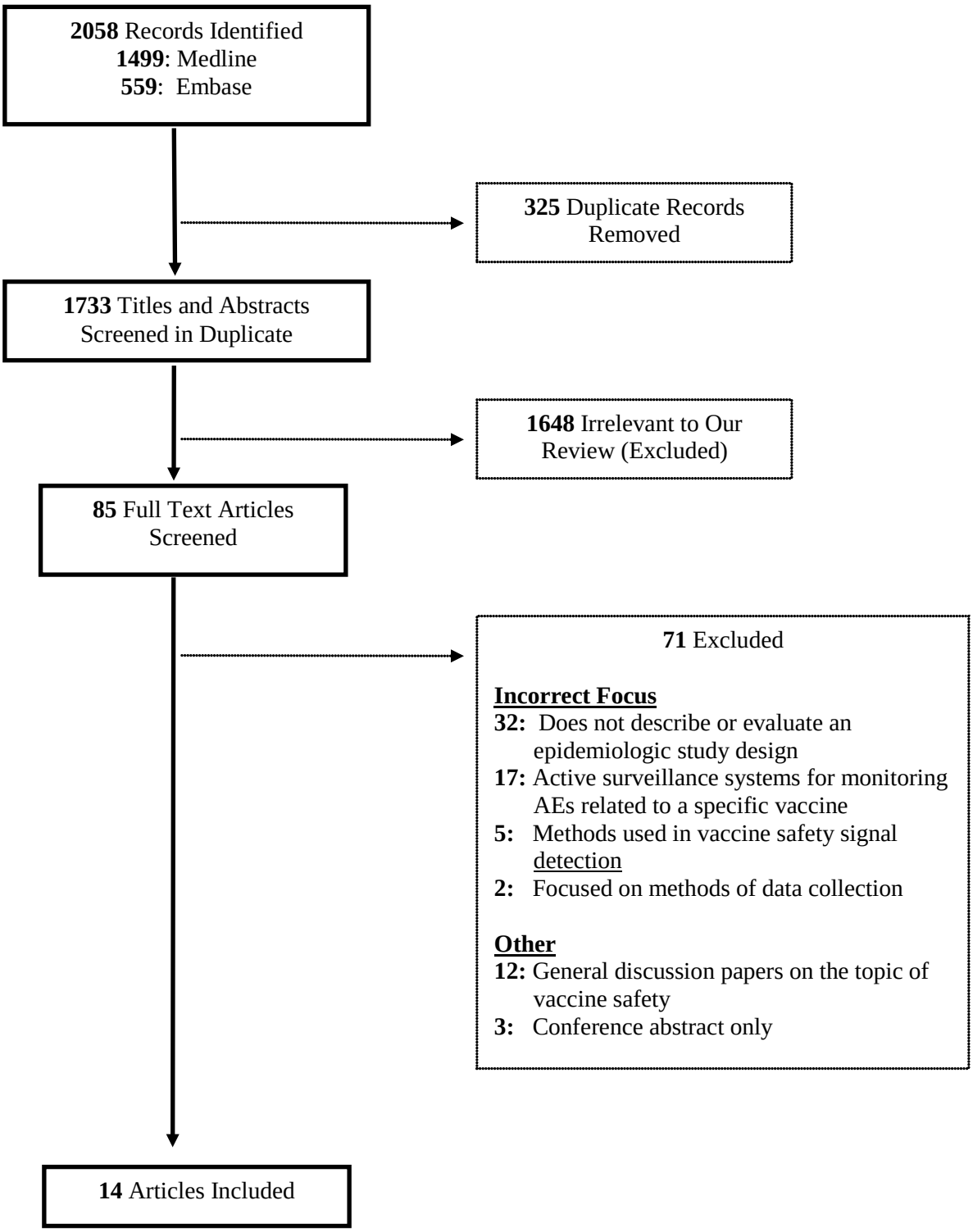

Table 3.2-1: Characteristics of included articles

First Author	Year	Journal	Article Type	Study Design(s) Described
Farrington, C.P.(3)	1996	American Journal of Epidemiology	Review	Cohort Case-Control Self-Controlled Case Series
Rodriguez, L.C. (4)	1999	Epidemiological Reviews	Review	Cohort Case-Control Case-series
Andrews, N.J.(5)	2001	Vaccine	Review	Cohort Case-Control Self-Controlled Case Series
Smeeth, L. (10)	2002	Vaccine	Review	Case-Control
Farrington, C.P. (12)	2004	Vaccine	Review	Case-Crossover Case-Coverage Ecological Self-Controlled Case Series
Chen, R.T. (6)	2004	Vaccine	Review	Cohort Case-Control
Whitaker, H.J. (13)	2006	Statistics in Medicine	Review	Self-Controlled Case Series
Glanz, J.M. (7)	2006	Journal of Clinical Epidemiology	Retrospective Simulation Study	Cohort Case-Control Risk-Interval Self-Controlled Case Series
Hocine, M.N. (11)	2007	Vaccine	Re-analysis for Research Study	Case-Control Self-Controlled Case Series
McClure, D.L. (8)	2008	Vaccine	Sequential Prospective Simulation Study	Matched-Cohort Case-Control Risk-Interval Self-Controlled Case Series
Whitaker, H.J. (14)	2009	Statistical Methods in Medical Research	Review	Self-Controlled Case Series
Andrews, N.J. (9)	2011	Biologicals	Review	Historical Cohort Case-Control Self-Controlled Case Series
Weldeselassie, Y.G. (15)	2011	Epidemiology and Infection	Review	Self-Controlled Case Series
Maclure, M. (16)	2012	Pharmacoepidemiology and Drug Safety	Review	Case-Crossover Self-Controlled Case Series

Figure 3.2-2: Study Designs Reviewed

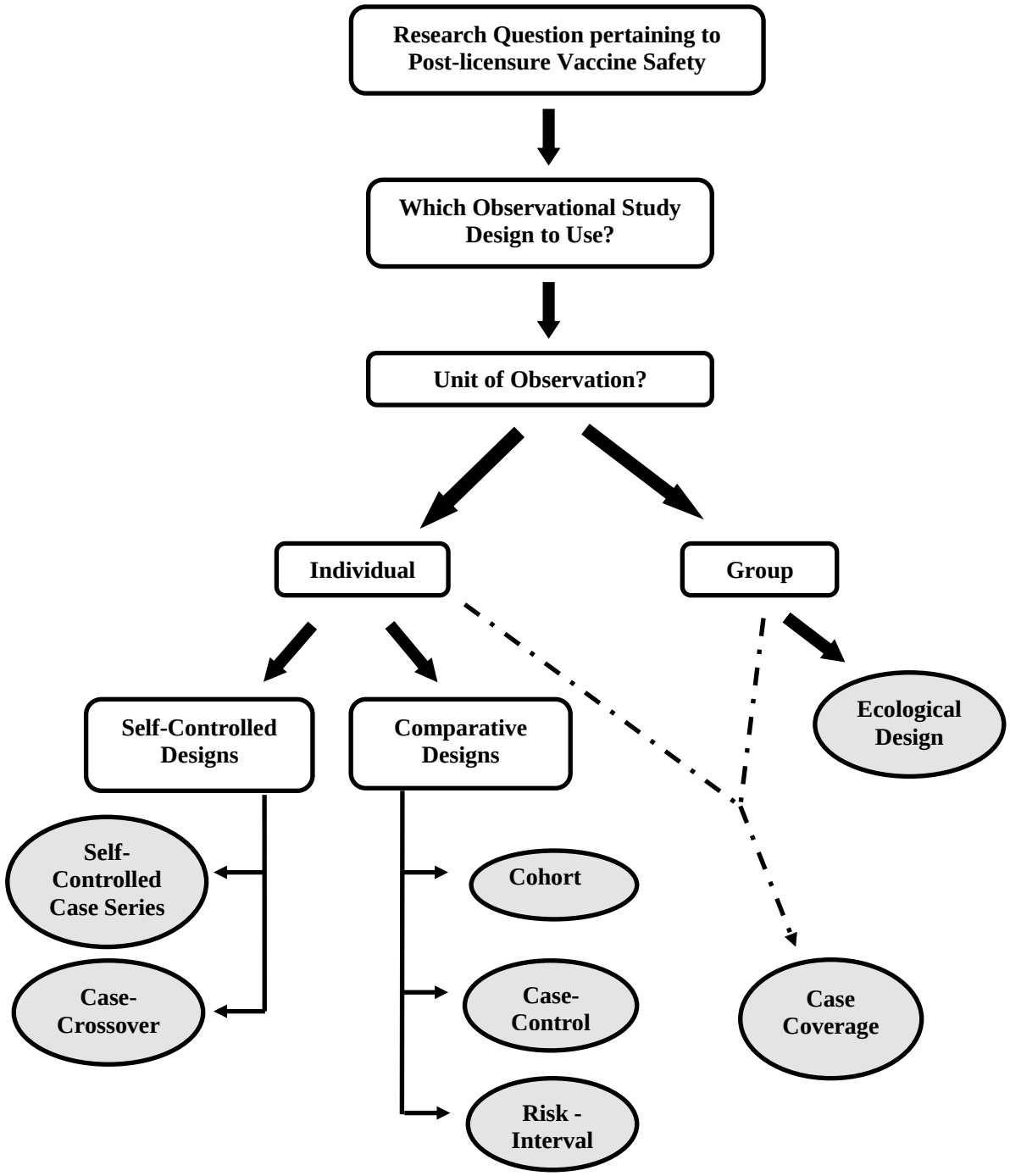

Table 3.2-2: Features of study designs in the context of vaccine safety

Study Design	Study Population	Group of interest / exposure of interest / time interval of interest	Outcome	Comparator
Cohort	Group of individuals, some of which received the vaccine of interest and some of which who did not receive the vaccine	Group of individuals who received the vaccine	Post-vaccination Event of interest	Group of individuals who did not receive the vaccine
Case-Control	Individuals who experienced the event of interest (cases) and individuals who did not experience the event (controls)	Individuals who experienced the event of interest (cases)	Odds of outcome with vaccination exposure	Individuals who did not experience the event of interest – matched to cases by important confounding variables
Case-Coverage	Group of individuals who experience the event of interest and a population for which vaccine coverage data is available	Individuals who experience the event of interest	Vaccine coverage in cases and in the population	Entire population for which coverage data is available (includes cases and controls)
Risk-Interval	Individuals who received the vaccine of interest	Pre-specified 'risk' period immediately post-vaccination	Risk of event of within specified time periods with respect to vaccination	Pre-specified 'control' period further removed from vaccination
Ecological	Populations or sub-populations defined by geography or by time	Level of vaccination coverage, or vaccination program	Rates of event of interest at the population-level	Another population of subpopulation defined by geography or time, having a different level of vaccination coverage, or a different level of exposure to a vaccination program
Self-Controlled	Individuals who	Pre-specified	Events of	Pre-specified

Case Series	experience event of interest within a specified time period	'risk' period defined by the date of vaccination	interest occurring within specified time periods with respect to vaccination	'control' period defined by the date of vaccination
Case-Crossover	Individuals who experience the event of interest	Pre-specified 'event' period immediately before the event of interest	Vaccination occurring within specified periods with respect to the time of event	Pre- specified 'control' period before the 'event' period

APPENDIX 1: Search strategies

The following searches were conducted on April 18, 2012:

Database: Embase Classic+Embase <1947 to 2012 April 18>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

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1 exp *vaccine/ae, co, to [Adverse Drug Reaction, Complication, Drug Toxicity] (18206)

2 exp *vaccination/ae, co [Adverse Drug Reaction, Complication] (3641)

3 *immunization/ae [Adverse Drug Reaction] (584)

4 vaccination reaction/ (1032)

5 ((vaccin$ or immuni$) adj1 (death$ or mortality or safe$ or harm$ or risk$ adverse$ or complicat$ or toxic$)).tw. (4397)

6 or/1-5 (25771)

7 exp *postmarketing surveillance/ (7377)

8 exp *epidemiology/ (206910)

9 *cohort analysis/ (4031)

10 *methodology/ (14277)

11 *case control study/ (2903)

12 *longitudinal study/ (3019)

13 *prospective study/ (3126)

14 *follow up/ (13146)

15 (cohort$ or case series or case control$ or surveillance).ti. (161802)

16 *case study/ (2832)

17 or/7-16 (398742)

18 6 and 17 (768)

19 limit 18 to english language (692)

20 (animal$ not human$).sh,hw. (7306249)

21 19 not 20 (680)

22 21 use emczd (559) EMBASE SEARCH

23 exp *Vaccines/ae, co, po, to, mo (9780)

24 exp *Vaccination/ae, co, mo (2033)

25 exp Immunization/co, mo (351)

26 ((vaccin$ or immuni$) adj1 (death$ or mortality or safe$ or harm$ or risk$ adverse$ or complicat$ or toxic$)).tw. (4397)

27 or/23-26 (14734)

28 epidemiologic methods/ (205046)

29 epidemiologic research design/ or research design/ (1832896)

30 exp epidemiologic studies/ (3118704)

31 exp Product Surveillance, Postmarketing/ (28184)

32 (cohort$ or case series or case control$ or surveillance).ti. (161802)

33 or/28-32 (4823813)

34 27 and 33 (2507)

35 limit 34 to (english language and humans) (2062)

36 35 use prmz (1499) MEDLINE SEARCH

37 22 or 36 (2058)

38 remove duplicates from 37 (1761)

Table 3.2-3 (Appendix): Summary of characteristics of study designs in the context of evaluating vaccine safety

Study Design	Description	Suitability	Strengths	Weaknesses
Cohort	• Traditionally, this design begins with ascertainment of vaccination status then follow-up is done for incidence of illness in each group, either prospectively or retrospectively • Can be modified to a matched-cohort in which individuals exposed to the vaccine are matched one-to-one to unexposed individuals on factors such as sex and birth date (or variation thereof) • Historical cohorts using an existing database to look back at rates of outcomes by level of exposure	• Suitable for rare exposures • Can be used to analyze multiple outcomes • Can be used for both unique events and recurrent events (provided recurrent events are independent) • Works best with a very large study population and when all confounding variables can be measured • Not ideal when vaccine-related adverse events are rare, or few unvaccinated controls are available and / or there are unmeasured confounders between vaccinated and unvaccinated groups • For a traditional cohort design, it is required that vaccine coverage is not approaching 100 percent • Historical cohorts are possible to implement for outcomes occurring a long time after vaccination	• Traditional cohort design is simple to understand • Has the most power for any given number of cases • Incidence rate, relative risk, confidence intervals and absolute and attributable risk can be calculated • Minimizes survivor bias	• If primary data collection is required, this design is impractical and expensive for rare outcomes as the sample size must be very large to achieve good power • For primary data collection, it is expensive for adverse events with long latency periods • Traditional cohort design may suffer from confounding by variables related both to avoidance of vaccination and to the outcome of interest (i.e. ethnicity, socioeconomic status, health states) • May be long duration • Exposure may change • Maintaining follow-up can be difficult • Detailed study of mechanism not possible • When using existing databases there can be restricted amounts of data on confounding variables
Case-Control	• Individuals with the adverse event of interest are cases and a sample of those without the adverse event are selected as a control group • Each case is matched to one or more controls based on potentially confounding factors • Age at event onset in the case is used as the reference age for ascertaining vaccination exposure – within a specified time interval prior to the reference age • Influence of vaccination on the	• Suitable for rare events or those with long latencies • Can be used even if vaccine coverage is high in cases as long as not all controls have received the vaccine • Well-suited to electronic database research for obtaining multiple controls per case • Can be used to investigate the risk of adverse events occurring at any time after vaccination as well as during specified time windows	• Lower cost than cohort studies for rare events if primary data collection is required • Require smaller overall sample sizes than cohort studies • Able to estimate relative incidence for rare events • Can study multiple causes of events (i.e. multiple exposures) • Smaller sample size	• Finding appropriate controls to match with cases can be difficult, particularly in studies not utilizing population-based databases – can result in loss of data due to incomplete matching • may suffer from confounding by variables related both to avoidance of vaccination and to the outcome of interest (i.e. ethnicity, socioeconomic status, health states) • Less efficient than cohort studies

	event of interest is obtained by comparing the proportions of exposed cases and controls. • Odds ratio is used to determine the ratio of odds of developing the adverse event in vaccinated vs. unvaccinated children.		facilitates collection of a larger number of variables, enabling control of confounding • Confounding can be controlled by matching cases to controls on confounding variables	when prevalence of exposure is low • Need to adjust for confounding factors on which cases and controls were not matched • Since the sampling fraction is not typically known, it is not possible to calculate attributable risk • Study of mechanism not possible • Relies on retrospective recall and records • Can only study one outcome variable at a time
Case-Coverage	• Compares vaccine coverage between cases and a control group, which consists of the whole population • Similar to an unmatched case-control design with the population as a control group but in case-coverage design, both cases and non-cases are included in the controls	• Design is only suitable when there is reliable coverage data	• For primary data collection, efforts are concentrated on cases, requiring less resources than the case-control design	• Control for confounding using stratified analyses may not be possible with aggregate coverage data • Can only be undertaken when there is reliable coverage data • The population for which coverage data is available may not correspond exactly to that from which the cases are drawn (may produce biased estimates)
Risk-Interval	• When vaccine coverage is high, the cohort design can be modified to a risk-interval design in which rates of outcomes are compared in different periods with respect to vaccination • Design includes only vaccinated individuals • Time intervals before and after vaccination are used • The risk-interval encompasses a period immediately following vaccination during which events are classified as exposed cases • The non-risk interval encompasses time periods outside of the risk-interval during which events are classified as unexposed cases • Incidence rates of events in each	• Suitable for acute, self-limiting events following vaccination because the control periods includes time periods before and after vaccination • Suitable for acute exposures and outcomes	• Requires much less data than a cohort study • Power approaches that of cohort • Bias relating to the differences between vaccinated and unvaccinated populations is eliminated by only including vaccinated individuals	• Time-varying confounders such as seasonality or age must be explicitly controlled for in the analysis • Susceptible to the healthy vaccinee bias which can lead to an underestimate of the true background incidence of disease – can be corrected by censoring the time period preceding vaccination from the analysis or starting follow-up after vaccination

	interval are calculated by dividing the total number of events by the total person-time at risk in a particular period • Relative incidence is calculated by comparing the risk in the hypothesized risk period to the control period			
Ecological	• Group-level design with groups typically defined by a place or a time • Comparisons are made between rates or frequencies of adverse events in sub-groups with different vaccine coverage levels • Can also be undertaken using cases only and comparing the distribution of cases between two time periods – one 'exposed' and one 'unexposed'	• Suitable for use in vaccination campaigns and new vaccination programs	• Ability to use control mechanisms such as a before and after comparison in the same population • High vaccine coverage improves power of this design • Can be undertaken using routinely collected data which makes the design economical	• Possibility of confounding with seasonal and temporal effects - can be minimized by using short exposed periods • Inability to control for individual-level confounding • Ecological fallacy - associations observed at the group level do not necessarily translate to the individual level
Self-Controlled Case Series (SCCS)	• Used to study adverse events occurring within a specified time period following vaccination • Requires data only on cases for whom events occurred within a pre-defined observation period • Individuals who do not experience events do not contribute any information about the association between vaccination and the outcome, and can be excluded from the analysis • Cases act as their own controls by contributing time at risk and events in each risk period • Incidence rates of events in exposed time periods are compared to incidence rates in unexposed time periods • For long or indefinite risk periods	• Most suitable for acute adverse events occurring within defined, short time intervals after vaccination • Particularly useful when information on confounders is incomplete • Can also be used to analyze recurrent independent events within an individual, or non-independent recurrent events if the events can be clustered in episodes and the first episode is used. • Requires event not to inhibit subsequent vaccination (ex. If vaccination is contraindicated after the occurrence of an event, further vaccination would be inhibited)	• Less expensive and faster to conduct than cohort studies for rare events • Power approaches that of a cohort study in some situations • More powerful and less expensive than case-control studies • More economical than the risk-interval design because only cases are included • Reduced potential for confounding as individuals act as their own controls, so this controls implicitly for all fixed confounders • Absolute and attributable risk can be estimated if the proportion of cases captured	• Cannot determine the absolute risk of adverse events and cannot obtain absolute measures of effect unless a population-based analysis is being conducted – produces relative incidence only • Can only cope with a single outcome at a time • Time-varying confounders (seasonality and age) must be explicitly controlled for as covariates in model • For non-recurrent events the method works only when the event risk is small over the observation period. • Self-controlled designs can have the issue of misclassification bias when there is difficulty ascertaining exposure status and

	- unexposed cases are included so that age and exposure risk are not confounded. • Allows estimation of the strength of association between a time-varying exposure and a potentially recurring adverse event or a rare non-recurring event • The design can be modified if the post-exposure risk period is not indefinite by starting the observation period at the time of the exposure, and including only vaccinated cases – design then becomes a self-controlled risk interval design (combination of risk-interval and SCCS)		from a defined population is known • Design requires fewer patients and fewer variables – advantage in terms of computational efficiency and data privacy	timing in databases • Susceptible to the healthy vaccinee bias which can lead to an underestimate of the true background incidence of disease – can be corrected by censoring the time period preceding vaccination from the analysis or starting follow-up after vaccination.
Case-Crossover	• Case-only design (individuals who had the event of interest) that includes individuals who cross over between levels of exposure • Standard case-crossover designs are unidirectional, looking at exposure retrospectively from the time of the outcome • Controls are sampled from the case's person-time contributed prior to the event. • Vaccinations are ascertained in a defined 'event' time period immediately prior to the event and in one or more 'control' periods of the same duration from before the 'event' period. • This results in a set of exposure variables for the 'event' and 'control' periods which then can be analyzed as a case-control study.	• Suitable for studying transient effects of vaccinations on the immediate risk of events with acute onset • Not suitable for assessing cumulative effects of vaccinations or events with long latencies. • Should be used when the date of vaccination is well recorded, when unmeasured fixed characteristics of the patients are suspected confounders, and when time-varying confounders can be accounted for. • Requires the underlying probability of vaccination to be the same in all intervals – therefore is not suitable for pediatric vaccinations or seasonal vaccines.	• By analyzing data within individuals, all individual-level and unmeasured confounders can be controlled for • Simple to design as definition of the population from which to sample controls is not required • Loss of data from incomplete matching is less likely to arise than in case-control studies • Ethical benefit by not requiring healthy controls • Design requires fewer patients and fewer variables – advantage in terms of computational efficiency and data privacy • By excluding person-time after the outcome, case-crossover designs eliminate a major opportunity for reverse causality	• Requires a strong assumption that the underlying probability of vaccination should be the same in all intervals – this limits the applicability of the method • Possibility of biases that occur before the measured outcome event such as confounding by contraindication when early signs of the outcome prevent use of the vaccine • As the control period always precedes the event period, unidirectional case-crossover designs are susceptible to exposure-trend bias. If exposure to a vaccine is increasing over time in the source population (such as after initiation of a new vaccination program), the case window will be more exposed than the control window, especially if those windows are long or far apart. • Self-controlled designs can be

				susceptible to misclassification bias when there is difficulty ascertaining exposure status and timing in databases

Table 3.2-4 (Appendix): Examples of vaccine safety studies implementing the featured study designs

Study Design	Description of Study	Study Population	Group of interest / exposure of interest / time interval of interest	Outcome compared between group / exposure / time interval of interest and comparator	Comparator
Cohort	(33) Retrospective cohort study of children aged 1-6 years who received intramuscular vaccinations for whom data was available in the US Vaccine Safety Datalink	Children aged 1-6 who received intramuscular vaccinations (including inactivated influenza, hepatitis A, and diphtheria tetanus-acellular pertussis (DTaP) vaccines)	Intramuscular vaccinations administered in the arm	Medically attended local vaccine reactions	Intramuscular vaccinations administered in the thigh
Case-Control	(34) Case-control study comparing exposure to antibody-stimulating proteins and polysaccharides from vaccines in autistic children vs. matched controls	Autistic children and matched controls	Children with autism	Level of cumulative amount of antigen exposure based on published guidelines of antigen content in specific vaccines	Matched controls
Case-Coverage	(35) One of the analyses is a case-coverage study comparing MMR vaccine coverage between cases of autism and the population overall	Children with core autism, atypical autism or Asperger's syndrome and the overall population of the North East Thames region	Children with core autism, atypical autism or Asperger's syndrome (cases)	MMR vaccine coverage	The North East Thames region overall (controls)
Risk-Interval	(32) Risk-interval study evaluating the association between influenza vaccine and Guillain-Barre Syndrome (GBS)	Elderly patients in the U.S. national Medicare database who received an influenza vaccine between September and December 2000 and 2001	Risk period immediately following vaccination (weeks 0-6 post-vaccination)	Risk of GBS within specified time periods with respect to vaccination	Control period following the risk period (weeks 9-14 post-vaccination)
Ecological	(31) Ecological analysis comparing baseline rates of Guillain-Barré Syndrome (GBS) to those from after a mass measles vaccination campaign	Children aged 9 months to 15 years between 1990 and 1994 in Colombia, Brazil, Argentina and Chile	Mass measles vaccination campaigns in 1992 and 1993, and latent periods thereafter	Rates of GBS	Remainder of study period outside of measles vaccination campaigns (and associated latent periods)

Self-Controlled Case Series	(36) Self-controlled case series study to assess the association between routine pediatric vaccinations and wheezing in premature infants	Premature infants born at specified health maintenance organizations (HMO's) between1997 to 2002 who had a wheezing lower respiratory disease (WLRD) within the first 18 months of life	'Risk' periods – days 1–7, 8–14, 15–30, and 31–44 post-vaccination	Encounters for WLRD within specified time periods with respect to routine pediatric vaccinations	'Control' period – days 45-90 post-vaccination
Case-Crossover	(29) A case-crossover study assessing the association between vaccination and relapse in patients with Multiple Sclerosis	Multiple Sclerosis patients in the European Database for Multiple Sclerosis who had a relapse between the years of 1993 and 1997	Specified 2-month 'event' period immediately before the relapse	Vaccinations occurring in specified periods with respect to the time of relapse	Four specified 2-month 'control' periods prior to the 'event' period

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CHAPTER 4

4.1 Thesis Discussion

Although vaccines are rigorously evaluated for safety in pre-licensure studies, it is imperative that safety evaluation continue after licensure. Pre-licensure studies do not have sufficient sample sizes to detect very rare adverse events, do not evaluate long-term effects of vaccines, and do not use adequately heterogeneous populations that are representative of the general population exposed to vaccines (1).

Pre-licensure studies are typically powered to detect adverse events as rare as 1 in 10,000 (2). In population-level exposures though, even extremely small risks can have a notable impact. For example, according to post-licensure estimates of the risk of intussusception attributable to RotaShield vaccine of 1 in 4670 to 9474 vaccinees, up to an additional 732 cases per year would be expected to occur in the United States if the vaccination program had been fully implemented (3). Once a vaccine is licensed and is introduced into routine use, post-licensure safety evaluations are conducted which may be comprised of active and passive adverse event reporting, and epidemiologic studies (4). Once a possible association is identified from active and passive surveillance, epidemiologic studies can be implemented to evaluate and quantify associations between vaccinations and adverse events. Study designs that are implemented for vaccine safety include the traditional comparative designs such as the cohort and case-control, ecological designs, and designs modified from these including the case-coverage and risk-interval designs. Recently, self-controlled designs such as the self-controlled case series and case-crossover designs have

emerged as popular choices for this purpose as they help to eliminate bias associated with comparing vaccinated and unvaccinated individuals and implicitly control for fixed confounding (5, 6).

In view of the recent implementation of a publicly funded rotavirus vaccination program in Ontario, we undertook the work encompassed by this thesis to help establish a foundation and inform the design of an epidemiologic study to evaluate the association between this vaccine and intussusception in Ontario. We have successfully used administrative data housed at ICES to quantify the background incidence of intussusception in the pediatric population of Ontario. We validated our method of identifying cases of intussusception using a gold standard case definition and primary data collection of cases in Ottawa, Ontario. Although our algorithm had a very high specificity (>99.99%), the rarity of intussusception translates to a limited post-test probability. In a subgroup of infants (<1 year) in our study population, the post-test probability was 77.1%, meaning that each infant identified by our algorithm as having intussusception had a 77.1% probability of being a true case. Due to the further reduction in prevalence in older children and adolescents, the post-test probability would be even further reduced. This highlights the fact that the degree of misclassification of the algorithm will vary depending on the prevalence in the population it is applied to. This limitation affects our absolute estimate of intussusception incidence, and would result in any estimate of absolute or relative change in rates to be biased towards the null.

There are certain pieces of information that we currently know about the rotavirus vaccine in Ontario that will help inform our choice of study designs. Unfortunately, no vaccine-specific billing code for rotavirus vaccine was added to the Ontario Schedule of

Benefits by the Ministry of Health and Long-Term Care upon the introduction of the vaccination program (7). Without a vaccine-specific billing code, vaccination events specific to rotavirus vaccine cannot be identified using the OHIP database housed at ICES. Without the ability to ascertain individual vaccination status, our options of study designs to evaluate rotavirus vaccine using ICES data are severely limited. This highlights the importance of adding vaccine-specific billing codes to the Ontario Schedule of Benefits as new vaccines are introduced. A population-level ecological analysis would be the only option for evaluating the association between the introduction of the rotavirus vaccination program and rates of intussusception. As we have quantified the baseline incidence of intussusception in Ontario, we could now implement a time-series analysis to determine if the institution of the rotavirus vaccination program is associated with an increase of intussusception incidence at the population level, using ICES data. A similar analysis using ICES data was conducted in 2006 to evaluate the association between the introduction of a universal influenza vaccination program and the incidence of Guillain-Barre Syndrome (8). If an ecological design were implemented for rotavirus vaccine safety, our ability to detect a change in intussusception rates would depend on a number of key factors that also contribute to the calculation of the population attributable fraction. Firstly, the strength of any association between the vaccine and intussusception would be paramount. Secondly, the prevalence of the exposure – in this case, the coverage of the vaccine would be very important. Unfortunately, rotavirus vaccine coverage is not measurable using ICES data as we are unable to ascertain vaccination events. The power of the ecological design in detecting a change in intussusception incidence after the introduction of the rotavirus vaccination program depends entirely on the proportion of cases attributable to the vaccine. These issues of vaccine coverage and attributable risk have

previously been cited as explanations for the inability of ecological analyses of the since-withdrawn RotaShield vaccine to detect an association between the vaccine and intussusception rates at a population level, even though the association had been demonstrated by studies using different designs (9).

If a vaccine-specific billing code had been implemented for rotavirus vaccine, we would have been able to conduct a self-controlled case series analysis, which would control implicitly for fixed confounding and would eliminate the bias associated with comparing vaccinated and unvaccinated children. This design is appropriate for this application due to the acute nature of the outcome of interest and the strong dependency of the level of risk on the time since vaccination demonstrated in previous studies (10, 11). This approach to evaluating the rotavirus vaccine could be implemented in other jurisdictions having the ability to ascertain individual-level exposure status using administrative data.

However, given the absence of vaccine-specific billing codes, in order to obtain rigorous evidence of the existence or non-existence of an association between the vaccination and intussusception primary data collection would be required. Due to the rarity of intussusception, this could most efficiently be done in a case-control study or a self-controlled case series analysis, in which cases of intussusception are identified via hospital records and the status of vaccination is determined. This approach was used previously by Patel et al. in a study evaluating intussusception risk after rotavirus vaccination in Mexico and Brazil (10). Case-finding and ascertainment of vaccination status could be implemented using the existing active surveillance system in Canada, IMPACT, which currently operates in 12 hospitals across the country (12). Alternately, a large cohort of vaccinated children could be selected and followed for incident cases of intussusception so that a risk-interval

design could be used, however this would be very resource-intensive and costly to implement because of the large number of children that would be required in order to obtain a sufficient number of cases for the analysis.

On a larger scale, and for evaluation of vaccinations including rotavirus and others, the need for a vaccine registry in Ontario is apparent. Efforts are currently underway by the Ontario government to implement such a system. A registry could facilitate post-licensure vaccine safety surveillance by consolidating data on all vaccine recipients in Ontario, and would allow for rigorous safety evaluations. Until a registry is in place, researchers will continue to evaluate vaccine safety including that for rotavirus vaccine using the available data.

4.2 Thesis Conclusions

In conclusion, we carried out studies to help guide the design of a study to evaluate the safety of the recently publicly funded rotavirus vaccine in Ontario with respect to the risk of intussusception. Using health administrative data and validation of our algorithm with chart data from the Children's Hospital of Eastern Ontario, we quantified the background incidence of intussusception prior to the introduction of the publicly funded vaccination program. We also conducted a systematic review of epidemiologic study designs used to evaluate post-licensure vaccine safety, and summarized the suitability, strengths and weaknesses of each design.

In the context of evaluating rotavirus vaccine safety in Ontario using health administrative data, we concluded that due to an inability to identify vaccination events using

OHIP data, an ecological design would be the only option. Although a time-series analysis could be used to appraise the change in intussusception incidence at a population level after the introduction of the vaccination program, a low population attributable fraction could limit the power of the analysis. If vaccine-specific billing codes had been introduced in Ontario for rotavirus vaccine, the ability to identify vaccination events would have permitted the use of the self-controlled case series design (SCCS). Given the acute nature of intussusception and the effect of time since vaccination on the risk of the event, the SCCS would be an appropriate choice.

Future post-licensure vaccine safety surveillance efforts could be facilitated in the province of Ontario by the simultaneous establishment of vaccine-specific billing codes with the introduction of new vaccines and new vaccination programs. Further, a provincial vaccine registry would be invaluable to the development of ongoing vaccine surveillance for safety and effectiveness in Ontario.

4.3 References

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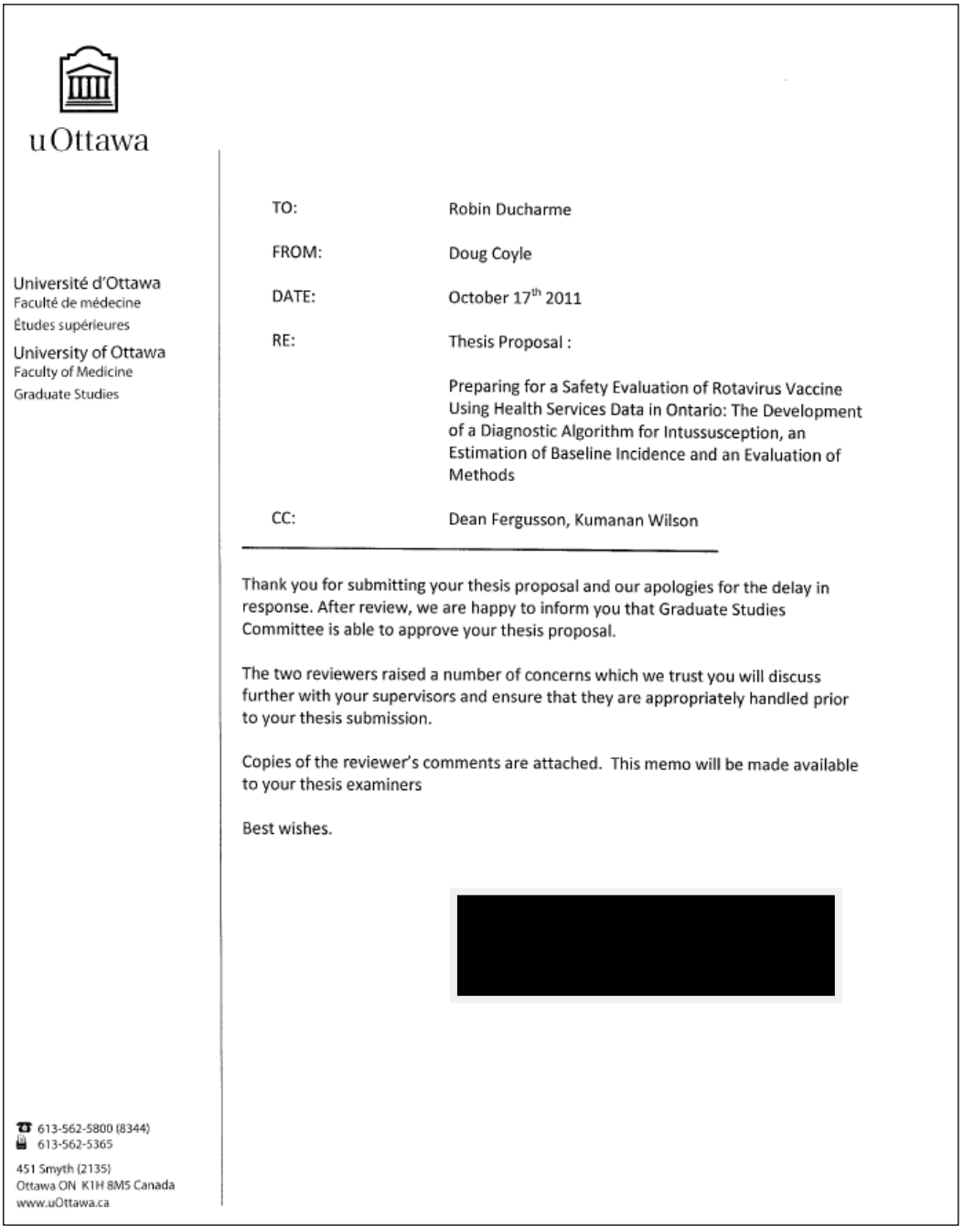
CHAPTER 5

APPENDIX 1: Proposal approval from Graduate Studies Committee



uOttawa

Université d'Ottawa
Faculté de médecine
Études supérieures
University of Ottawa
Faculty of Medicine
Graduate Studies

TO: Robin Ducharme

FROM: Doug Coyle

DATE: October 17th 2011

RE: Thesis Proposal :

Preparing for a Safety Evaluation of Rotavirus Vaccine Using Health Services Data in Ontario: The Development of a Diagnostic Algorithm for Intussusception, an Estimation of Baseline Incidence and an Evaluation of Methods

CC: Dean Fergusson, Kumanan Wilson

Thank you for submitting your thesis proposal and our apologies for the delay in response. After review, we are happy to inform you that Graduate Studies Committee is able to approve your thesis proposal.

The two reviewers raised a number of concerns which we trust you will discuss further with your supervisors and ensure that they are appropriately handled prior to your thesis submission.

Copies of the reviewer's comments are attached. This memo will be made available to your thesis examiners

Best wishes.

[redacted]

☎ 613-562-5800 (8344)
613-562-5365

451 Smyth (2135)
Ottawa ON K1H 8M5 Canada
www.uOttawa.ca

APPENDIX 2: REB approval and renewal from The Ottawa Hospital

UNIVERSITY OF OTTAWA HEART INSTITUTE
INSTITUT DE CARDIOLOGIE DE L'UNIVERSITÉ D'OTTAWA

uOttawa

Ottawa Hospital Research Ethics Boards / Conseils d'éthique en recherches

725 Parkdale Avenue, Box 411, Ottawa, Ontario K1Y 4E9 613-798-5555 ext. 14902 Fax: 613-761-4311
http://www.ohri.ca/ohreb

December 2, 2011

Dr. Kumanan Wilson
Ottawa Hospital - Civic Campus
[redacted]

Dear Dr. Wilson:

Re: Protocol # 2011771-01H **Preparing for a Safety Evaluation of Rotavirus Vaccine Using Health Services Data in Ontario. The Development of a Diagnostic Algorithm for Intussusception, an Estimation of Baseline Incidence and an Evaluation of Methods**

Protocol approval valid until - **December 1, 2012**

Thank you for your letter dated November 22, 2011. I am pleased to inform you that this protocol underwent expedited review by the Ottawa Hospital Research Ethics Board (OHREB) and is approved. No changes, amendments or addenda may be made to the protocol without the OHREB's review and approval.

If the study is to continue beyond the expiry date noted above, a Renewal Form should be submitted to the OHREB approximately six weeks prior to the current expiry date. If the study has been completed by this date, a Termination Report should be submitted.

The Ottawa Hospital Research Ethics Board is constituted in accordance with, and operates in compliance with the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; Health Canada Good Clinical Practice: Consolidated Guideline; Part C Division 5 of the Food and Drug Regulations of Health Canada; and the provisions of the Ontario Health Information Protection Act 2004 and its applicable Regulations.

Yours sincerely,

[redacted]

Raphael Saginur, M.D.
Chairman
Ottawa Hospital Research Ethics Board

/cb

UNIVERSITY OF OTTAWA HEART INSTITUTE
INSTITUT DE CARDIOLOGIE DE L'UNIVERSITÉ D'OTTAWA

uOttawa

Ottawa Hospital Research Ethics Boards / Conseils d'éthique en recherches

725 Parkdale Avenue, Box 411, Ottawa, Ontario K1Y 4E9 613-798-5555 ext. 14902 Fax: 613-761-4311
http://www.ohri.ca/ohreb

November 5, 2012

Dr. Kumanan Wilson
Ottawa Hospital - Civic Campus
[redacted]

Dear Dr. Wilson:

RE: Protocol# - 2011771-01H **Preparing for a Safety Evaluation of Rotavirus Vaccine Using Health Services Data in Ontario. The Development of a Diagnostic Algorithm for Intussusception, an Estimation of Baseline Incidence and an Evaluation of Methods**

Renewal Expiry Date - December 1, 2013

I am pleased to inform you that your Annual Renewal Request (listed above) was reviewed by the Ottawa Hospital Research Ethics Board (OHREB) and is approved. No changes, amendments or addenda may be made in the protocol without the OHREB's review and approval.

Renewal is valid for a period of one year. Approximately one month prior to that time, a single renewal form should be sent to the OHREB office.

The Tri-Council Policy Statement requires a greater involvement of the OHREB in studies over the course of their execution. As well, you must inform the Board of adverse events encountered during the study, here or elsewhere, or of significant new information which becomes available after the Board review, either of which may impinge on the ethics of continuing the study. The OHREB will review the new information to determine if the protocol should be modified, discontinued, or should continue as originally approved.

Yours sincerely,

[redacted]

Raphael Saginur, M.D.
Chairman
Ottawa Hospital Research Ethics Board

/kd

APPENDIX 3: REB approval and renewal from CHEO

OCT 27 2011

RESEARCH ETHICS BOARD APPLICATION FORM
FOR RETROSPECTIVE CHART REVIEW AND SECONDARY ANALYSES OF CLINICAL DATA

Please submit the **original and one copy** of the application, protocol and applicable documents for review.
Please ensure that all questions are answered in full. Only complete applications will be accepted.

PROTOCOL TITLE:	PROTOCOL #
Preparing for a Safety Evaluation of Rotavirus Vaccine Using Health Services Data in Ontario: The Development of a Diagnostic Algorithm for Intussusception, an Estimation of Baseline Incidence and an Evaluation of Methods Note: This project will be a Master's Thesis for Robin Ducharme	11/152X *For office use only*

Indicate nature of the project
☒ Retrospective ☐ Prospective secondary use of clinical data

PRIMARY CHEO SITE INVESTIGATOR:

NAME	DIVISION OR PSU	TELEPHONE
Eric Benchimol	Gastroenterology	[redacted]

SECONDARY CHEO CO-INVESTIGATORS *(use supplementary pages as required.)*

NAME	DIVISION OR PSU	TELEPHONE	SIGNATURE

MEMBERS OF THE RESEARCH TEAM WHO WILL HAVE ACCESS TO THE INFORMATION *(Other than those named above)*

NAME	ROLE ON THE RESEARCH TEAM	TELEPHONE	SIGNATURE
Robin Ducharme	Graduate Student (MSc candidate, University of Ottawa)	[redacted]	[redacted]
Steven Hawken	Senior Methodologist and ICES Researcher	[redacted]	[redacted]

PLEASE LIST ANY CO-INVESTIGATORS WITH A PRIMARY AFFILIATION TO THE UNIVERSITY OF OTTAWA (OTHER THAN CHEO PHYSICIANS). The CHEO REB will inform the university of the outcome of its review. The University will then conduct an abridged administrative review of all projects previously approved by the CHEO REB.

Dean Fergusson	Departments of Medicine, Surgery, & of Epidemiology and Community Medicine / OHRI	[redacted]	[redacted]
Kumanan Wilson	Department of Medicine / OHRI	[redacted]	[redacted]

RETROSPECTIVE CHART REVIEW AND SECONDARY ANALYSES OF CLINICAL DATA – CONT'D

SUMMARY OF CHART REVIEW AND SECONDARY USE OF CLINICAL DATA PROPOSALS

Please provide a brief description of the proposed research (approximately one page), which must include the following information:

1. The data abstraction form or the list of data fields to be collected should be appended to this form. Name, Date of Birth, & Full Postal Code should not be collected.
2. Any probable linkage of data (i.e., techniques used to link together records which relate to the same individual in one or more data sets). Why this is necessary and how this will be achieved?
3. Rationale and hypotheses.
4. Anticipated benefit.
5. Anticipated harms and how these will be addressed.

N.B.: It is good practice to assign a unique study number to each subject. The study number can be linked to the CHEO unique hospital number in a separate password-protected file. The study data would be held in a file in which only the study number appears. This then ensures that the study data are completely de-identified and decreases the risk of personal information becoming accessible should it be lost or stolen.

SUMMARY OF CHART REVIEW AND SECONDARY USE OF CLINICAL DATA PROPOSALS (Cont'd):

Name additional REB's who have reviewed the application and indicate the status of the review.	Approved	Disapproved	Pending (anticipated date of approval)
Ottawa Hospital Research Ethics Board	❑	❑	❑Awaiting CHEO approval
ICES Privacy Officer	❑	❑	❑ Awaiting CHEO approval
_____	❑	❑	❑ _____

FUNDING OR SPONSORING AGENCY:

☐ Study both funded and initiated by an Industry (Pharmaceutical or other), specify company name:

_____

_____

Please provide name and address of contact person: _____

_____

A fee of **$3,000.00** will be charged for the review of any research project partially or fully funded by private industry, and is applied whether the study is submitted to full board or expedited review. Consideration will be made for exemption from the review fee, on a case-by-case basis. Requests for an exemption must be made in writing to the Chair, CHEO Research Ethics Board.

CHEO Research Ethics Board

APPROVAL

Chair's Signature: [redacted]

Date: December 15, 2011

CHEO

CONTINUING REVIEW FORM – ANNUAL RENEWAL – DELEGATED (EXPEDITED) REVIEW

For Minimal Risk Protocols originally reviewed under the delegated stream,
Or Full Board protocols re-directed to delegated annual renewal.

REB PROTOCOL NUMBER:	**11/152X**	**SPONSOR'S PROTOCOL NUMBER:**	**n/a**	**CHEO RI COST CENTRE**	**n/a**
PROTOCOL TITLE:	Preparing for a Safety Evaluation of Rotavirus Vaccine Using Health Services Data in Ontario: The Development of a Diagnostic Algorithm for Intussusception, an Estimation of Baseline Incidence and an Evaluation of Methods				
PRIMARY CHEO SITE INVESTIGATOR:	**Dr Eric Benchimol**	**TELEPHONE** [redacted]		**EMAIL:** [redacted]	

SECONDARY CHEO CO-INVESTIGATORS *(use supplementary pages as required)*

Have any of the co-investigators been added or removed since the last approval? ☐ Yes ☒ No

If Yes, specify names below.

NAME:	DIVISION OR PSU	TELEPHONE	EMAIL

STATUS OF RECRUITMENT:

If study is closed, specify date of the last patient enrolled locally:	Date: n/a – no active recruitment in this study
Number of potential subjects (patients) approached for study participation locally since last approval:	n/a
Number of subjects (patients) recruited locally since last approval:	n/a
Total number of subjects (patients) recruited locally since the beginning of the study:	n/a

CONTINUING REVIEW FORM – ANNUAL RENEWAL - DELEGATED (EXPEDITED) REVIEW – CONT'D

STUDY RELATED PROBLEMS ENCOUNTERED WITH SUBJECTS, RECRUITMENT, OR STUDY PROCEDURES:

Has any unexpected problems been noted since last approval? ☐ Yes ☒ No

Has the REB been informed of these? ☐ Yes ☒ No If yes, indicate date approved: _____

Has the study team issued major or minor modifications to the study procedures in response to these problems?

☐ Yes ☒ No If yes, date submitted: _____

MODIFICATIONS SINCE LAST REB APPROVAL:

Have the study procedures been changed (describe below):

Inclusion/Exclusion Criteria ☐ Yes ☒ No Source of subject (patient) population? ☐ Yes ☒ No

A Protocol Deviation Reporting From must be submitted to the REB, and included with this annual renewal form, when these changes were unintended & not previously approved by the Board

☐ Yes ☐ No

Have the consent and assent forms been modified since last approval? ☐ Yes ☒ No

Has the REB been informed of these changes?

☐ Yes A copy of the most recent approved version of the Consent and Assent Forms should be appended to the submission form.

☐ No The revised versions of the Consent and Assent Forms should be appended to the submission. Revisions to the text should be clearly identified in bolded text.

IN THE SPACE BELOW, BRIEFLY DESCRIBE THE PROGRESS OF THE STUDY TO DATE.

Renewals cannot be considered if this section is not completed. If you have published an article with preliminary findings, attach a copy of the article to this submission.

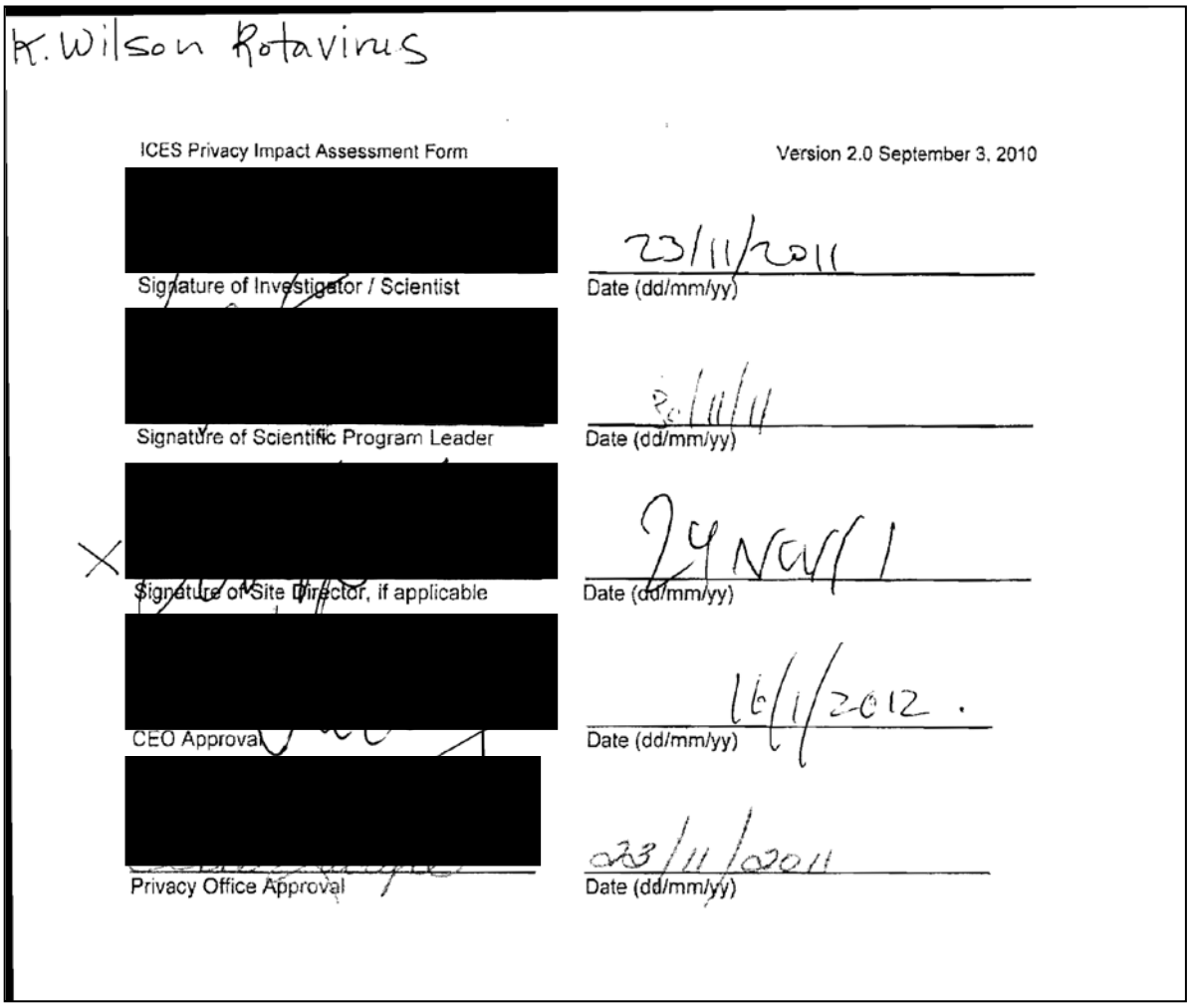
We have completed data collection via retrospective chart review.

The study data has been successfully linked to ICES and the majority of the analyses have been completed. We are currently completing the remaining analyses and writing up the results of the study.

CHEO Research Ethics Board
APPROVAL
Chair's Signature: [redacted]
Date: December 7, 2012

Signature of Primary CHEO Site Investigator:	Date:
[redacted]	OCT 21/12

APPENDIX 4: ICES Study approval



K. Wilson Rotavirus

ICES Privacy Impact Assessment Form — Version 2.0 September 3, 2010

[redacted]

Signature of Investigator / Scientist — Date (dd/mm/yy): 23/11/2011

[redacted]

Signature of Scientific Program Leader — Date (dd/mm/yy): 24/11/11

[redacted]

Signature of Site Director, if applicable — Date (dd/mm/yy): 24 NOV 11

[redacted]

CEO Approval — Date (dd/mm/yy): 16/1/2012.

[redacted]

Privacy Office Approval — Date (dd/mm/yy): 23/11/2011

APPENDIX 5: Data extraction sheet for chart review

Please note that the format of this extraction table has been modified from its original format in Microsoft Excel and broken into sections to fit this page.

	No identifying information should be entered in this spreadsheet - provide Subject ID number only				
	Instruction: For each individual subject, enter "1" for YES or "0" for NO for each individual diagnostic criterion				
Subject ID Number	**Level 1 of Diagnostic Certainty**				
	VERIFICATION	**Surgical criteria:**	**Radiologic criteria:**		**Autopsy criteria:**
	Demonstration of an alternative cause of bowel obstruction or intestinal infarction at surgery (e.g., volvulus or congenital pyloric stenosis)	Demonstration of invagination of the intestine at surgery	Demonstration of invagination of the intestine by either air or liquid contrast enema;	Demonstration of an intra-abdominal mass by abdominal ultrasound with specific *characteristic features*[1] that is proven to be reduced by hydrostatic enema on postreduction ultrasound	Demonstration of invagination of the intestine.
001	0	1	0	1	0
002	1				

Major Criteria											
1. Evidence of intestinal obstruction:			**2. Features of intestinal invagination:**						**3. Evidence of intestinal vascular compromise or venous congestion:**		
History of bile-stained vomiting;	Examination findings of acute abdominal distension and abnormal or absent bowel sounds;	Plain abdominal radiograph showing fluid levels and dilated bowel loops.	abdominal mass;	rectal mass;	intestinal prolapse;	plain abdominal radiograph showing a visible intussusceptum or soft tissue mass;	abdominal ultrasound showing a visible intussusceptum or soft tissue mass;	abdominal CT scan showing a visible intussusceptum or soft tissue mass.	Passage of blood per rectum;	Passage of a stool containing "red currant jelly" material;	Blood detected on rectal examination.
1	0	1	1	0	0	0	0	0	1	1	0

Minor Criteria								Other data items	
Predisposing Factors:		Abdominal pain	Vomiting[2]	Lethargy[3]	Pallor[3]	Hypovolemic shock	Plain abdominal radiograph showing an abnormal but non-specific bowel gas pattern	Date of diagnosis (i.e. date the patient first sought help for condition which led to diagnosis) - enter in format **dd/mm/yyyy**	Known cause of IS? Enter cause if it is known, or enter "0" if none
Age <1 year	Male sex								
0	1	0	1	1	1	0	0	xx/xx/xxxx	0

APPENDIX 6: List of Ottawa area postal codes included in chart review

Postal Code	Area	Postal Code	Area
K0A	Ottawa	K2C	Nepean
K1A	Ottawa	K2E	Nepean
K1B	Ottawa	K2G	Nepean
K1C	Orleans	K2H	Nepean
K1E	Orleans	K2J	Nepean
K1G	Ottawa	K2K	Kanata
K1H	Ottawa	K2L	Kanata
K1J	Ottawa	K2M	Kanata
K1K	Ottawa	K2P	Ottawa
K1L	Ottawa	K2R	Nepean
K1M	Ottawa	K2S	Stittsville
K1N	Ottawa	K2T	Kanata
K1P	Ottawa	K2V	Kanata
K1R	Ottawa	K2W	Kanata
K1S	Ottawa	K4A	Orleans
K1T	Ottawa	K4B	Navan
K1V	Ottawa	K4C	Cumberland
K1W	Orleans	K4K	Rockland
K1X	Ottawa	K4M	Manotick
K1Y	Ottawa	K4P	Greely
K1Z	Ottawa	K4R	Russell
K2A	Ottawa		
K2B	Ottawa		

APPENDIX 7: Additional results from Intussusception study

Table 5.7-1: Results of sub-analyses and sensitivity analyses

Algorithm	Sensitivity (95%CI†)	Specificity (95% CI†)	PPV (95% CI†)	NPV (95% CI†)
Algorithms Using CIHI DAD: Sub-analyses by Age Group				
ICD-9 or ICD-10 code for intussusception (in children under 1 year)	88.52 (77.78, 95.26)	99.99 (99.99, 100.00)	77.14 (65.55, 86.33)	100.00 (99.99, 100.00)
ICD-9 or ICD-10 code for intussusception (in children over 1 year)	87.64 (78.96, 93.67)	99.99 (99.99, 99.99)	70.91 (61.48, 79.18)	100.00 (100.00, 100.00)
Algorithms Using CIHI DAD: Sub-analyses by Age Group and Sex				
ICD-9 or ICD-10 code for intussusception (in females under 18 years old)	89.36 (76.90, 96.45)	99.99 (99.99, 99.99)	70.00 (56.79, 81.15)	100.00 (99.99, 100.00)
ICD-9 or ICD-10 code for intussusception (in males under 18 years old)	89.32 (81.69, 94.55)	99.98 99.98, 99.99)	73.60 (64.97, 81.08)	99.99 (99.99, 100.00)
ICD-9 or ICD-10 code for intussusception (in females over 1 year old)	88.46 (69.85, 97.55)	99.99 (99.99, 100.00)	60.53 (43.39, 75.96)	100.00 (100.00, 100.00)
ICD-9 or ICD-10 code for intussusception (in males over 1 year old)	87.30 (76.50, 94.35)	99.99 (99.99, 100.00)	76.39 (64.91, 85.60)	100.00 (99.99, 100.00)
ICD-9 or ICD-10 code for intussusception in CIHI DAD (females under 1 year)	85.71 (63.66, 96.95)	100.00 (99.99, 100.00)	81.82 (59.72, 94.81)	100.00 (99.99, 100.00)
ICD-9 or ICD-10 code for intussusception in CIHI DAD (males under 1 year)	83.72 (69.30, 93.19)	99.99 (99.98, 99.99)	75.00 (60.40, 86.36)	99.99 (99.99, 100.00)

Algorithms Using CIHI DAD: Sub-analyses by Date (pre-2006 vs. post-2006)				
ICD-10 code for intussusception (between 1-Apr-02 and 31-Mar-06)	97.44 (86.52, 99.94)	100.00 (100.00, 100.00)	88.37 (74.92, 96.11)	100.00 (100.00, 100.00)
ICD-10 code for intussusception (between 1-Apr-06 and 31-Mar-11)	76.56 (64.31, 86.25)	100.00 (99.99, 100.00)	79.03 (66.82, 88.34)	100.00 (99.99, 100.00)
ICD-10 code for intussusception (Level 1 cases only between 1-Apr-02 and 31-Mar-06)	100.00 (89.11, 100.00)	100.00 (99.99, 100.00)	74.42 (58.83, 86.48)	100.00 (100.00, 100.00)
ICD-10 code for intussusception (Level 1 cases only between 1-Apr-06 and 31-Mar-11)	88.24 (76.13, 95.56)	99.99 (99.99, 100.00)	72.58 (59.77, 83.15)	100.00 (100.00, 100.00)
Algorithms Using CIHI DAD: Sensitivity analysis Excluding Hospitalizations Outside CHEO				
ICD-9 or ICD-10 code for intussusception in admissions to CHEO only (excluding other hospitals)	88.67 (82.48, 93.26)	99.99 (99.99, 100.00)	82.61 (75.86, 88.12)	100.00 (99.99, 100.00)

[†] Exact confidence intervals were calculated using the Binomial distribution.

Algorithm Misclassification – additional results

Of the 16 cases not captured by our algorithm, the majority (69%) were of Level 2 or Level 3 diagnostic certainty. This was expected because Level 2 and 3 cases are less straightforward to diagnose than the Level 1 cases, which may have led to less consistency with ICD coding at the hospital level, or even a lower probability of hospital admission. Importantly, 96% of the Level 1 cases were appropriately captured by our algorithm. These cases were the most important to capture because by definition, cases of Level 1 diagnostic certainty have been confirmed by radiologic or surgical criteria, and as we observed in our

study, often received treatment to reduce the intussusception either by surgery or hydrostatic enema.

The median ages of the captured vs. missed true positive cases are presented below. The algorithm was equally effective in both male and female children, with 11% of true positive cases missed in boys and girls.

Table 5.7-2: Algorithm misclassification and age

	Captured (n=134)	**Missed (n=16)**	**p-value for Wilcoxon Rank Sum Test**
Median age (IQR)	1.23 (0.70 to 2.49)	3.27 (0.80 to 5.97)	0.0642

As our algorithm captured the vast majority of the true positive Level 1 cases but missed a greater proportion of Level 2 and 3 cases, the demographic differences observed between the captured and missed cases are likely directly attributable to the demographic differences between Level 1 and Levels 2 and 3 cases (presented below).

Table 5.7-3: Age by level of diagnostic certainty

	Level 1 (n=125)	**Levels 2 and 3 (n=25)**	**p-value for Wilcoxon Rank Sum Test**
Median age (IQR)	1.19 (0.69 to 2.30)	2.43 (1.06 to 6.02)	0.0047

We believe that our algorithm's ability to capture the majority of the Level 1 cases is an expected finding and adds validity to the study. Given the proposed application of this algorithm (for rotavirus vaccine safety evaluations), it will be very important to capture the Level 1 cases and those in infants, as these will be most relevant to the vaccine safety evaluation.

APPENDIX 8: Letter of acceptance from the Journal of Pediatrics

From: Journal Office <journal.pediatrics@cchmc.org>
Date: 14 May, 2013 3:50:32 PM EDT
To: Dr. Eric Benchimol
Subject: Your Manuscript # 2013285R1 submitted to JPediatr

Ref.: Ms. No. 2013285R1
Validation of Diagnostic Codes for Intussusception and Quantification of Childhood Intussusception Incidence in Ontario, Canada: A Population-Based Study
The Journal of Pediatrics

Dear Dr. Benchimol,

Thank you for revising and resubmitting your manuscript. The Editors appreciate your efforts. We are pleased to accept your revised manuscript for publication in The Journal of Pediatrics. Please note that Figure 1 and Tables II, IV, VI, and VII will be published in the online version of The Journal; a reference to the electronic material will appear in the print version. We have made other editorial changes, which you will see in the proofs.

We will forward your manuscript to Elsevier, Inc. Before the final publication date, the publisher will send you galley proofs and other relevant material. Please read the proofs carefully and contact the publisher if anything is unclear or incorrect; the authors have final responsibility for the accuracy of the publication.

The Journal of Pediatrics is pleased to be added to Elsevier's Sponsored Articles Program, which offers authors the opportunity to sponsor the cost of their accepted article. Details about this program can be found at http://www.elsevier.com/locate/sponsoredarticles.

Congratulations.

William F. Balistreri, M.D.
Editor

/mlh

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APPENDIX 11: Data extraction sheet for Methods Review

Please note that the format of this extraction table has been modified from its original format in Microsoft Excel and broken into sections to fit this page.

Study Identification				Confirm Eligibility	Basic Study Data			
1	2	3	4	5	6	7	8	9
RefMan ID	**First Author**	**Year of Publication**	**Journal**	**Focused on describing / critiquing / evaluating at least one epidemiologic study design used to evaluate the association between a vaccine and a pre-specified adverse outcome, OR article focused on comparing at least two of such study designs?**	**Type of Article**	**Study Design (s) Discussed (Use one cell per design)**	**General Description of Design**	**What is compared between groups?**
505	XXXX, X	XXXX	Vaccine	Yes	Review	Case-Control	*Each case is matched to one or more controls based on potentially confounding factors such as age or region *The age at onset in the case is used as the reference point in the case and its controls for determining vaccination exposure	* The number of cases and controls with vaccination within specified intervals prior to onset are compared

Methodological Features								
10	11	12	13	14	15	16	17	18
Measure of risk used and description of how it is calculated	**Measures of association used and description**	**Issues with Confounding and How it is Accounted For**	**Strengths / Advantages (point form)**	**Comments on Suitability of Design**	**Limitations / disadvantages**	**Types of bias and Ways to Control**	**Comments on statistical power**	**Other comments**
Not stated	* Odds ratios as obtained from conditional logistic regression	* Some of confounding accounted for by matching *Need to adjust for other confounding factors in analysis	* Lower cost than cohort for rare events * Easy to analyze in most statistical packages	*Suitable for rare events	*Requires a population to be defined from which the cases arose and the controls can be obtained *Need to adjust for confounding factors on which cases and controls were not matched	*Recall bias in retrospective studies, including differential recall of vaccination in cases and controls	*Less power than cohort or SCCS	

APPENDIX 12: Reviewer's Guide for Methods Review

Epidemiologic Study Designs for Post-Licensure Vaccine Safety:
A Qualitative Methodological Review

REVIEWER'S GUIDE

Review Rationale

The Government of Ontario began a publicly funded rotavirus vaccination program using Rotarix™ vaccine in August 2011. In view of an anticipated increase in vaccine uptake, it is an opportune time to proceed with the design and development of a post-marketing safety evaluation plan in Ontario. My overall Thesis project (including this methodological review) will provide Public Health Ontario with the key information required to implement a safety evaluation for rotavirus vaccine in the future.

There are several study designs and methods used to evaluate post-licensure vaccine safety signals. We currently do not know which study design and / or method would be ideal for evaluating the safety of the rotavirus vaccine. In order to implement the most rigorous analysis method for post-licensure safety monitoring of rotavirus vaccine using Ontario's health administrative data, we will conduct a systematic literature review to identify and evaluate the existing study designs and methods of analysis for post-licensure vaccine safety signal evaluation. The identification and evaluation of methods will provide an overview of each study design's strengths and limitations to guide future work in post-licensure pediatric vaccine safety evaluation, including rotavirus vaccine.

Review Objective

To **identify, describe** and **discuss** the available epidemiologic study designs used to evaluate post-licensure vaccine safety signal evaluation (i.e. association between a specific vaccine and a pre-specified outcome).

Research Questions

A. What are the available epidemiologic study designs for evaluation of post-licensure vaccine safety signals?

B. What are the strengths and limitations of each study design and under which circumstances is each design most suitable?

Review Methods

In order to answer the aforementioned research questions, a **protocol** for a systematic **methodological** review was developed.

A **systematic review** is a research method that comprehensively identifies, appraises and summarizes evidence relevant to a specific question using a pre-specified, transparent methodology.

It is important to note the following three important characteristics of the current systematic review:

1. This review is essentially a **qualitative**, not a quantitative study. We will *qualitatively* summarize data from the selected, relevant papers.
2. This review **focuses on study designs used to evaluate post-licensure vaccine safety signals**, rather than safety outcomes associated with any specific vaccine.
3. The types of studies that we will include in this review will be those **discussing or evaluating a study design** used to in the assessment of post-licensure vaccine safety signals. We will not include studies that simply *employ* a specific design.

Your Role as a Reviewer

As you may know, it is common practice in systematic reviews to have at least two reviewers. Reviewers independently screen titles and abstracts identified by the literature search and/or independently extract pre-defined data items from selected data sources. They then compare their findings and reconcile any disagreement.

The method of using two reviewers aims to ensure that all targeted data items are captured as per the systematic review protocol, and aims to enhance the **internal validity** of the review by reducing error and minimizing bias.

Screening

A comprehensive search strategy was developed in collaboration with an Ottawa Hospital Librarian using MeSH (Medical Subject Heading) terms and relevant key words. References were searched and obtained from Medline and Embase (OvidSP Interface).

A copy of the **search output** will be given to you in electronic format for screening. The citations will be provided to you in a Reference Manager database (Reference Manager 12 Software, Thomson Reuters Inc.).

The study inclusion and exclusion criteria are listed in the Study Protocol. Your decision on whether to include or exclude each citation (based on the Study Protocol) will be entered and maintained in a Microsoft Office Excel spreadsheet (Microsoft Inc.).

Title and Abstract Screening: Level 1

For the first level of title and abstract screening, we will retain all records which appear to be focused on discussing a method related to post-licensure vaccine safety in humans (regardless of whether the method relates to passive or active surveillance, or to data collection, study design or statistical analysis). We will retain all papers discussing a method or methodological concepts related to any part of the post-licensure vaccine safety process.

Instructions for recording screening decisions:

- If you judge a citation to be relevant to the review based on title and abstract (i.e. if you think we should review the full text), please enter "1" in the cell next to the citation number.
- If you judge the citation to be irrelevant to the review based on title and abstract, please enter ".".
- Please note that articles should only be excluded at the title and abstract stage if there is enough information to be certain that it does not meet our inclusion criteria, or that it meets our exclusion criteria.

To assist you in title and abstract screening, a checklist of "things to look for" was prepared. Please see Robin for more information or for clarification if required.

<u>Things to Look For – PICOS</u>

1. **Population: Humans**

   Exclusion: Studies focused on animals

2. **Intervention: Any vaccine**

   Exclusion: Studies focused on interventions other than vaccines

3. **Comparator: No comparator, or no vaccine**

4. **Outcomes: Any safety outcome**

   Exclusion: Efficacy or effectiveness outcomes only (see Robin for more information)

5. **Study Design: Methods Paper** (i.e. article discussing or describing a method)

   Exclusion: Studies employing a method but not focused on discussing or describing it.

Reconciliation of Screening Decisions (Level 1)

Your screening decisions will be compared to the screening decisions of the other independent reviewer. Disagreements will be discussed and resolved by consensus, **based on the systematic review protocol.**

Title and Abstract Screening: Level 2

In Level 2 of title and abstract screening, we will screen the records retained in Level 1 of screening for retention in the review. At this level of screening, we will narrow down the results by retaining articles that meet the following criterion:

1. Articles focused on describing or evaluating at least one **study design / method** used for post-licensure vaccine safety **signal evaluation**;

We will apply the following **exclusion criteria** in Level 2 of screening:

1. Articles focused on **reporting or methods of reporting** of adverse events following immunization (AEFI);

2. Articles focused on individual adverse event reports following immunization;

3. Articles focused on methods of data collection for the purpose of evaluating vaccine safety;

4. Articles focused on methods used in vaccine safety **signal detection** (i.e. data mining in passive surveillance databases).

5. Articles describing any specific spontaneous reporting system for vaccine safety such as the Vaccine Adverse Event Reporting System (VAERS);

6. Articles describing any specific active surveillance system implemented for monitoring adverse events related to a specific vaccine;

7. Articles not focused on describing or evaluating a method.

For this stage of screening and for Level 3 (full-text screening), we will record the main reason for excluding each article. Reasons for exclusion should be classified under the pre-specified exclusion criteria as outlined above if possible. All other reasons will be recorded and will be classified into groups at a later time.

Reconciliation of Screening Decisions (Level 2)

Your screening decisions will be compared to the screening decisions of the other independent reviewer. Disagreements will be discussed and resolved by consensus, **based on the systematic review protocol.**

Collection of Data Sources

Full-text articles selected during title / abstract screening will be obtained by electronic **journal** search or through **internet** search. The libraries of the University of Ottawa and of The Ottawa Hospital, as well as the internet, will be used for the acquisition of data sources.

Confirmation of Inclusion

You will systematically scan each obtained full-text article to ascertain the fulfillment of pre-determined eligibility criteria, and will communicate with the other independent reviewer if you judge any article to be ineligible. Your full-text screening decisions will be compared to the screening decisions of the other independent reviewer. Disagreements will be discussed and resolved by consensus, **based on the details outlined in this Reviewer's Guide.**

Full-Text Screening: Level 3

In Level 3 of screening, we will screen the full text of each article retained after reconciliation of the independent screening decisions from Level 2. At this stage, we will identify the final articles to be included in the review, from which we will extract data. As we will be reviewing the full text of articles at this stage of screening, we will be able to identify those that clearly meet our inclusion criteria, and those that meet any of the exclusion criteria. For this reason, we will apply more stringent inclusion and exclusion criteria during full-text screening. As such, **the following inclusion criteria will be applied during full-text screening:**

1. Articles **focused** on describing / critiquing / evaluating at least one epidemiologic study design used to evaluate the association between a vaccine and a pre-specified adverse outcome, or articles focused on comparing at least two of such study designs;

Hint #1: The article must be **focused on study designs and have a **detailed** discussion / description of at least one study design. Articles focused on another aspect of vaccine safety but briefly mentioning epidemiologic study designs in the body or the discussion of the paper are **not** suitable. You may find it helpful to review the article's objectives in order to determine the focus.*

**Hint #2: The study designs we are interested in are those used to evaluate the association between a vaccine and a pre-specified outcome, rather than methods used to identify new risks associated with a vaccine (i.e. signal detection by passive or active surveillance).The epidemiologic study designs we intend to capture are often used to evaluate / confirm associations between vaccines and adverse outcomes which may have been detected through passive or active surveillance activities, or even pre-licensure studies.*

Full-text Screening Exclusion Criteria:

1. Articles focused on **reporting or methods of reporting** of adverse events following immunization (AEFI);
2. Articles focused on individual adverse event reports following immunization;
3. Articles focused on methods of data collection for the purpose of evaluating vaccine safety;
4. Articles focused on methods used in vaccine safety **signal detection** (i.e. data mining in passive surveillance databases).

5. Articles describing a spontaneous reporting system for vaccine safety such as the Vaccine Adverse Event Reporting System (VAERS) and / or qualities / limitations of such systems;

6. Articles describing any specific active surveillance system implemented for monitoring adverse events related to a specific vaccine;

7. Articles focused on adverse event case definitions to be used for reporting purposes;

8. General discussion papers on the topic of vaccine safety including how assessments are conducted;

9. Articles **not focused** on describing or evaluating an epidemiologic study design.

Data Extraction

Each article included in the review will be filed electronically in the shared drive. Copies of the articles will be available to you electronically or in print format.

An electronic data extraction form will be developed to capture pre-defined data items.

The extraction form will contain instructions and / or definitions for each data item for clarification. One reviewer will pilot-test the data extraction form on one article, and then make any amendments deemed necessary.

Relevant Documentation

The following documents will be made available to you for your reference and use during the course of the review.

Working Files

1. Reference Manager Database
2. Microsoft Excel® Screening Spreadsheet
3. Data Extraction Form

APPENDIX 13: List of Activities related to thesis

Research Activities Directly Related to Thesis:

- Project Coordination
- Development of the project protocol
- Prepared and submitted applications to the Research Ethics Boards at The Ottawa Hospital and the Children's Hospital of Eastern Ontario
- Prepared and submitted project documentation for review and approval by the Institute for Clinical Evaluative Sciences (ICES)
- Maintenance of all regulatory documents
- Conducted a Chart Review at the Children's Hospital of Eastern Ontario (CHEO) which involved:
    - Data abstraction form development and pilot testing
    - Data abstraction
    - Management of datasets and study documentation
- Conducted a systematic literature review which entailed:
    - Review protocol development
    - Search strategy development and execution of search
    - Maintenance of reference databases
    - Selection of studies
    - Data abstraction form development and pilot testing
    - Data abstraction
    - Synthesis of results and discussion

- Development and testing of algorithms for case identification from ICES data, and final data analysis:
    - Data manipulation and analyses with the use of SAS Statistical Software
    - Maintenance of study datasets and data documentation

Other Activities Related to Thesis Project:

- Collaborator on a research contract between Public Health Ontario and the Institute for Clinical Evaluative Sciences (ICES)
- Delivered a presentation on the background and methods of the project to members of the Primary Care and Population Health Program (PCPH) at ICES (March 2012)
- Assisted in the preparation of a grant application to the Physicians' Services Incorporated (PSI) Foundation (Sep 2011)
- Lead author of a technical report titled "Rotavirus Vaccines and Intussusception: Algorithm for Case Identification and Baseline Incidence of Intussusception", submitted to Public Health Ontario (Sep 2012)
- Delivered a presentation on the background, methods and preliminary of the project to the Gastroenterology Research Group at CHEO (Nov 2012)
- Presented a research poster at the Ottawa Hospital Research Institute's Annual Research Day (Nov 2012)
- Prepared and submitted a manuscript from my thesis work to the Journal of Pediatrics
- Presented Methods and results at ICES Technical Rounds (May 2013)