SEVERE RESPIRATORY SYNCYTIAL VIRUS (RSV) INFECTION IN PRETERM INFANTS AND LATER ONSET OF ASTHMA

by

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Abstract

Respiratory Syncytial Virus (RSV)-hospitalizations have a substantial disease burden during an infant's first year of life, and long-term consequences such as asthma remain unclear. This study aimed to quantify the incidence rates of RSV-hospitalization in the first year life and asthma during our 5-year individual follow-up, and evaluate the association between asthma and preceding RSV-hospitalization among preterm infants. A retrospective cohort was constructed from population-based databases in Nova Scotia. RSV-hospitalization and potential risk factors were entered into regression models to evaluate their effect on asthma development. In our final cohort of 3,916 prematurely born infants, the incidence rate of RSV-hospitalization was 25/1000 infants. The cumulative incidence rate of asthma in our cohort was 3.7%. Our Cox PH regression model yielded a HR of 1.58 (1.03-2.41). Our Cox PH results support an association between RSV-hospitalization and asthma in preterm infants.

List of Abbreviations Used

RSV	Respiratory Syncytial Virus
LRTI	Lower Respiratory Tract Infection
CLD	Chronic Lung Disease
CHD	Congenital Heart Disease
Pz	Palivizumab
REGAL	RSV Evidence – a Geographical Archive of the Literature
WHO	World Health Organization
BRaVe	Battle Against Respiratory Viruses
RCT	Randomized Controlled Trial
GA	Gestational Age
ICU	Intensive Care Unit
PICNIC	Pediatric Investigators Collaborative Network on Infections in Canada
IgG	Immunoglobulin G
RR	Risk Ratio
OR	Odds Ratio
SGA	Small for Gestational Age
NS	Nova Scotia
MZ	Monozygotic
DZ	Dizygotic
ED	Emergency Department
CPS	Canadian Pediatric Society
NSAPD	Nova Scotia Atlee Perinatal Database
CIHIDAD	Canadian Institute for Health Information Discharge Abstract Database
MSI	Medical Services Insurance physician-billing database
HCN	Health Card Number
RCP	Reproductive Care Program
SES	Socioeconomic Status
QAIPPE	Quintile of Annual Income Per Person Equivalent
ICD	International Classification of Diseases

CCDSS	Canadian Chronic Disease Surveillance System
PH	Proportional Hazards
K-M	Kaplan-Meier
REB	Research Ethics Board
NSDOH	Nova Scotia Department of Health and Wellness
CI	Confidence Interval
HR	Hazard Ratio
PH	Proportional Hazards
GEE	Generalized Estimating Equation

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1 Introduction

Respiratory Syncytial Virus (RSV) is the leading cause of lower respiratory tract infections (LRTIs) such as pneumonia and bronchiolitis in infants and young children (1). Infants born prematurely (<37 weeks gestational age) and those with underlying cardiopulmonary conditions such as chronic lung disease (CLD)/bronchopulmonary dysplasia (BPD) and congenital heart disease (CHD) are at a heightened risk for severe RSV-LRTIs. These infections frequently result in hospitalizations throughout infancy and early childhood and cost a combined $18 million American dollars per annum (2,3). The virus infects most infants by the time they reach two years of age (4).

No vaccines against RSV are presently available. A monoclonal antibody, Palivizumab (Pz), is the only proven medical intervention available to eligible infants and is administered prophylactically. Considerable variation in Pz prophylaxis administration exists both globally and in Canada, primarily due to its expense (~$6,000 in drug costs per season per child) (3,5–7). As a result, only high-risk infants are deemed eligible for prophylaxis by their respective provincial or territorial program. In Nova Scotia, this program is coordinated by a provincial Palivizumab utilization committee. They are responsible for reviewing data concerning evidence on clinical benefit, cost and utilization of Pz from previous RSV seasons to revise current guidelines.

There is evidence in support of and against the theory that severe lower respiratory tract infections are associated with asthma development later in childhood (8–14). Prospective epidemiologic studies identified in the fifth REGAL (RSV Evidence – a Geographical Archive of the Literature) review have suggested that severe RSV LRTI is a significant risk factor for on-going respiratory morbidity including recurrent wheezing and asthma within the first decade of life (12). It is not known if severe virus-associated LRTI promotes the development of asthma or if children with a predisposition to asthma are more likely to be hospitalized with RSV. We aimed to determine the incidence rates of severe RSV infection measured by hospitalizations (a marker used to capture severe

RSV-LRTI cases, hereby referred to as RSV-hospitalizations) and to determine if there is an association between RSV-hospitalizations and asthma in a retrospective cohort study. The resulting evidence can aid Pz administration guidelines to prevent severe RSV-hospitalizations, and potentially help decrease the risk of asthma development in prematurely born infants.

2 Background

2.1 Respiratory Syncytial Virus Associated Lower Respiratory Tract Infection

2.1.1 Disease Burden

RSV is the leading cause of viral LRTI in infants and young children, accounting for 60 - 80% of all LRTIs in infants younger than 12 months of age (15–17). The incidence of RSV varies by geographical location, seasonality, diagnostic criteria, and the populations under study. An estimated 33 million cases of RSV, 3.4 million hospitalizations, and 199,000 subsequent deaths occur each year globally in children under 5 (8,9,18,19). Estimates based on American surveillance data from 1990-1999 show that RSV infection is the leading viral cause of infant mortality, with a rate nine times that of influenza in a cohort of infants less than 12 months of age (20). Approximately 30-40% of RSV infections contracted in the first year of life result in LRTIs including bronchiolitis and pneumonia (15,21).

A comprehensive review by Arruda et al. found that RSV accounted for 60.7% (34/56) of all LRTI-hospitalizations in a cohort of premature infants (17). The REGAL series is a collection of robust systematic reviews focused on providing a comprehensive review of the published literature on RSV in Western countries over the past 20 years. The fifth installment of the series identified several retrospective studies that found RSV infection caused up to 16 times more hospitalizations and emergency department visits in children aged less than 5 years than influenza (19). In a cohort of prematurely born infants, RSV accounted for 33.1% (143/432) of all LRTI cases during the first year of life (17). Reducing the burden of RSV has become a priority of the World Health Organization (WHO) highlighted through their BRaVe (Battle Against Respiratory Viruses) initiative (22).

Almost half of all North-American children are infected during their first RSV season (winter outbreak) and nearly all children are infected by two years of age (3,16,23,24). A randomized controlled trial (RCT) investigating the effect of Pz-prophylaxis on recurrent wheezing in a population of moderately premature infants (33-

35 weeks gestational age (GA)) aged 6 months or less at the beginning of the RSV season found the cumulative incidence rate of all RSV infections to be 14% (30/215), during the first year of life in the placebo arm of the trial (25).

Incidence rates for RSV-hospitalizations are highly variable, but have been estimated to occur in 1-3% of all infants born in developed countries (3,21,26–28). Hospitalization rates for RSV acute respiratory infections tend to increase with decreasing age, with the highest rates occurring during an infant's first few months of life (19). Retrospective studies identified in the first REGAL review have consistently shown rates of RSV-hospitalization to be the highest during the first year of life (19,29–32). Incidence rates of RSV-hospitalization during an infant's first year ranged from 3.2 per 1000 infants (33) to 42.7 per 1000 infants (34). The second rigorous REGAL review focused on summarizing RSV risk, morbidity, and mortality in preterm infants identified multiple prospective and retrospective population based studies that found elevated rates of RSV-hospitalization in preterm infants compared to term-born infants with rates ranging from (5/1000 children - >100/1000 children (35). Two randomized clinical trials investigating the effect of prophylaxis on the incidence of RSV-hospitalizations and RSV-related morbidity found the annual incidence of RSV-hospitalizations in the placebo arms of the trial to be 8.1% (19/234) in a cohort of preterm infants ($\leq$ 35 weeks GA) aged $\leq$ 6 months (36) and 5.1% (11/215) in a cohort of infants aged 33-35 weeks GA (25) respectively. In a cohort of Nova Scotia - born moderately premature infants (aged 32-35 weeks 6 days GA), 88 of 2811 prematurely born infants (3.1%) were hospitalized due to an RSV-associated illness (37).

Over the past two decades, multiple studies from Canada, the United States and Europe have investigated the national trends in RSV-hospitalization in infants and children. Some studies found a rise in RSV- hospitalizations (38–40), others have found the rates to remain fairly constant over similar time periods (41,42), and one study found a decrease in the incidence rate of RSV-hospitalizations (43).

Evidence on the incidence of medically attended RSV without hospitalization is very limited, and it appears that the outpatient burden of RSV on healthcare resources hasn't been thoroughly examined (19). A prospective, population based study conducted by Hall et al. found RSV was associated with 8.4-13.7% of emergency department visits and 30.9-31.7% of office visits for acute respiratory infections occurring during the infants' first year of life during their 3-year study period (44). In a double-blinded placebo controlled trial of moderately preterm infants (33-35 weeks GA) allocated to receive either Pz-prophylaxis or a placebo, the incidence rate for all medically attended RSV not requiring hospitalization in the placebo group was 4.7% (10/215) during the infants' first year of life (25). A prospective cohort study from Brazil which followed infants for one year after birth, found RSV accounted for 29% (88/301) of non-hospitalized cases of LRTIs (17). A prospective study from the United States investigating the relative impact of Influenza and RSV infection in young children found RSV infection required an emergency department visit at a rate two fold greater than influenza infection (21.5 versus 10.2 visits per 1000 children per year) in their cohort of children less than 7 years of age (45).

Numerous studies have found that severe RSV infection in infants and children warranting hospitalization is associated with considerable short and long-term morbidity. The first publication from the REGAL review series (19) identified several studies that reported a greater association between RSV-hospitalization and the development of severe disease and high healthcare resource utilization compared to non-RSV LRTI-hospitalizations as measured by longer stay in hospital, higher risk of intensive care unit admission, and an increased use of supplementary oxygen (30,38,46). Infants on average spend 2-11 days in hospital for RSV-LRTIs, and 2-12% of these infants are admitted to the Intensive Care Unit (ICU) for additional care (30,32,47–51). Prospective epidemiology studies summarized in the fifth publication of the REGAL review series have demonstrated that RSV-hospitalizations are a significant risk factor for transient early wheezing, recurrent wheezing, and asthma within the first decade of life (12). Mortality rates for RSV in western nations are very low (< 0.5%) (30,32,38,46,50,51), but appear to have remained relatively stable despite advancements in neonatal care (19).

Prematurely born infant's hospitalized with RSV have been found to have a lower quality of life and increased healthcare costs compared to hospitalized infants not infected with RSV (35,52,53). A prospective study in 46-hospitalized infants and children aged <30 months born prematurely (<35 weeks GA) and 45 aged-matched controls not hospitalized for RSV found RSV-infected patients had significantly poorer health and functional status in hospital than the control subjects (54). In a recent prospective study by Carbonell-Estrany et al., the responses to the respiratory subscale in the preschool children quality of life questionnaire was significantly lower (P=0.001) through the first six years of life in preterm infants born 32-35 weeks GA hospitalized for RSV infection in the first year of life compared to infants not hospitalized for acute respiratory illness (52). An additional study from Norway that did not specify the viral type demonstrated that being hospitalized for acute bronchiolitis in infancy was associated with a reduced quality of life nine months later (55).

The burden of RSV infection on the Canadian healthcare system is considerable. One in 38 visits to the emergency department and one of 13 consultations with family practitioners presenting from November through January can be attributed to the virus in children under 5 years of age (5,44). RSV-associated hospitalizations in Canada number an estimated 5,800 to 12,000 children (2). A prospective study conducted by the Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) estimated the cost of RSV hospitalization for children aged 1-4 to be US $18.5 million dollars per annum (2). During the five-year period during 1997-2002 in the United States, RSV-hospitalization costs totaled $1.1 Billion US dollars (56).

2.1.2 RSV Characteristics

RSV is classified into the subfamily *Pneumovirinae* of the *Paramyxoviridae* family of lipid-enveloped, single-stranded, and negative-sense RNA viruses (4). The RSV genome encodes 10 proteins, 2 of which are non-structural (4). The virus has two different genotypes currently identified, RSV virus A and B, which both circulate the globe concurrently with the A genotype dominating (4,57,58). There is no animal

reservoir for human RSV and thus the reservoir for the virus during the off season remains unknown (4). The RSV season in Canada and other northern hemisphere nations begins between November and January and persists for 4-5 months (2,59).

The incubation period for RSV typically lasts four-five days, but may extend two-eight days (15, 20). Initial infection occurs through inoculation of the mouth, nose or eyes by large particle droplet or direct contact (15, 21). The virus replicates in the nasopharyngeal epithelium and may spread to the lower respiratory tract one to three days later (18, 21).

2.1.3 Risk Factors for Severe RSV Infection, Development of LRTIs and Hospitalization in Vulnerable Populations

Most infants who are hospitalized with RSV infection have no identifiable risk factors, and are otherwise healthy (12,33). Infants born prematurely comprise the next most common cohort of RSV-infected individuals (61). Infants qualify as preterm if they are born prior to reaching 37 weeks gestational age, a time measured from the first day of the mother's last menstrual cycle to birth. The WHO estimates almost 9% of all live births each year occur prematurely, the majority (>80%) falling between 32 and 37 weeks GA (62). Preterm infants are at an increased risk for complicated RSV-LRTI and require hospitalization for supportive care at a five to ten-fold increased rate compared to term infants during their first year of life (5,7,21,63,64). Proposed explanations for why premature infants are at a heightened risk include their smaller airways, a developing immune system, and an insufficient transfer of anti-RSV antibody Immunoglobulin G (IgG) from the mother to the fetus (4,11,21,57). Lung maturation occurs at its highest rate during the third trimester of pregnancy and when interrupted, smaller lung volumes and other lung structure complications occur (65).

Chronic lung disease (CLD) is a condition used to describe infants who have experienced lung injury due to premature birth and diagnosed infants require treatments such as mechanical ventilation and extra oxygen to assist with breathing. Infants with

CLD and other underlying cardiopulmonary pathology are at risk for more complicated infection compared to healthy, term-born infants (66–68). Infants with hemodynamically significant congenital heart disease (CHD) have a higher risk of complicated RSV infection (69). CHD is a broad diagnostic term used to describe various problems affecting the heart that are present at birth. CHD is considered hemodynamically significant if at least one of the following are present: left and right shunts requiring medication, congenital heart disease waiting for surgery, or ongoing cyanosis (70). Higher rates of hospitalization and use of mechanical ventilation are associated with CHD-diagnosed infants infected with RSV when compared to healthy infants (71). Other populations vulnerable to complicated RSV infection are those with serious underlying medical disorders such as immunodeficiency, cystic fibrosis, congenital airway complications, pulmonary malformations, and Down syndrome (12,21).

Numerous risk factors for RSV-hospitalization have been identified in several individual studies and summarized in multiple systematic reviews (21,28,35,72–78). Results were generally consistent across studies despite the differences in time frame, study location, population, and RSV testing strategy (28). Several host-specific and environmental factors place infants, particularly those born prematurely, at a higher risk for RSV-hospitalization (2,5,12,21,35,66,67).

Multiple recent systematic reviews have highlighted several studies that show male infants are at a heightened risk for more severe RSV infection compared to female infants (19,21,28,72,77). A Spanish case-control study and a Canadian prospective cohort study highlighted in the Mauskopf systematic review found odds ratios (OR) for the risk of RSV-hospitalization of male infants compared to female infants of 1.36 (95%CI 1.01-2.11) and 1.91 (95%CI 1.10-3.31) respectively in cohorts of moderately premature infants (32-35 weeks GA) (79,80). A literature review conducted by Simoes et al. found a summary risk ratio of RSV infection comparing boys to girls to be 1.43 (95%CI 1.40-1.45) (72). A proposed explanation for this phenomenon is that male infants have shorter and narrower airways than their female counterparts and thus are more likely to develop bronchial obstruction from RSV infection (72). Despite the majority of evidence

supporting male sex as a risk factor for RSV hospitalization, Ryan et al. did not find male sex to be a significant risk factor for RSV hospitalization in a cohort of moderately premature (32-35 weeks GA) Nova Scotia born infants (37).

Atopy can be defined as the tendency to develop allergic diseases, such as allergic rhinitis, atopic dermatitis (eczema), and asthma (81). In epidemiological studies, atopy is typically measured by proxy variables like maternal history of asthma or wheezing. Multiple systematic reviews summarizing risk factors for RSV infection in preterm infants have identified infants with atopy to be at an increased risk of RSV-hospitalization (19,21,28,35). Two Spanish studies (FLIP, FLIP-2), one Canadian (PICNIC), two Dutch (RISK, RISK II), and one multinational study (PONI) evaluated risk factors for RSV hospitalization in preterm infants aged 32-35 weeks GA to be used in developing risk models for prophylaxis eligibility (79,80,82–85). An association between a maternal history of atopy and asthma with RSV-hospitalization was supported by findings from two prospective Dutch studies OR 1.9 (95%CI 1.1-3.2) (82) and OR 1.5 (95%CI 1.1-2.1) (84), and the Spanish case-control study (FLIP) (OR=1.90 95%CI 1.19-3.01). The prospective PICNIC investigators study found an inverse association, indicating that a maternal history of asthma may lower the risk of asthma development (OR 0.42, 95%CI 0.18-0.996) (80). In a cohort of Nova-Scotia infants preterm infants (32-35 weeks GA), maternal history of asthma was not determined to be an independent predictor of RSV-associated hospitalizations (37). The second prospective Spanish FLIP study (FLIP-2) and other prospective studies also did not find an association (83,86,87). A prospective study conducted in the United States followed term-infants from birth to 18 months and found that parental history of asthma was significantly associated with LRTIs accompanied by wheezing symptoms (OR 2.06, 95%CI 1.36-3.11) (88). A nested case-control study of Danish infants less than 18 months of age (89) estimated the relative risk of RSV-hospitalization among infants with a maternal history of asthma compared to matched controls without a maternal history of asthma to be 1.72 (95%CI 1.44-2.06). A retrospective study from the United Kingdom found maternal history of atopy or asthma was a weak risk factor for severe LRTI in the first year of life (OR 1.90, 95%CI 0.99-3.65, P=0.05) (90).

Birth during the first half of the RSV season has consistently been found to a significant risk factor for RSV-hospitalizations (21,28,72,74,77). Recent systematic reviews by Mauskopf et al and Figueras-Aloy et al., both investigated the risk and associated morbidity of RSV-hospitalization in healthy preterm infant populations and identified studies that found birth at the start of or during the RSV (Nov-Jan) season to be significantly associated with RSV hospitalization with odds ratios ranging from 2.60 (95%CI 1.60-4.20) – 4.88 (95%CI 2.57-9.29) (28,35). These results are supported by a large American population based study across three northern states where they found birth during the months November to January (RSV season in this geographical area) increased the risk of RSV-hospitalization among 2-month olds (Risk Ratio (RR) 1.21, 95%CI 1.09-1.35) compared to infants born in October (91). In a cohort of premature Nova Scotian infants (32-35 weeks GA), birth during the beginning of the RSV season was determined to be a significant independent risk factor (OR 2.58, 95%CI 1.62-4.09, P<0.0001) for RSV- hospitalization (37). These observed effects are likely due to increased exposure to RSV.

Several prospective and retrospective studies identified from multiple systematic reviews have found preterm infants exposed to tobacco smoke in utero to be at a heightened risk for severe RSV infection requiring hospitalization (19,21,28,35,83,92). Several systematic reviews highlighted the second Spanish FLIP-2 study, which found an odds ratio of 1.61 (95%CI 1.16-2.25 P=004) for infants exposed to tobacco smoke in utero compared to unexposed infants (83). A prospective study conducted by Ambrose et al. in a population of prematurely born infants found exposure to maternal smoking had a hazard ratio of 1.98 (P=0.022) compared to unexposed infants (92). A prospective cohort study from the United Kingdom found infants exposed to maternal smoking during pregnancy had 4.84 times (95%CI 1.61-14.58) greater odds of being hospitalized for RSV compared to unexposed infants (93).

Small weight for gestational age (SGA) is when an infant's weight at birth falls below the 10^{th} percentile, a measure developed by Kramer and colleagues for Canadian-

born infants (94). Few studies have evaluated SGA as a risk factor for RSV-hospitalization. Multiple systematic reviews identified only one study that found SGA to be a significant risk factor for developing severe RSV infection requiring hospitalization (OR 2.19, 95%CI 1.14-4.22, P=0.019) (80), while others did not find a significant effect (37,82).

Only a few studies have investigated intrauterine growth restriction as a risk factor for RSV hospitalizations (37,80). The Canadian PICNIC study group found a significant association between an infant being small for their gestational age (<10th percentile) and RSV-hospitalization (OR 2.19, 95%CI 1.14-4.22) (80), while Ryan et al. did not find a significant association after adjusting for other variables (37).

Systematic reviews have also identified the variables: number of siblings, specifically those of daycare age (approximately 2-4 years old), and household crowding to be significant risk factors for RSV-hospitalization (19,21,28,37). The second REGAL systematic review found the presence of preschool or school aged siblings to be a significant predictor or RSV hospitalization with odds ratios ranging from 2.04 (95%CI 1.53-2.74) – 5.30 (95%CI 2.80-10.10) in cohorts of prematurely born infants (35). Findings from the Tucson cohort study, a large prospective cohort study investigating lower respiratory tract illness during the first year of life, found a significant association between the number of persons sharing a bedroom and hospitalization for RSV (OR = 4.0 95%CI 1.5-10.7) (78). Two additional studies, one case-control, one prospective cohort, not captured in the second REGAL review found that living with school-aged siblings was a significant risk factor for RSV-hospitalization in multivariable models (odds ratios of 1.64 (95%CI 1.40-2.07) and 1.86 (95%CI 1.01-3.40) (95,96). Results from two cohort studies found the odds of being hospitalized for RSV in preterm infants from crowded households compared to non-crowded households of 1.69 (95%CI 0.99-2.83) and 1.91 (95%CI 1.19-3.07) (37,79,80). These associations are likely influenced by an increased exposure to RSV.

2.2 Asthma

2.2.1 Burden of Illness Associated With Asthma

Asthma is a heterogeneous group of conditions that result in recurrent, reversible airway constriction associated with coughing, breathing difficulties, and shortness of breath (97,98). Asthma has a large individual and societal burden. Throughout the past four decades, there has been a substantial increase in global prevalence, morbidity, mortality, and economic burden of asthma (99).

Almost 300 million people globally are living with asthma and its global prevalence rose 100% from 1985 – 2001 (74,99). This figure is likely under estimated because asthma is both under diagnosed and under treated (99). Asthma in children under five is difficult to diagnose because the clinical symptoms of asthma are variable and unspecific (100). Additionally, episodic respiratory symptoms such as coughing and wheezing are common in children this age who are not asthmatic (100). The prevalence of asthma in Nova Scotia (NS) is the highest in Canada at 9.1 percent (compared to the 8.1 percent national average), and hence asthma is an important, relevant, local problem (101). Women have almost double (11.5% vs. 6.6%) the asthma prevalence of men in Nova Scotia (101), but pre-pubescent males have been found to have higher asthma rates than their female counterparts (102,103). Higher prevalence rates of asthmatic risk factors such as smoking may contribute towards Nova Scotia's high asthma prevalence rate (104,105). A recent systematic review on the clinical, economic, and humanistic burden of asthma in Canada found the hospital rates for asthma in Canadian children ranged from 10.9-86.7 per 1000 children year, and physician visits for asthma ranged from 0.8-3.6 visits per patient per year (106).

Asthma has substantial individual and population-level economic costs. Average annual costs range from $366 to $647 per patient, and total annual population-level costs in Canada vary by province: ~ $46 million in British Columbia to ~$141 million in Ontario (106). Ungar et al (2001) estimated the average annual costs for medication per asthmatic child to be $352.87 (107). In Ontario, the total cost of asthma in children aged

0-14 was estimated to be $883.48 per child from the healthcare perspective. Indirect costs due to time loss from work, productivity loss, and functional impairment also increase the overall burden of the disease (106). An Ontario study found outpatient claim costs for persons with asthma exceeded those without asthma by approximately $200.00 per person per year (108).

2.2.2 Risk Factors for Asthma Development

Asthma pathogenesis is not fully understood. Epidemiology studies have found environmental and individual-level risk factors to be associated with asthma development. In a review conducted by Ding et al., environmental tobacco smoking was found to be associated with the development of childhood asthma (105). Small birth weight for gestational age, living in an urban setting, and having a low socioeconomic status have also been associated with increased risk of asthma development (105,109,110). Infants who have a maternal history of asthma were also found to be at an increased risk for physician-diagnosed asthma by their seventh birthday compared to those without (111). Infant birth during the winter months (RSV season), is associated with a heightened risk for asthma development (74,112).

RSV-hospitalizations occurring during infancy and early childhood have been hypothesized to be a risk factor for asthma development, but the relationship is not fully understood. RSV-hospitalization during infancy may have acute and long-term impacts on airway, lung and immune system development which may result in an increased risk of developing childhood asthma (66). Preexisting abnormal lung function, genetic susceptibility, altered immunology, and some environmental mediators have also been hypothesized to influence the relationship (12). The prospective RSV Bronchiolitis in Early Life study supports an association between severe RSV infection in childhood (measured by hospitalization or emergency department visit) and physician-diagnosed asthma in children. Almost half (48%) of the children who developed severe RSV-LRTI in the first year of life were diagnosed with childhood asthma by age seven (111). Multiple other observational studies have found an increased frequency in wheezing

illnesses and asthma during childhood (among term-born infants) when preceded by significant RSV infection, but it is not clear if the association is causal (11,32,86,87,111,113,114).

A twin study conducted by Thomsen et al. (2006) followed 8280 pairs of Danish twins from birth during the period 1994-2000, and estimated values of genetic and environmental variance components within the same twin and between the two twins in a pair. Due to the fact that monozygotic (MZ) twins share all their genes while dizygotic twins (DZ) only share on average half of their genes, any larger covariance or resemblance between MZ and DZ twins would indicate that genetic factors influence disease liability, assuming the twins had a shared environment and early upbringing. The authors compared the resemblance/covariance between MZ and DZ twins, and the authors found that shared, additive genetic effects accounted for all of the covariance between RSV hospitalization and asthma development suggesting a common genetic source for severe RSV infection and asthma. Using direction of causation modeling, the authors found that severe RSV infection serves as an indication of an underlying genetic predisposition (atopy) towards asthma development, not the direct cause (115). However multiple other retrospective and prospective studies have not found that a maternal history of asthma influences the relationship between RSV-hospitalization and asthma development, so it's association with RSV-hospitalization and asthma remains uncertain (10,86,87,116).

RSV infection may alter the trajectory of children without a predisposition to asthma towards asthma development (116,117). In a population-based retrospective cohort study conducted by Carroll et al. (2009), the relationship between severity of bronchiolitis and development of childhood asthma (measured between 4 and 5.5 years of age) was investigated (116). Bronchiolitis severity was defined by categorizing children into mutually exclusive groups based on their most advanced level of health care, which included hospitalization, emergency department (ED) visits, and outpatient groups from health clinics and family practices. Multivariable logistic regression models yielded the odds ratios of development childhood asthma to be 1.86, 2.41, and 2.82 in the outpatient,

emergency department, and hospitalization groups respectfully when compared to the control group of no bronchiolitis visits (116). These relationships were adjusted for a number of covariates including birth weight, maternal smoking during pregnancy, and other siblings at birth. The relationship between bronchiolitis severity and childhood asthma development remained similar after investigating the interaction effect of maternal history of asthma (116).

These studies illustrate that the relationship between RSV-hospitalization and asthma may proceed in both directions. It is possible that either respiratory infection in early life induces the development of chronic airway inflammation and airway wall remodeling resulting in persistent wheeze and asthma, or some infants have pre-existing, over-active Th2 responses (immune response to extracellular parasites) or other genetic predispositions towards developing asthma, which in turn induces susceptibility to complicated viral infection (89,118). It has been proposed that the effects of an acute inflammatory response to a lower respiratory tract infection are age dependent, caused by the rapid growth and pronounced changes to the immune system occurring during infancy (66). Infancy may serve as a period of greater vulnerability to long-term consequences of respiratory infections on lung structure and function (66).

2.3 Preventive Interventions for RSV Infection

2.3.1 Anti-RSV Antibody

Although many vaccines are currently in development, there is currently no RSV vaccine and no antiviral treatment interventions. Behavioral measures such as avoiding cigarette smoke exposure and RSV-infected persons are important measures to prevent RSV infection and transmittance (5,6). A Cochrane review found that practicing good hand-hygiene in home decreases the spread of respiratory tract infections in children, and breastfeeding has also been shown to be protective against viral respiratory tract infections (3,119). Prophylaxis using the monoclonal antibody Palivizumab (Pz) is currently the only proven medical intervention available. Palivizumab has been available for qualifying high-risk infants since becoming licensed by the Food and Drug Administration in 1998.

Palivizumab is produced through recombinant DNA technology, and is composed of 95% human and 5% murine (rodent) amino acid sequences (3). Palivizumab binds to a glycoprotein found on the surface of RSV called F protein at the A antigenic site, blocking viral attachment to the respiratory cell (24,120–122). Consequently, Pz inhibits viral transcription (122). Palivizumab does not inhibit RSV replication in the nasal mucosa. As a result, Pz-prophylaxed infants are not protected against infection to their upper respiratory tract, only against the virus spreading to the lower respiratory tract and the subsequent manifestation of bronchiolitis (24).

To date, no resistance to Pz has emerged and all RSV strains have been effectively neutralized by Pz in vitro (24). Pz is the clinically proven option to protect high-risk infants against RSV infection (24).

2.3.2 The Clinical Efficacy of Palivizumab as a Prophylactic Intervention for RSV infection

The clinical efficacy of Palivizumab was evaluated in two prospective randomized clinical trials. The first was conducted by the IMpact RSV- study group and evaluated the performance of Pz versus a placebo in a population of infants born prematurely or with CLD (36). Overall, Palivizumab reduced RSV-hospitalizations by 55% in the Pz-treated group in comparison to controls. Children with prematurity without CLD had a 78% reduction in RSV-associated hospitalizations (36).

The second double-blinded clinical trial found a 45% reduction in RSV-associated hospitalization rate for Palivizumab patients (123). It was concluded that Pz is safe and effective for the prevention of serious RSV illness in premature children and those with CHD. No significant difference in reported adverse events was observed between the control and Pz treated groups.

2.3.3 Palivizumab Administration Guidelines

Palivizumab is a prophylactic treatment that costs $6000.00 per child per RSV season. It is not administered to all preterm infants, primarily due to economic limitations (7). A recent systematic review of Pz cost-effectiveness and cost-utility studies yielded inconclusive results (124). The review identified 28 articles consisting of 13 cost-utility studies (outcomes based on cost per quality adjusted life-year gained) and 15 cost-effectiveness studies (outcomes based on per life year gained or hospital admission prevented). Cumulatively, 12 studies found Pz a cost-effective intervention, 12 did not find the prophylaxis cost-effective, and 4 studies' findings were inconclusive (124).

The American Academy of Pediatrics recommends that infants born < 29 weeks gestational age, or with heart or lung disease should be offered this intervention during the first year of life and in some instances, up to two years (5,6). The Canadian Pediatric Society (CPS) issued new guidelines in 2015 recommending preterm infants $\leq$30 weeks 0

days gestation who are less than 6 months of age at the start of the RSV season could receive Pz prophylaxis, as well as children with hemodynamically significant CHD or CLD requiring ongoing treatment who are <12 months of age (3). Past administration guidelines have recommended moderately premature infants (32 weeks 0 days – 35 weeks 6 days) with associated risk factors to receive the intervention. Substantial heterogeneity in Pz recommendations exists among infants in this gestational age range.

A provincial program governs Palivizumab utilization in Nova Scotia, which follows CPS national guidelines. All infants born prematurely (<30 weeks gestational age) or with a lung (CLD) and or heart disease (CHD) are considered eligible candidates for Pz prophylaxis during their first year of life (70). An eligibility form for Pz-prophylaxis outlined in Appendix B. Infants diagnosed with CHD and CLD qualify for Pz prophylaxis because of their association with higher rates and longer durations of RSV-hospitalizations when compared to healthy infants (3). Infants with immunodeficiencies and certain other risk factors may be eligible to receive the intervention (3,24).

Pz is administered intramuscularly every 30 days during RSV season for a maximum of five doses (3). Some programs across Canada administer the second dose 20 days after the first dose in order to prevent a low trough level despite no evidence of an increased RSV-hospitalization rate before administration of the second dose on a standard dosing schedule (24). A presumed therapeutic level of 30 mg/mL to 40 mg/mL can be maintained for the typical duration of the RSV season with only 4 doses (3). This course of therapy is beneficial if doses 2, 3 and 4 are given 38 days apart versus 30 (3). The frequency of dosing is dependent on the infant's birth month in relation to the RSV season. Thus, an infant could receive the maximum 5 doses if born in September and only 2 if born in January.

2.4 Study Rationale

We know that preterm infants are at high risk for RSV-hospitalization and are thus offered Pz, but studies highlighted in multiple systematic reviews have not focused on this group when evaluating the relationship between RSV-hospitalization and asthma development (12–14,19,21). A study focused on evaluating the risk of asthma development after preceding RSV-hospitalization in the preterm population would help address this lack of evidence. A retrospective cohort design spanning 15 years was used to capture enough prematurely born infants hospitalized with RSV and diagnosed with asthma to provide sufficient power to detect a statistically significant relationship if present. This study design ensured temporality was maintained and made use of multiple, high-quality administrative databases containing a comprehensive library of demographic and environmental variables.

Having an evidence-based knowledge of which children are most at risk for long-term respiratory complications allows public health decision makers to identify vulnerable populations, such as prematurely born infants, as candidates for early prophylaxis. We hypothesized that the incidence of asthma will be increased in children with preceding RSV-hospitalization occurring during the first year of life.

3 Objectives

The objectives of this study were:

To determine in a cohort of prematurely born Nova Scotia (NS) infants aged ≥ 29 weeks 0 days GA to 35 weeks, 6 days GA:

1) The incidence rates of RSV-hospitalizations in the first year of life

2) The incidence rates of asthma in children up to 5 years of age, compare the incidence rates in children with and without preceding RSV-hospitalization, and evaluate the relationship between RSV-hospitalization and asthma development.

4 Methodology

4.1 Study Design

Infants were identified at birth and followed forward in time to a maximum age of five years, 0 days using a retrospective cohort design. Multiple databases were linked in order to follow children forward in time, as described below. This thesis is a subset of a larger project evaluating the Nova Scotia Provincial RSV Prophylaxis Program.

4.2 Study Population

The study population consisted of Nova Scotia born infants ≥29 weeks, 0 days GA to 35 weeks, 6 days GA who were born during the period July 1st 1998-December 31st 2009. Infants were followed from birth to a maximum age of five years (during the period of July 1998 to December 2014). Criteria for censorship included the time of asthma diagnosis, departure from the province, or death. Early neonatal deaths (0-7 days), late neonatal deaths (7-28 days), and post-neonatal deaths (28-364 days) in our cohort were excluded from the inception of the cohort, because their early death would have restricted the infant's exposure to RSV. The cohort was established from the Nova Scotia Atlee Perinatal Database (NSAPD) using subjects' date of birth and gestational age information. If gestational age information was missing from the dataset; infants were excluded from the analysis because we cannot be certain that they were born prematurely. Infants born in NS from other provinces were not eligible, as their outcome data wasn't captured by our dataset. Infant data from home births may not be completely entered into administrative data sources and were therefore excluded. Patients with CLD, CHD, or who are immunodeficient, were excluded. Infants with CLD, CHD and those who are immunodeficient differ from premature infants across associated risk factors for RSV-hospitalization and asthma development.

4.3 Data Sources

Data pertaining to our cohort of premature infants was obtained from the Nova Scotia Atlee Perinatal Database (NSAPD), the Nova Scotia Vital Statistics Database, the Palivizumab Utilization Program Database, the Canadian Institute for Health Information Discharge Abstract Database (CIHI DAD) and the Nova Scotia Medical Services Insurance physician-billing database (MSI). Linking these databases assembled the cohort. Individual level data linkage used identifiers (health card number (HCN) and date of birth) to connect each infant's information through the datasets for five years during the period July 1998 to December 2014. A list of linking variables can be found in Appendix A.

4.3.1 Reproductive Care Program (RCP)–Nova Scotia Atlee Perinatal Database (NSAPD)

The NSAPD is maintained by the RCP and contains comprehensive data on demographic and clinical characteristics of the prenatal, delivery and neonatal periods of children born in NS. It includes information on risk factors and comorbidities that provide eligibility for Pz receipt, and covariates that may possibly influence the risk of RSV infection and asthma development (125). The information recorded in the NSAPD is extracted from prenatal, delivery, and neonatal records by trained coders using annually updated coding manuals. The NSAPD uses a continuous data quality assurance program, which publishes periodic abstraction studies to verify the validity of the data, and has been used to validate other administrative databases (126,127). Missing data on the extracted variables pertaining to infants and delivery is very small (approximately 0%) while some maternal variables such as maternal smoking are missing from approximately 10% of records. A list of the linkage variables and potential confounding factors and the rationale for their inclusion provided in Appendix A.

4.3.2 Nova Scotia Pz Utilization Program Database (Formally Nova Scotia Blood Coordinating Program Database)

Prior to the inception of the NS Pz Coordinating Program, Pz was offered to high-risk infants at the IWK Health Center since it's approval in 1998, but this process was not provincially regulated until 2003. The Nova Scotia Palivizumab Coordinating program and database was created in 2003 at the request of the Nova Scotia Department of Health. The NS Pz utilization committee meets yearly to review current evidence on Pz cost and utilization. The database provided information on all Nova Scotia-born infants who have received Pz prophylaxis since 2003 (128). This information was used to inform our second objective as a potential covariate in our Cox proportional hazards regression model. An assessment of the accuracy of the database has not been conducted. A list of variables extracted from this dataset can be found in Appendix A.

4.3.3 Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD)

The CIHI DAD includes administrative, clinical, and demographical information on hospital discharges. Data are received directly from acute care facilities or their respective health authority (129). Multiple diagnoses are recorded for each patient, categorized into the primary diagnosis (the disease or condition responsible for the hospital admission) or secondary diagnoses. This study will consider all diagnoses coded for each patient. The database includes the infant's health card number, date of birth, the attending physician, hospital number and admission and discharge diagnoses coded using ICD 9 (pre 2001) and ICD 10 (2001-present). The CIHI DAD captured our primary exposure variable, RSV-associated respiratory illness inpatient hospital visits and our outcome variable asthma.

Information stored in CIHI DAD is of high quality. CIHI has a data quality framework to systematically assess, improve, and document data quality (129). Numerous data quality studies have verified the quality of the information contained in

the CIHI DAD (129). Variables to be extracted from this database are listed in Appendix A.

4.3.4 Medical Services Insurance (MSI) Physician Billing Database

The MSI database records physician billing information from each patient visit. It is housed and managed by the Nova Scotia Department of Health, and contains data from 1997-2015 fiscal years. Data elements include individual patient's demographic information, physician and billing information, and diagnostic and procedural codes (130). Multiple case verification studies have investigated the accuracy of physician billing diagnoses in Canada across a variety of diagnoses and conditions have validated the accuracy of diagnostic codes within physician visit claims (131–133). Three diagnoses codes are available from the database, and both primary and secondary diagnoses explicitly coded as asthma-specific illnesses were considered in this study. The MSI database captured asthma diagnoses occurring in hospital outpatient and physician office visits outside of a hospital admission setting with the use of ICD-9 diagnostic codes.

4.4 Data Collection

The following variables were included in our dataset to describe the characteristics of the cohort, and be evaluated as potential covariates in our multivariable regression models.

Individual variables

Birth Month and Year

Birth month and year was used in our study to develop season-specific RSV-hospitalization rates, and report the crude number of asthma diagnoses per fiscal year. The birth month and year variable was treated continuously and values ranged from July 1998 to December 2014.

Birth Weight

Birth weight was dichotomized into normal birth weight (≥2500 g) and low birth weight (<2500 g) to help describe the physical characteristics of our cohort. Birth weight was also used by the RCP to code the small birth weight for gestational age variable in our dataset.

Small Birth Weight for Gestational Age

Birth weight for GA was calculated according to Kramer's criteria for Canadian newborns, which is based on the birth weight, GA and sex of the infant (94). Small for gestational age was dichotomized into (1) ≤ 10^{th} percentile and (0) ≥ 10^{th} percentile.

Infant Sex

Sex refers to the biological characteristics of an infant and is primarily associated with physical and physiological features, while gender refers to the social constructed norms and identities of an individual (134). Our study uses sex as a variable, because it is the physiological aspects of the infant that influence RSV-hospitalization and asthma development opposed to their gender identity, and it is the only information available to

identify them at birth. Infant sex was categorized as a binary variable with (1) representing male sex and (0) representing female sex.

Number of Preschool-Aged Siblings (≤5 Years of Age)

The number of preschool-aged siblings is not directly coded in the Nova Scotia Atlee Perinatal Database. Therefore a proxy variable was synthesized by totaling previous maternal birth records of the infant's siblings who were at preschool age (children ≤ 5) during the study period. The variable was then dichotomized into either (0) no preschool-aged siblings, or (1) presence of preschool-aged siblings.

Household Crowding

Overcrowding has long been considered an epidemiological risk factor for infectious disease spread, and while the study definition slightly overlaps with preschool-aged siblings, they represent separate distinct risk factors and should be evaluated independently (37,80,83). Previous maternal births of children ≤ 18 and the marital status of the mother (if the infant was raised in a single-parent or a duo-parent household) were combined to create a proxy variable to measure household crowding. The resulting variable was dichotomized into (1) household crowding (≥ 5 individuals per household), or (0) no household crowding (< 5 individuals per household).

Palivizumab Prophylaxis

RSV prophylaxis is achieved through administration of the monoclonal antibody Palivizumab (Pz). Administration of Pz was treated as a binary variable; (0) if not administered, and (1) if administered. Infants must have received a minimum of one dose of prophylaxis in order to be considered 'Pz-prophylaxed'.

Exposure to Tobacco Smoke

Tobacco smoke exposure is measured by three variables in the NSAPD. Maternal smoking status pre-pregnancy, smoking status at the time of admission, and smoking status at the first and 20 week prenatal visits. These variables were combined into a single proxy variable: 'tobacco smoke exposure'. Infants were considered exposed (1) if they

were exposed to tobacco smoke in any of the three measures, or otherwise were considered unexposed (0) (not exposed in any of the three measures).

Low Socioeconomic Status (SES)

Socioeconomic status was estimated using the Quintile of Annual Income Per Person Equivalent (QAIPPE). QAIPPE represents a size-adjusted measure of household income based on 2006 Canadian census summary data. The average income per person equivalent data was used to rank all dissemination areas (the smallest geographical area for which all census data are disseminated), and then the population was divided into approximate quintiles providing an estimate of average income by neighborhood. The Nova Scotia RCP categorized the mother's neighbourhood income quintile in the NSAPD based on all women in the database. The quintiles were categorized as 'lowest', 'middle-low', 'middle', 'middle-high', and 'highest' quintiles.

APGAR Score at both 1 and 5 Minutes

The APGAR test evaluates the infant's physical condition. It is administered 1 and 5 minutes after birth. A score of 7 or higher indicates the infant is adapting to extrauterine life while a score below 7 indicates the infant is in need of medical attention. Little research exists evaluating this variable as a risk factor for RSV-hospitalization or asthma development, because it was designed as an evaluative score for infants at the time of birth, not as a predictive tool. For the purposes of this study, APGAR scores were treated as binary variables, with a score of 7 or higher indicating good health (0) and a score below 7 indicating poor health status (1).

Mode of Delivery

The route of infant birth is recorded in the Atlee Perinatal database under "mode of delivery", which can either be by vaginal or caesarean section delivery. The variable will be treated binary with (1) representing caesarean section birth, and (0) representing vaginal birth.

Exposure and Outcome Variables

RSV-Hospitalizations

RSV- hospitalization is defined as a minimum of one hospital admission for a RSV illness from the CIHI DAD during the infant's first year of life. RSV-LRTIs severe enough to warrant hospitalization were used as the primary exposure because RSV illness that leads to hospitalization is a marker for serious illness acuity, and the accuracy of hospital RSV diagnoses is reliable. RSV-hospitalizations were identified from the dataset by using the International Classification of Disease Codes (ICD) -9 and -10 supplied in Appendix A. Only diagnoses explicitly coded as RSV (including RSV-bronchiolitis, RSV-bronchitis, RSV-pneumonia, and RSV-unspecified) were included in our definition. Our definition excluded respiratory illnesses where the cause of the infection is unspecified. Consequently, some non-confirmed RSV-hospitalizations were missed, but our definition mitigated the effect of misclassification bias by not including respiratory illnesses that may have been caused by other microorganisms. Ambulatory diagnoses of RSV were not included in our analyses. Severe RSV-illness diagnosed in an ambulatory setting would have also required hospitalization, and would have been captured by the CIHI DAD.

Both primary (reason for physician visit) and secondary diagnoses (other diagnosis detected at visit) were considered for our study's objectives. We have decided to include both primary and secondary diagnoses because secondary diagnoses are often associated with, or are the cause of the primary diagnosis. The accuracy of determining which of the diagnoses is responsible for the hospital admission is not perfect, but including secondary diagnoses will help capture all inpatient RSV diagnoses. However we recognize that by including secondary diagnoses, the incidence rate of RSV-hospitalization may be overestimated because we would capture RSV-hospitalizations that are not responsible for the hospital admission and would otherwise have gone uncounted. Hospitalization for RSV will be dichotomized into having the condition (1) or not (0).

Asthma

Our definition of asthma adheres to definitions provided by Canadian Chronic Disease Surveillance System (CCDSS) and Teresa To's 2008 publication, which define asthma in administrative datasets as 1 hospitalization or 2 outpatient physician visits for asthma within a three year period (135,136). For outpatient physician visits, the date of diagnosis was the date of the first physician visit. The CIHI DAD and the MSI Physician Billing database ICD 9 and ICD 10 codes captured our primary outcome variable asthma in the infants' first five years of life during the period of July 1998 – December 2014. Only diagnoses coded explicitly as asthma (categorized in ICD codes as extrinsic, intrinsic, chronic obstructive, other forms, and unspecified asthma) were evaluated. Both primary and secondary diagnoses were considered. Similar to RSV-hospitalizations, we recognize that by including secondary diagnoses, the incidence rate of asthma may be overestimated because we would capture asthma diagnoses that might not be responsible for the hospitalization or outpatient physician visit. The development of asthma was treated as a binary variable for this study ((1) asthma, (0) no asthma).

Infants diagnosed with asthma prior to a RSV-hospitalization diagnosis during the first year of life were censored at the time of asthma diagnosis and were considered non-exposed asthma cases in our analyses. If an infant was hospitalized with RSV and diagnosed with asthma on the same day, these cases were classified as unexposed asthma cases because it is clinically impossible for a viral infection to cause a chronic disease such as asthma on the same date it was diagnosed.

4.5 Statistical Analysis

All statistics for this study were conducted using STATA software for windows version 15, StataCorp 2017 College Station, Texas.

Demographic and baseline characteristics of the cohort were described. The size of the eligible cohort was calculated based on the sex, gestational age (by week) and month of birth of the participants. The numbers of RSV-hospitalizations were reported under their corresponding diagnostic code and by the fiscal year range they were diagnosed in. The same protocol, with the addition of asthma outpatient and physician office visits from the MSI database, was employed for determining the number of asthma diagnoses per ICD code.

Objective 1: To determine the incidence rate of RSV-Hospitalizations

The incidence rate of RSV-hospitalizations was calculated by dividing the number of new RSV-hospitalizations occurring during the first year of life by the total study population of eligible infants at risk for RSV-hospitalization. The attack rate of RSV in each GA range was reported.

Objective 2: To determine the incidence rates of asthma with and without RSV-Hospitalization

The cumulative incidence rate of asthma was calculated by dividing the number of new asthma cases diagnosed in our study period by the total population of infants at risk for asthma development using person-year units. The cumulative asthma incidence rate was stratified on the presence or absence of RSV-hospitalization, and the rate ratio was calculated by dividing the RSV-exposed rate by the RSV-unexposed rate. This rate ratio was calculated with 95% confidence intervals to determine the strength of the association between RSV hospitalization and asthma development, and was considered significant at $P < 0.05$. A rate difference equation was calculated by subtracting the

incidence rate of the non-RSV infants from the incidence rate of RSV infected infants in order to evaluate the clinical importance of the difference between asthma incidence rates. The rate difference was also considered significant at the $P < 0.05$ level. These measures illustrate the burden of asthma in RSV-infected and non-infected populations in our study cohort.

The association between RSV-hospitalization and asthma was evaluated using a Cox proportional hazard (PH) regression model to assess the association of RSV-hospitalization on the time to asthma onset while accounting for different lengths of follow-up. Bivariate analysis was used to independently assess the association between covariates and asthma development. Variables found to be significant (at a $P < 0.15$ significance level) were eligible for inclusion in the multivariable Cox proportional hazards model. All variables significant from the bivariate analyses were included in the model, and were subsequently removed if found not to be a confounder. If the RSV-hospitalization hazard ratio changed by more than 10%, then the variable was classified as a confounder and was controlled for in the regression model. If there is less than a 10% change, there is likely to be little or no confounding from that variable and it was therefore removed from the model (137). Tests for effect modification between RSV-hospitalization and independent variables significant from the bivariate analysis were conducted by comparing the likelihood ratios from a model with and without the interaction term to see if the interaction term is statistically significant. A test of the proportional hazards assumption was conducted using Schoenfeld's global test to ensure the two hazard functions were statistically proportional. Kaplan-Meier (K-M) curves were used to visually display the time to asthma diagnosis in both the intervention and control groups. The log rank sum test tested the significance between estimated K-M survival curves.

Given that asthma diagnosis in early childhood (children < 5 years), particularly during the first year of life, is a highly contested issue (100), we decided to conduct a sensitivity analysis by removing all asthma physician visits and hospitalizations occurring during the first year of life from the Cox PH regression model, and incidence rate

calculations. Infants must meet the study definition after the first year of life in order to be classified as an asthma case. An additional sensitivity analysis was conducted by removing all Pz-prophylaxed infants from the incidence rate calculations and Cox PH regression model to see what affect this had on our HR estimates and incidence rate calculations.

A logistic regression model was also used as a supplementary analysis to evaluate the association between RSV-hospitalization and subsequent asthma development within the first five years of life. All infants are required to have a full five years of follow up, and the short duration of our follow-up period will like result in a similar estimation of the risk of developing asthma as the Cox PH model. Bivariate and multivariable analyses were conducted using the same procedure employed in the Cox Proportional Hazard model.

4.6 Minimal Detectable Effect Size

Minimal detectable effect size (hazard ratio) was calculated based upon estimations of sample size and expected asthma development in RSV-hospitalized and non-hospitalized populations. The number of prematurely infants born from July 1998 to December 2009 in Nova Scotia without CLD and CHD predetermines the size of the cohort. The estimated size of the cohort is estimated to be 4,500 (infants aged >29 weeks 0 days GA to 35 weeks 6 days GA).

The calculations below assumed a level of significance (α) of 0.05 with a power ($1-\beta$) of 0.80. Using a 2-tailed approach, our study estimated the number of person-time years to be 22,500 person-years based on the estimated size of the cohort and average length of follow-up. This estimation assumed a follow-up of five years per person. Previous literature estimates RSV-hospitalizations to occur in 5% of a preterm infant population during the first year of life (25), and asthma development to occur in 30% of infants with RSV-hospitalizations and asthma to occur in 15% in non-infected infants (10,87). Applying these proportions to our study's estimated population, we estimated a fail probability (overall probability of an event of interest) of 0.16. The effect of covariates on the relationship between RSV-hospitalizations and asthma development (r^2) was estimated at 10% and 30%. These parameters approximate an HR of 1.26 assuming an r^2 of 0.1 (10%). If we increase r^2 to 0.3, the estimated HR slightly increases to 1.30. These approximations were used to provide an estimated minimal detectable effect size for our study population.

4.7 Ethical Considerations

Ethical approval to conduct this study was granted by the Research Ethics Board (REB) of the IWK and the Privacy office of the Nova Scotia Department of Health and Wellness (NSDOH). All information is de-identified by Reproductive Care Program analysts before our study team had access to the data, was encrypted on IWK servers, and no cell sizes smaller than 5 individuals were reported. All work was conducted in a restricted-access area of the IWK on a password-protected terminal. Photo ID was required to access the site. Electronic files were protected behind the IWK firewall, and remote access to the files was not granted.

5 Results

5.1 Description and Characteristics of Study Cohort

The final eligible study cohort consisted of 3,916 infants. A diagram of the study cohort derivation is shown in Figure 1. Thirty-three infants were excluded for early neonatal death (0-7 days), nine for late neonatal death (7-28 days), and six for post-neonatal death (28-364 days) totaling 48 infants excluded for death during the first year of life. An additional 280 infants were excluded for CHD or CLD diagnosis. Baseline characteristics of participants can be found in Table 1. The majority of infants (66%) were born at a later gestational age (34 weeks 0 days – 35 weeks 6 days GA). More male infants were present in our cohort (53.6%) than female (46.4%), and more infants were born vaginally (57.1%) than by caesarean section (42.9%). Only 9.2% of the infants were born in the bottom 10^{th} percentile of birth weight for gestational age. The infants were fairly evenly distributed across the socioeconomic quintiles. Over a quarter (26.9%) of infants were exposed to maternal smoking prenatally. Of the 15 variables described, eight variables contained missing values, which ranged from 0.3% (birth weight) to 4.0% (marital status, household crowding).

5.2 Objective 1: RSV-Hospitalization Incidence During the First Year of Life

Ninety-six infants were hospitalized for RSV during the first year of life. The vast majority of RSV-hospitalizations (90.7% (n=87/96)) were coded as acute bronchiolitis, and were coded under the primary diagnosis (90.0% (n=86/96)). The highest absolute number of RSV-hospitalizations (n=21) occurred during the 2006-2007 fiscal year (Table 3), and the attack rate of RSV was highest among infants born between 33 + 0 to 33 + 6 weeks GA at 45/1000 infants (Table 4). No infant who received Pz-prophylaxis was hospitalized with RSV during their first year of life. The overall incidence rate of RSV-hospitalizations in the first-year of life was 25 per 1000 infants (95%CI 19.7-29.6) (Table 4). The RSV-hospitalization incidence rate increased slightly to 27 per 1000 infants (95%CI 21.8-32.6) when Pz-prophylaxed infants were removed.

5.3 Data-Analysis Objective 2: Relationship Between RSV-Hospitalizations and the Development of Childhood Asthma

5.3.1 Incidence of Asthma

Over the course of the five-year individual follow-up, 655 infants were diagnosed with asthma. Table 5 shows asthma cases by ICD diagnostic code, with the majority (n=440/655; 67.2%) of cases coded as unspecified asthma by ICD-9-CM 493.90 and ICD-10-CM J45.90. The rate of asthma diagnosis over our study period for both the RSV-hospitalized group and non RSV-hospitalized group is visually presented by Kaplan-Meier curves (Figure 2). A log rank test found a significant difference between the survival curves of the RSV-hospitalized infants and non-RSV hospitalized infants in the probability of developing childhood asthma (P = 0.03). Table 6 shows the distribution of asthma cases in RSV-hospitalized and non-hospitalized groups by infant age. Looking at a plot of the density of asthma cases by the time to asthma diagnosis stratified on the presence of RSV-hospitalization (Figure 3), the number of asthma diagnoses occurring in the RSV-hospitalized group appear to peak around 20 months of age, and drop sharply afterwards. Comparatively, the non RSV-hospitalized group had a much slower decrease in cases and a smaller peak. Figure 4 illustrates the distribution of asthma cases by the time after RSV-hospitalization, which showed a peak of asthma diagnoses around 15 months after RSV-hospitalization. The highest absolute number of asthma diagnoses occurred during a five-year window (April 2004 – May 2009) in the middle of our study period. Most infants met the study criterion of two physician visits for asthma within three years (n=541) compared to being hospitalized for asthma (n=119). Five infants met both asthma study criteria on the same date. No infants who received Pz-prophylaxis (n=259) developed asthma during our study period.

Table 7 shows the cumulative incidence rate of childhood asthma (37.1 per 1000 person-years) and the rates stratified based on the presence (57.9 per 1000 person-years) or absence (36.7 per 1000 person-years) of preceding RSV-hospitalization. The risk ratio of the asthma incidence rates stratified on the presence of RSV-hospitalization narrowly

missed reaching significance (1.58, 95% CI 0.98-2.41), and the risk difference was also not significant at 21.2/1000 infants (95% CI -0.3 – 46). When Pz-prophylaxed infants were removed, the cumulative incidence rate increased to 40.0 per 1000 person-years. Stratifying on the presence (57.9 per 1000 person-years) or absence (39.6 per 1000 person-years) of RSV-hospitalization, the unexposed rate increased slightly.

When asthma hospitalizations and physician visits occurring in the first year of life were removed in the sensitivity analysis, the cumulative incidence rate of childhood asthma changed to 41.1 per 1000 person-years (Appendix C). When stratified on the presence of preceding RSV-hospitalization, the incidence rates of the RSV-hospitalized and non-hospitalized groups increased to 70.1 per 1000 infants and 40.5 per 1000 infants respectfully. The resulting rate ratio in the constrained cohort increased to 1.73 (95%CI 1.08-2.65) and the rate difference to 29.6/1000 infants (95%CI 0.0-59).

5.3.2 Bivariate Relationship Between RSV-Hospitalizations and Potential Covariates with Subsequent Asthma Development

Table 8 shows the bivariate hazard ratio (HR) estimates from the Cox proportional hazards regression for each of the independent variables evaluated for inclusion in the multivariable model as potential confounders. Results from the bivariate analysis found seven variables to be significantly associated with childhood asthma development ($P < 0.15$ significance level). Infants hospitalized with RSV, born biologically male, exposed to maternal smoking during pregnancy, and who received a low APGAR score 1 minute after birth were all found to increase the risk of developing childhood asthma in the bivariate models. Infants born in GA ranges 29 weeks 0 days – 29 weeks 6 days and 30 weeks 0 days – 30 days 6 days, ≥ 1 preschool-aged sibling in the household, and have upper-middle socioeconomic status all showed a lower risk of developing childhood asthma in the bivariate models.

Bivariate analysis results from the sensitivity analysis (removing asthma diagnoses occurring in the first year of life) found GA, SES, and the presence of siblings <5 to decrease the risk of developing childhood asthma (significant at a $P<0.15$ level)

(Appendix C). Hospitalization for RSV, male sex, and a low APGAR score 1 minute after birth all increased the risk for asthma development. These variables were eligible for inclusion in the multivariable model. Removing Pz-prophylaxed infants from the bivariate Cox PH analyses resulted in six variables significant at P<0.15 to be associated with asthma development in the unadjusted model (Appendix D). These variables were eligible for inclusion in the multivariable model.

Appendix E shows the bivariate odds ratio estimates from the logistic regression for each of the independent variables evaluated for inclusion in the multivariable model. The same seven variables from the Cox PH bivariate analysis were found to be significant at the P < 0.15 level, and were eligible for evaluation in the multivariable logistic regression model.

5.3.3 Multivariable Relationships Between RSV-Hospitalizations and Potential Covariates with Subsequent Asthma Development

RSV-hospitalizations and the other six covariates significant at P <0.15 from the bivariate analysis were included in a Cox proportional hazards regression model. The regression procedure included 91 infants with a RSV-hospitalization and 3,825 infants who were not hospitalized with RSV. Five infants were hospitalized with RSV after being diagnosed with asthma, and were subsequently censored at the time of asthma diagnosis.

RSV-hospitalizations were found to be independently associated with the development of childhood asthma (HR=1.58, 95%CI 1.03-2.41, P=0.036), and the Cox PH model met the proportional hazards assumption (Schoenfeld's global test chi2 = 3.19, P= 0.074). No independent variables evaluated in the multivariable Cox proportional hazards model were significant confounders. Effect measure modification was evaluated for the variables eligible for the multivariable model, but no statistically significant interaction effects were observed.

When children with asthma diagnoses in the first year of life were removed, RSV-hospitalizations were also found to be independently associated with later asthma development, but the constrained model also did not meet the Cox PH assumption (Schoenfeld's global test P=0.016). No independent variables evaluated in the multivariable model confounded the relationship between RSV-hospitalization and asthma, and no statistically significant interactions were observed (Appendix C). When Pz-prophylaxed infants were removed from the regression model, RSV-hospitalizations were not found to be significantly associated with later asthma development (HR=1.46, 95%CI 0.95-2.23, P=0.081), but did meet the proportionality assumption (Schoenfeld's global test P=0.071). Similar to the other models, no independent variables evaluated in the multivariable model confounded the relationship between RSV-hospitalization and asthma, and no significant interaction effects were observed.

The results from the Logistic Regression were similar to the Cox PH model, but narrowly didn't reach statistical significance. No independent variables significant after the bivariate analysis were found to significantly confound the relationship between RSV-hospitalizations and asthma development. The odds of developing asthma were 1.61 (95%CI 0.99-2.62, P=0.056) times higher among infants hospitalized for RSV than non-hospitalized infants in the first five years of life.

Table 1: Study Population Characteristics

Cohort Characteristic	*N (3,916)*	*%*	*Missing Values (%)*
Infant Sex			
Male	2,098	53.6	0
Female	1,818	46.4	
Birth Month (RSV season)			
January	307	7.8	0
February	284	7.3	
March	332	8.5	
April	305	7.8	
May	336	8.6	
June	336	8.6	
July	353	9.0	
August	350	8.9	
September	343	8.8	
October	333	8.5	
November	296	7.6	
December	341	8.7	
Gestational Age (GA)			
29 weeks + 0 days – 29 weeks + 6 days	103	2.6	0
30 weeks + 0 days – 30 weeks + 6 days	152	3.9	
31 weeks + 0 days – 31 weeks + 6 days	219	5.6	
32 weeks + 0 days – 32 weeks + 6 days	344	8.8	
33 weeks + 0 days – 33 weeks + 6 days	515	13.1	
34 weeks + 0 days – 34 weeks + 6 days	922	23.5	
35 weeks + 0 days – 35 weeks + 6 days	1,661	42.5	
Socioeconomic Status Quintile			
Highest	621	15.9	35 (.9%)*
Upper-middle	858	21.9	
Middle	821	21.0	
Lower-middle	786	20.1	
Lowest	795	20.3	
Preschool-aged children (≤5 years)			
0 siblings	2,071	52.9	0
1 sibling	1,352	34.6	
2 siblings	425	10.8	
3 siblings	66	1.7	
4 siblings	*A*	*A*	
APGAR score (1 min)			
Healthy score (7-10)	2,869	73.3	19 (0.5%)
Low score (0-6)	1,028	26.2	
APGAR score (5 min)			
Healthy score (7-10)	3,717	94.9	24 (0.6%)

Low score (0-6)	175	4.5	
Mode of Delivery			
C-Section	1,681	42.9	0
Vaginal	2,235	57.1	
Siblings ≤18 years			
0	1,766	45.1	0
1	1,284	32.8	
2	570	14.6	
3	206	5.2	
4	59	1.5	
5	21	0.5	
6	5	0.1	
7	*A*	*A*	
10	*A*	*A*	
Marital Status			
Married/Common Law	2,625	67.0	156 (4.0)
Single/Divorced/Separated/Widowed	1,135	29.0	
Household Crowding (≥ 5 Individuals/household)			
Yes	211	5.4	156 (4.0)
No	3,549	90.6	
Birth weight (grams)			
Birth weight (≥2500g)	1,419	36.3	14 (0.3%)
Low birth weight (< 2500g)	2,483	63.4	
Birth weight for gestational age			
< 3rd Percentile	103	2.6	14 (0.4%)
3rd to < 5th Percentile	52	1.3	
5th to < 10th Percentile	210	5.3	
10th to < 50th Percentile	1,450	37.0	
50th to < 90th Percentile	1,627	41.5	
90th to < 95th Percentile	222	5.7	
95th to < 97th Percentile	85	2.2	
≥ 97th Percentile	153	3.9	
Smoked during pregnancy			
Yes	1,055	26.9	83 (2.1)
No	2,778	71.0	
Palivizumab Prophylaxis Receipt			
Yes	259	6.6	0
No	3,657	93.4	

* Missing values are a summation of two forms of missing values: i) coded as missing (29 (.7%)), and ii) missing from dataset (6 (.2%))

'A' represents a cell value less than 5

Table 2: RSV-Hospitalizations by ICD Diagnostic Code

Cohort Characteristic	N (%)	Primary Diagnoses	Secondary Diagnoses	Tertiary Diagnoses	Missing Values (%)
ICD-9-CM 079.6 (RSV)	*A* (*A*)	*A* (*A*)	-	-	-
ICD-9-CM 466.11 (Acute bronchiolitis due to RSV)	11 (11.5)	11 (12.8)	-	-	
ICD-9-CM 480.1 (Pneumonia due to RSV)	*A* (*A*)	*A* (*A*)	-	-	
ICD-10-CM B97.4 (RSV)	*A* (*A*)	*A* (*A*)	-	-	
ICD-10-CM J12.1 (RSV pneumonia)	*A* (*A*)	*A* (*A*)	-	-	
ICD-10-CM J21.0 (Acute bronchiolitis due to RSV)	76 (79.2)	66 (76.7)	9 (100)	*A*	
ICD-10-CM J20.5 (Acute bronchitis due to RSV)	*A* (*A*)	*A (A)*	-	-	
Total RSV-Hospitalizations	96 (100)	86 (100)	9 (100)	*A*	

'A' represents a cell value less than 5

Table 3: Number of RSV-Hospitalizations by Fiscal year

Fiscal Year	N	%	Missing (%)
July 1st 1998 – Mar 31st 1999	6	6.3	-
Apr 1st 1999 – Mar 31st 2000	*A*	*A*	
Apr 1st 2000 – Mar 31st 2001	*A*	*A*	
Apr 1st 2001 – Mar 31st 2002	12	12.5	
Apr 1st 2002 – Mar 31st 2003	5	5.2	
Apr 1st 2003 – Mar 31st 2004	10	10.4	
Apr 1st 2004 – Mar 31st 2005	15	15.6	
Apr 1st 2005 – Mar 31st 2006	*A*	*A*	
Apr 1st 2006 – Mar 31st 2007	21	21.9	
Apr 1st 2007 – Mar 31st 2008	*A*	*A*	
Apr 1st 2008 – Mar 31st 2009	11	11.5	
Apr 1st 2009 – Mar 31st 2010	*A*	*A*	
Apr 1st 2010 – Dec 31st 2010	*A*	*A*	
Total	96	100	

'A' represents a cell value less than 5

Table 4: RSV-Hospitalization Rate by Gestational Age Range

Gestational Age Range (Weeks + Days)	N (%)				Attack Rate / 1000 infants (95% CI)
	Study Cohort	RSV-Hosp.	Pz-Receipt	% Pz-Receipt in each GA range	
29 – 29 + 6	103 (2.6)	0 (0)	49 (18.9)	47.6	0 (0)
30 – 30 + 6	152 (3.9)	*A* (*A*)	55 (21.2)	36.2	7 (1.0-48)
31 – 31 + 6	219 (5.6)	7 (7.5)	78 (30.1)	35.6	33 (16-66)
32 – 32 + 6	344 (8.8)	*A* (*A*)	58 (22.4)	16.9	12 (4.0-31)
33 – 33 + 6	515 (13.1)	22(20.4)	14 (5.4)	*2.7*	45 (29-68)
34 – 34 + 6	922 (23.6)	25 (26.9)	*A* (*A*)	*A*	28 (19-41)
35 – 35 + 6	1,661 (42.5)	37 (40.0)	*A* (*A*)	*A*	23 (16-32)
Total	3,916 (100)	96 (100)	259 (100)	100	25 (2.0-3.1)

'A' represents a cell value less than 5

Table 5: Asthma Cases by ICD Diagnostic Code

Cohort Characteristic	N (%)	Missing Values (%)
Asthma by ICD-CM code		
ICD-9-CM 493.00 (Extrinsic asthma, unspecified)	105 (16.0)	-
ICD-9-CM 493.01 (Extrinsic asthma, with status)	27 (*A*)	
ICD-9-CM 493.10 (Intrinsic asthma, unspecified)	*A* (*A*)	
ICD-9-CM 493.20 (Chronic obstructive asthma, unspecified)	7 (1.1)	
ICD-9-CM 493.90 (Asthma, unspecified type, unspecified)	416 (63.5)	
ICD-9-CM 493.91 (Asthma unspecified type, with status)	10 (1.5)	
ICD-10-CM J45.00 (Asthma)	57 (8.7)	
ICD-10-CM J45.01 (Asthma)	*A* (*A*)	
ICD-10-CM J45.90 (Unspecified Asthma)	24 (*A*)	
ICD-10-CM J45.91 (Unspecified Asthma with acute exacerbation)	*A* (*A*)	
All Asthma Diagnoses	655 (100)	

'A' represents a cell value less than 5

Table 6: Asthma Cases by Age at Diagnosis

Infant Age (years) at Asthma Diagnosis	RSV-Hospitalization Status		Total
	Yes	No	
0-1	6	133	139
1-2	11	202	213
2-3	*A*	157	161
3-4	*A*	82	83
4-5	0	59	59
Total	22	633	655

'A' represents a cell value less than 5

Table 7: Asthma Incidence by Preceding RSV-Hospitalization Status

RSV-Hospitalization Status	Asthma Cases	Rate per 1000 person-years (95% CI)
RSV-H	22	57.9 (38.1-88.0)
No RSV-H	633	36.7 (33.9-39.6)
Total	655	37.1 (34.4-40.1)

Table 8: Cox PH Bivariate Analysis of Possible Covariates for Asthma Development

Predictive Variable	% Asthma	Hazard Ratio		P-Value
		Estimate	95% CI	
RSV-Hospitalization*				
Yes	24.2 (22/91)	1.58	1.03 – 2.41	**0.036**
No	16.6 (633/3,823)	1	-	-
Sex*				
Male	18.9 (397/2,098)	1.38	1.18 – 1.61	**< 0.001**
Female	14.2 (258/1,818)	1	-	-
Gestational Age*				
29 weeks + 0 days – 29 weeks + 6 days	8.7 (9/103)	0.49	0.25 – 0.96	**0.037**
30 weeks + 0 days – 30 weeks + 6 days	11.8 (18/152)	0.68	0.42 – 1.10	**0.110**
31 weeks + 0 days – 31 weeks + 6 days	13.2 (29/219)	0.78	0.53 – 1.14	0.196
32 weeks + 0 days – 32 weeks + 6 days	14.8 (51/344)	0.87	0.64 – 1.17	0.355
33 weeks + 0 days – 33 weeks + 6 days	19.4 (100/515)	1.17	0.93 – 1.47	0.170
34 weeks + 0 days – 34 weeks + 6 days	18.1 (167/922)	1.08	0.89 – 1.31	0.441
35 weeks + 0 days – 35 weeks + 6 days	16.9 (281/1,661)	1	-	-
Socioeconomic Status (SES)*				
Highest	18.2 (113/621)	0.95	0.75 – 1.22	0.700
Upper-Middle	13.8 (118/858)	0.71	0.56 – 0.91	**0.006**
Middle	15.8 (130/821)	0.83	0.66 – 1.05	0.121
Lower-Middle	17.4 (137/786)	0.92	0.73 – 1.17	0.510
Lowest	18.7 (149/795)	1	-	-
Siblings < 5 (Preschool Age)*				
≥ 1 Sibling	15.7 (290/1,845)	0.89	0.76 – 1.03	**0.125**
0 Siblings	17.6 (365/2,071)	1	-	-
Siblings < 18				
≥ 1 Sibling	16.6 (358/2,150)	1.00	0.85 – 1.16	0.966
0 Siblings	16.8 (297/1,766)	1	-	-
APGAR Score at 1 Minute*				
Low Score 0-6	18.2 (187/1,028)	1.14	0.96 – 1.35	**0.133**
Normal Score 7-10	16.2 (465/2,869)	1	-	-
APGAR Score at 5 Minutes				
Low Score 0-6	14.9 (26/175)	0.88	0.59 – 1.30	0.522
Normal Score 7-10	16.8 (625/3,717)	1	-	-
Mode of Delivery				
C-Section	16.0 (269/1,681)	0.92	0.79 – 1.07	0.290
Vaginal	17.3 (386/2,235)	1	-	-

Household Crowding (≥5 Individuals/Household)				
Yes	15.6 (33/211)	0.94	0.66 – 1.34	0.743
No	16.8 (597/3,549)	1	-	-
Birth weight for Gestational Age				
≤ 10th Percentile	18.6 (68/365)	1.13	0.89 – 1.46	0.310
> 10th Percentile	16.6 (586/3,537)	1	-	-
Smoke Exposure During Pregnancy*				
Yes	18.5 (195/1,055)	1.16	0.98 – 1.37	**0.083**
No	16.2 (450/2,778)	1	-	-

Note: Cohort includes 655 infants diagnosed with childhood asthma and 3261 who did not develop asthma

* Indicates significant variables (P<0.15 considered as covariates in the bivariate analysis to be tested in multivariable model

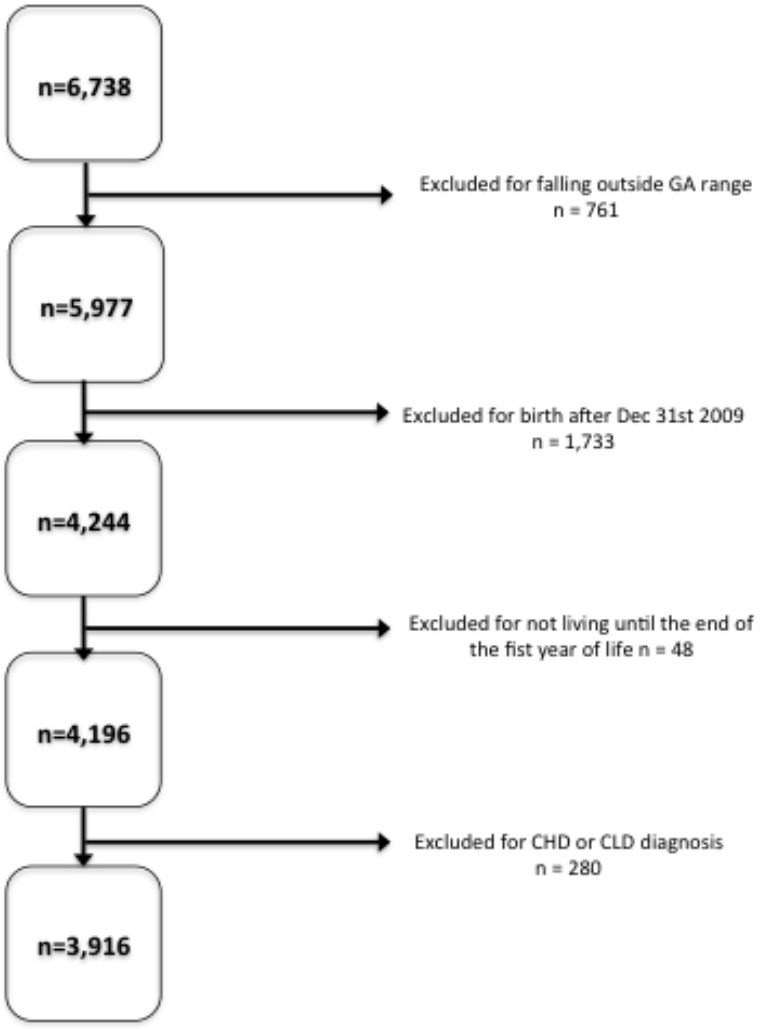

Figure 1: Flowchart of Study Cohort Derivation

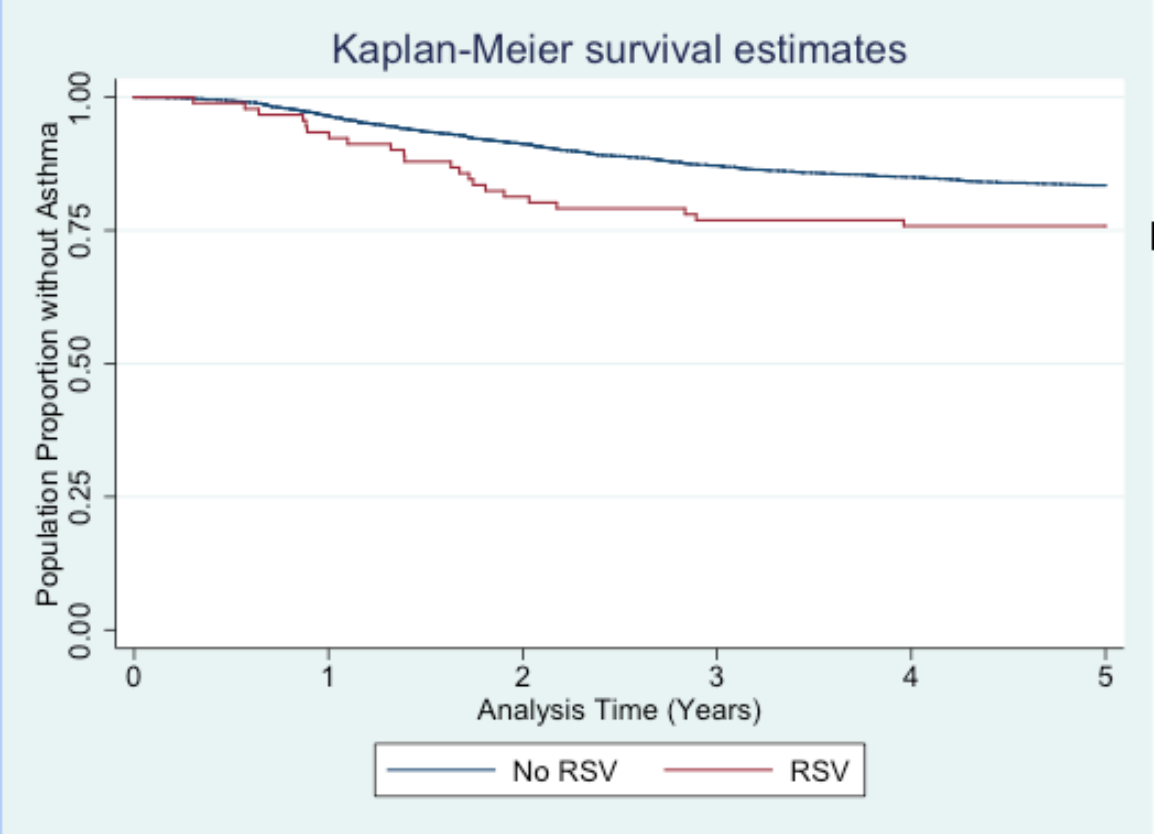

Figure 2: Kaplan Meier Functions (Failure = Developing Asthma) of RSV-Exposed and Unexposed Groups

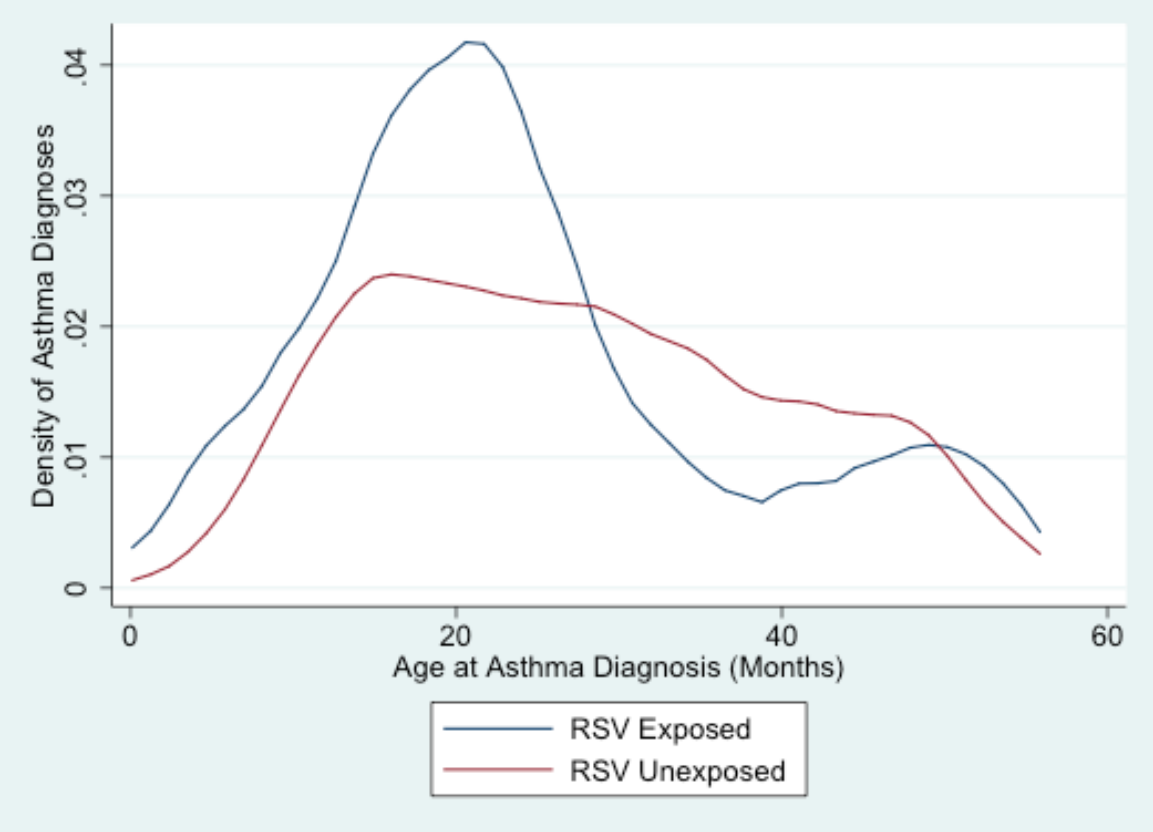

Figure 3: The Distribution of Asthma Diagnoses by Age at Diagnosis Stratified on RSV-Hospitalization Status

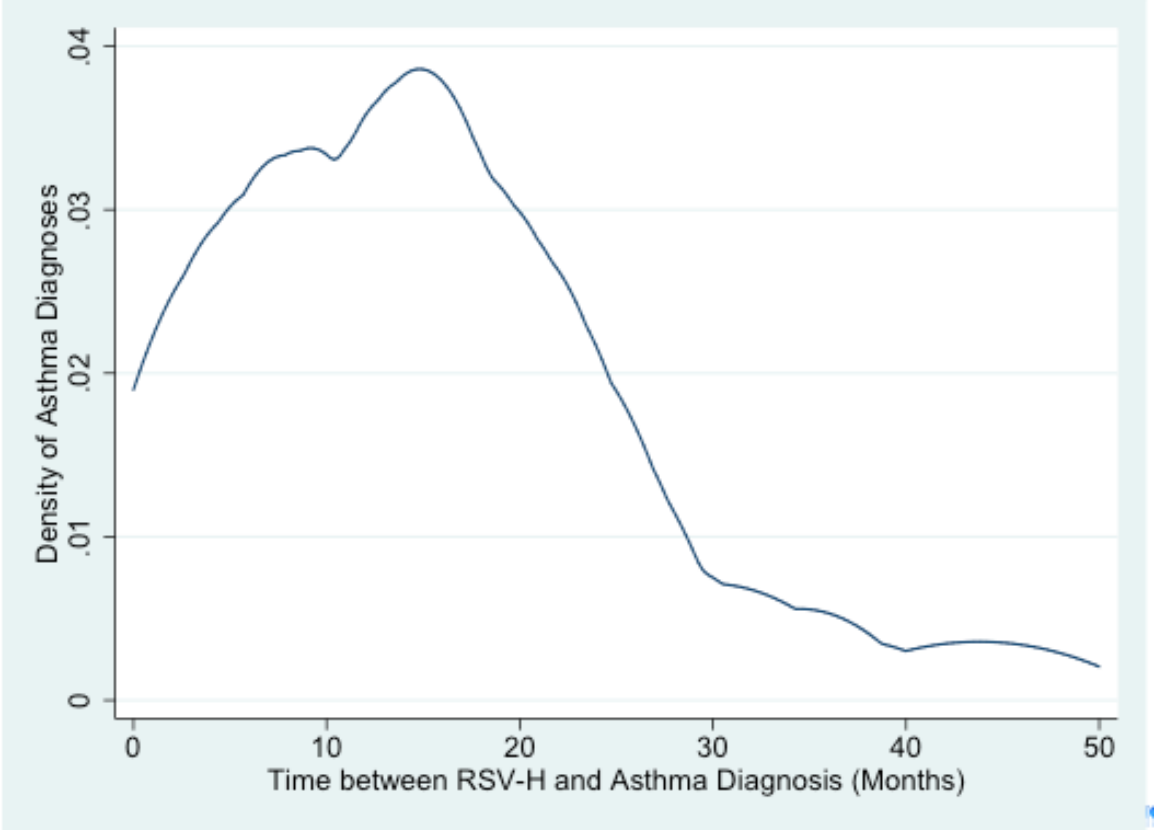

Figure 4: Distribution of Asthma Diagnoses by Time Between RSV-Hospitalization and Asthma Diagnosis

6 Discussion

6.1 Major Findings

6.1.1 Incidence of RSV-Hospitalization

This study aimed to quantify the incidence of RSV-hospitalizations occurring during the first year of life in a cohort of infants born from 29 weeks 0 days to 35 weeks 6 days GA. The cumulative incidence of RSV-hospitalizations in the first year of life during our study period was 25/1000 infants (2.5%).

The incidence rate of RSV-hospitalizations in our cohort was lower than most of the incidence rates found in the literature, and lower than our minimal detectable effect size estimation of 5%. Results from the Blanken et al. RCT found the incidence rate of RSV-hospitalization in the placebo arm to be 5.1% (11/215) in a cohort of prematurely born infants (33-35 weeks GA) during the first year of life (25). A systematic recent review conducted by Mauskopf et al. identified two additional studies investigating RSV hospitalizations in preterm infants born <35 and <36 weeks GA, which found RSV incidence rates of 8.1% (19/234) (138) and 3.2% (55/1721) (36) respectively during the first full RSV season after birth (28). Another recent systematic review from the REGAL series found the incidence of RSV-hospitalizations ranged from 0.3% per year to 4.3% during the first year of life (19). Ryan et al. in a population similar to our study found the incidence rate of RSV-hospitalization in healthy, prematurely born infants aged 32-35+6 weeks GA to be 3.1% (88/2811) (37). Stevens et al. conducted a retrospective cohort study in early premature infants (32-30 weeks GA) found the incidence rate of RSV-hospitalization to be 4.5% in the first year of life (139).

The incidence rates of RSV-hospitalizations presented in the literature vary substantially (28). The inconsistencies may be explained by differences in study characteristics and participants. The underlying differences in the population that the study participants are drawn from, the eligibility criteria used to distinguish which participants should be included (such as infants diagnosed with CHD and CLD, or those prophylaxed with Pz), and the length of time infants are observed in follow-up all affect

incidence rate calculations. If infants are followed for their first year of life or for their first full RSV season (36,138), different RSV incidence rates can be observed. Different criteria for what qualifies as a case of RSV (hospitalization or any diagnosis) and differences in how RSV diagnoses are ascertained (prospectively, or through administrative datasets) can also contribute to the observed disparity between rates. Our study used a conservative approach, only including ICD-CM codes explicitly coded as a RSV-hospitalization, whereas other studies used other case definitions such as including only RSV-bronchiolitis cases instead of all RSV-associated hospitalizations (113). Changing the parameters for what constitutes a RSV-hospitalization would result in different numbers of RSV cases counted. The time at which the study was conducted can also influence RSV hospitalization incidence rates due to changes in clinical practice guidelines and Pz-prophylaxis administration criteria. Recommendations have been trending towards only prescribing Pz for those infants most at risk for RSV-hospitalization (birth at early gestational ages, or those with cardiopulmonary conditions) (3,140,141).

The highest attack rate for RSV in our cohort was among infants born 33 weeks 0 days GA – 33 weeks + 6 days GA (Table 4). Past studies have shown infants born at younger gestational ages have higher rates of hospitalization due to RSV. In a study cohort similar to this study's, Ryan et al. did not find a significant association between gestational age and RSV-associated hospitalizations, suggesting that gestational age does not significantly influence an infant's chance of being hospitalized for RSV (37). However, a review by Abraha et al. found that the incidence of RSV-related hospitalization decreased with advancing gestational age, from 13.9% for infants born $\leq$ 26 weeks GA to 4.5% in infants born 29-32 weeks GA (21). A plausible explanation for observing the highest attack rate in infants aged 33 weeks GA to 33 weeks 6 days GA is the distribution of Pz-prophylaxis. In our cohort, a higher percentage of kids were prophylaxed at younger GA ranges (48% and 37% for infants born 29 and 30 weeks GA respectively) (Table 4). These are the infants who are traditionally at a higher risk for RSV-hospitalization compared to late prematurely born infants.

The year-to-year and seasonal variations in RSV incidence are important aspects of RSV epidemiology and having knowledge about RSV activity in Nova Scotia is important for guiding Pz-prophylaxis. Season to season RSV-hospitalization rates have been shown to vary up to two or three-fold in the same geographic region (19). Our study found RSV-hospitalizations to be the highest in the 2006-2007 fiscal year. Results from a Nova Scotia RSV surveillance system from the years 2005-2006, 2006-2007, and 2007-2008 seasons also found the absolute number of RSV identifications (not just those warranting hospitalization) during the 2006-2007-winter season to be the highest (n=89) in infants < 5 months of age (142).

6.1.2 Incidence of Childhood Asthma and Relationship with Preceding RSV-Hospitalization

The cumulative incidence rate of physician-diagnosed childhood asthma among our preterm infant study cohort from one year of age to a maximum five-year follow-up was 37.1/1000 person-years (3.7%). Similar to RSV-hospitalization incidence rates, asthma incidence rates are also difficult to compare between studies due to differences in study design, study populations, eligibility criteria, asthma definitions, length of study participant follow-up, and changes in asthma diagnostic criteria over time. With this in consideration, our incidence rate of physician-diagnosed asthma was still lower than many comparable studies (12.1% (10), 23% (112)), none of which exclusively evaluated prematurely born infants. An older study looking at the burden of childhood asthma across Canada had rates similar to our study with an observed overall rate of 4.7%, but found an elevated rate (7.4%), in the maritime provinces (143).

One possible explanation for the lower observed incidence rate of asthma seen in our cohort is our definition of asthma. Requiring two physician visits within three years or 1 hospitalization was a more conservative approach compared to some other studies' criteria, which used a survey response and three episodes of bronchial obstruction verified by a physician with no defined time period (10,144). To et al.'s case-verification study reported sensitivity and specificity values of 90.4% 69.6% respectively, illustrating the robustness of the asthma definition used in our study (136,145).

Stratifying the incidence rate of asthma based on the presence of preceding RSV-hospitalizations produced a rate of 57.9/1000 person-years in the RSV-hospitalized group, and 36.7/1000 person-years in the non-hospitalized group. Both rates were much lower than our minimal detectable effect size estimations (30% and 15% respectively). The resulting rate ratio (1.58), and risk difference (21.2/1000 infants) values were not statistically significant, indicating that there is not a significant unadjusted difference in asthma incidence rates between infants hospitalized for RSV, and those who were not. The rate ratio in our study was much smaller than those in the literature. A systematic review by Szabo and colleagues investigating asthma risk after RSV-hospitalization in infancy identified two studies evaluating asthma risk infants < 5 years of age with significant, unadjusted relative risks of 21.8 and 11.0 and risk differences of 22.3 and 13.2 respectively in cohorts of term-born infants (13). Also the review as a whole found asthma prevalence among individuals hospitalized for RSV during infancy was significantly higher than non-hospitalized comparison groups (13). Results from the fifth systematic review from the REGAL review series found that following severe RSV-hospitalization in early childhood (<2 years of age), asthma rates ranged from 8-48% (average follow-up 6-8) years (10,12,86,111,113,146–149). A possible explanation for the lower observed risk ratio in our study was the protective effect of Pz-prophylaxis in our preterm infant cohort. None of the Pz-prophylaxed infants were hospitalized with RSV or developed asthma, and this intervention is only administered to the infants who are at high risk for RSV-hospitalization. By neutralizing the infants at highest risk, the resulting rates are likely biased towards a null effect.

Results from our multivariable Cox proportional hazards model found hospitalization for RSV during the first year of life was significantly associated with developing childhood asthma during 5 years of follow-up (HR 1.58; 95%CI 1.03-2.41; P=0.036), and met the proportional hazards assumption (102). This hazard ratio is larger than our estimated minimal detectable effect size, despite our confidence intervals falling close to 1.00. This is likely because of our over estimation of asthma rates in the RSV-hospitalized and non-hospitalized groups. Results from the logistic regression model estimated the risk of asthma development over the five-year individual follow-up and

found RSV-hospitalization was narrowly not significantly associated with asthma development (OR=1.61, 95%CI 0.99-2.62, P=0.056). The effect size was similar between our Cox PH and logistic models because the follow-up period was only five years. However, because logistic model estimates are derived from data over time and information on event time is not considered, time could bias the results. Thus the difference between our Cox PH and logistic regression models can likely be attributed to the extent of which time was a confounder, and can help explain why our Cox PH model reached statistical significance while our logistic regression model did not. The low number of RSV-hospitalizations and asthma diagnoses in our study may have limited our ability to detect a statistically significant difference in our logistic regression model.

Our study's Cox PH regression results support the majority of findings from the literature, that RSV-hospitalization during the first year of life is associated with the development of childhood asthma. Preliminary results from the ongoing RCT by Blanken et al., found that prophylaxis with Palivizumab decreased the relative risk of recurrent wheezing (a precursor to asthma defined as three or more wheezing episodes in the first year of life) by 47% (95%CI 14-80) compared to placebo controls in prematurely-born infants 33-35 weeks GA (25). A recent meta-analysis investigating the relationship between RSV hospitalizations and asthma/wheezing found a significant pooled OR of 3.84 (95%CI 3.23-4.58) suggesting a strong association, but not necessarily a causal relationship (150). A systematic review apart of the REGAL series published last year concluded that evidence from an increasing number of studies suggests a strong association between RSV-hospitalizations in children less than three years of age and the development of childhood asthma in mixed populations (12). A review by Perez-Yarza and colleagues identified seven studies investigating the effect of RSV-hospitalization and physician diagnosed childhood asthma, a similar number identified by the Szabo et al. systematic review (13,14). Both reviews highlight overlapping sets of studies that vary in study design, populations under study, and follow-up periods. Henderson et al. found an adjusted odds ratio of 2.5 (95%CI 1.4-4.3) between RSV-hospitalizations during the first year of life and controls at 91 months follow-up in a robust, longitudinal birth-cohort study (86). Sigurs and colleagues estimated relative risks of 21.8 (95%CI 2.90-163.57),

9.2 (95%CI 2.8-30.6), and 6.8 (95%CI 2.7-17.3) at 30, 78, and 149 months of follow-up respectively between infants hospitalized for RSV and age, sex matched controls not infected with RSV (10,113,114). This study and two follow-up publications differ from our study because the authors did not specifically look at preterm infants, and the cohort was established on the 47 RSV-hospitalized cases identified, and therefore was not population-based. Bacharier et al., followed a cohort of RSV-hospitalized infants (n=206) for seven years, and found nearly half (48%) of children developed asthma by the end of the study period (111). Fjaerli and colleagues found a significant difference in the probability of developing asthma between RSV- infected infants (60%) and controls (7.8%), but did not control for confounding variables (41). A cohort study from Fjaerli et al. found a significant association between RSV-hospitalization and asthma development at seven years of age between RSV-hospitalized bronchiolitis cases (n=58) and age-matched controls (RR 7.7, 95%CI 3.2-18.6) (32). A nested case-control study in a population of Alaskan Native children, infants hospitalized for and RSV infection in the first two years of life were 3.1 times (95%CI 1.57-6.08) more likely to develop asthma at 70 months follow-up (151). One retrospective study from Finland identified by all three systematic reviews did not find a significant association between RSV infection and physician-diagnosed asthma in infants admitted to hospital for RSV in the first year of life (87).

Despite two systematic reviews and a meta-analysis suggesting an association between RSV-hospitalization and subsequent asthma development, an editorial written by Stein stated the evidence on the matter is inconclusive by pointing to issues with inadequate control of confounding variables, and conclusions based on a small number of subjects, usually after stratifying for subgroups that infer results with little clinical impact in the literature (152). Although many studies have investigated this association since its publication in 2010, this editorial provokes discussion concerning the continued uncertainty of the impact of RSV-related illness on subsequent asthma development. The body of literature suggests an association, but lacks the certainty to infer causation. With the exception of the ongoing RCT by Blacken and colleagues, all of the studies discussed above used an observational design, and therefore all inherently have confounding and

biases that cannot be completely controlled for. Most studies are not population-based, are a mixture of retrospective and prospective design, and do not exclusively evaluate premature infants their study populations. Measures of the association between RSV-hospitalization and asthma are also highly variable, making it difficult to summarize an accurate effect size. Establishing a consensus on what the true association between RSV-hospitalization and asthma considering these limitations and study differences is difficult and we believe our study's results add some clarity to the discussion, particularly by adding evidence in a cohort of prematurely born infants without CLD or CHD population.

Childhood asthma continues to be a substantial public health burden. Respiratory morbidity has been shown to result in reduced quality of life, and an increase in healthcare resource use (12). No known prevention strategies exist, largely due to the complex etiology of the disease. Accurate estimations of the association between RSV-hospitalization and asthma development in childhood are important both for understanding the etiology of asthma, and the long-term health impacts of RSV hospitalization, particularly amongst high-risk, prematurely born infants. Distinguishing a causative role for RSV in the pathogenesis of asthma is challenging because asthma includes multiple phenotypically distinct diagnoses. It has been postulated that this positive drift towards an association may also be influenced by premorbid lung function, a family history of asthma, and a genetic predisposition for asthma (152). Results from a Danish twin study indicate an underlying genetic predisposition and atopic sensitization may act as potential causes of childhood asthma, and severe RSV infections serve only as a mediator for these conditions (115). Another study found that when the population is selected based upon a family history of asthma, respiratory illnesses (including RSV) in the first year of life were associated with later asthma development (153). While our study does not provide evidence in support of these theories, it is important to recognize there may be other mechanisms of asthma development involving RSV-hospitalization that cannot be inferred by our study, but should be considered. Further investigation into atopic sensitization and the effect of family history of asthma on RSV-hospitalization and subsequent asthma development is needed.

The effect of Palivizumab on subsequent childhood asthma development is an interesting point of discussion. Of the 259 Pz-prophylaxed preterm infants in our study, none were hospitalized for RSV during the first year of life. This was a protective rate higher than secondary analysis of the robust IMpact study group clinical trial among preterm infants 28-35 weeks GA, and the double-blinded MAKI randomized controlled trial that both investigated the efficacy of the prophylaxis (25,36). The safety and efficacy of Pz has already been well established (154), what is of interest is that no Pz-prophylaxed infants on our study were diagnosed with asthma in childhood. Pz specifically targets RSV, so it is logical that the pathway would begin with Pz neutralizing RSV, inhibiting its role in subsequent asthma development. Turning to the literature, most studies have looked at the relationship between Pz and recurrent wheezing in childhood (18,25,155), but a recent retrospective cohort study investigated the effect of Pz-prophylaxis on asthma development. Multivariable and propensity-score adjusted models primarily yielded non-significant associations between Pz-prophylaxis and the prevention of asthma in childhood (112). A body of evidence to support the notion that Pz-prophylaxis decreases asthma risk is lacking. Results from the ongoing RCT by Blanken et al. investigating the effect of Pz on childhood asthma will prove insightful (13,25).

6.2 Strengths and Limitations

To our knowledge, this is the first cohort study examining the incidence of RSV-hospitalization and its relationship with asthma in a cohort of premature infants, and in a Canadian population. The availability of datasets allowing linkage of children from birth to early childhood through health system use for respiratory illness in Nova Scotia provides a robust resource to assess the link between RSV-hospitalization and asthma. The use of observational, population-based methods allows the estimation of effect size in this specific population within a real world context. Our study utilized a validated, robust algorithm for asthma diagnoses in administrative data sets, and our use of person-time years for our incidence rate calculations and cox proportional hazards regression model provided more accurate estimations of effect size.

Although the study has a number of strengths, there are some limitations we would like to acknowledge. A limitation concerning the retrospective nature of the study is that variables considered to be potential confounders that are not present in the dataset cannot be analyzed and controlled for in the analysis. For example, the ability to measure smoking in the household is limited to the proxy measure of maternal smoking status at the time of delivery, pre-pregnancy smoking status, smoking at the 1st prenatal visit and smoking at the 20 week prenatal visit. Passive smoke exposure during infancy and early childhood post-utero would have been interesting to consider as a potential confounder in our multivariate models. Maternal history of asthma was one variable of particular interest that was not present in our dataset. A hereditary link between RSV hospitalization and childhood asthma has been proposed, indicating that RSV-hospitalizations serve as an indication for a genetic predisposition to asthma, not the direct cause (115,153). It would have been beneficial for our study to investigate the effect of a genetic predisposition on our relationship between RSV-hospitalization and asthma development to see if our results supported or opposed those results found by previous studies. Infant deaths occurring after the first year of life during our study period were also not captured in our dataset, but due to the rarity of this event occurring in our population during our follow-up, it likely had a minimal impact on our results.

We were unable to identify twins and other non-singleton births in our dataset. This is a limitation because twin and other non-singleton births provide an interesting challenge. It is likely that these infants are not independent of each other with respect to RSV-hospitalization and asthma development. The same issue arises among similar aged, non-twin siblings who are likely to have correlated risk factors such as maternal smoking. Generalized estimating equation (GEE) methodology can account for this, but twin birth wasn't coded in the dataset and therefore could not be adjusted for.

The number of true cases of hospitalization for RSV is likely underestimated, which may have lowered our RSV-hospitalization incidence calculations and affected our effect estimates of RSV-hospitalization on asthma development. Many RSV-hospitalizations are not laboratory-confirmed as RSV-induced, and are coded as unspecified pneumonia or bronchiolitis instead of RSV-specific pneumonia (ICD-9-CM 480.1, ICD-10-CM J12.1) and bronchiolitis (ICD-9-CM 466.11, ICD-10-CM J21.0). A study compared reports from laboratory-confirmed cases with the primary and secondary diagnostic codes in patient's records and found that RSV-specific diagnostic codes were used for only 77% of the confirmed cases (156). Only RSV-specific codes were included in the analysis in order to minimize misclassification bias and ensure only true RSV-cases were included but consequently, it is likely that unconfirmed RSV-hospitalizations were missed.

Asthma shares common symptoms with other respiratory illnesses such as chronic bronchitis and transient wheezing disorders. As a result, many asthmatic cases are misdiagnosed leading to non-differential misclassification bias (157,158). Mild forms of asthma are often missed, and therefore counted as non-asthmatics in administrative datasets resulting in one-way misclassification bias. This problem is further exacerbated by the lack of a universal definition for childhood asthma (131,158,159). Werk and colleagues investigated what factors primary care physicians believe are important for establishing the initial diagnosis of childhood asthma (158). They found that physicians largely agreed upon certain symptoms are important for establishing a diagnosis (96% agree on recurrent wheezing, 89% recurrent cough) but disagreed on the combination of

factors that are important for diagnosis. As a result, errors in asthma diagnosis can occur at the level of physician diagnosis, or at the level of coding diagnoses into databases. The extent to which these errors occur was evaluated by To et al., (2006) and they found the agreement between the physician diagnoses and the administrative diagnostic codes to be very high (90.4% sensitivity and 69.6% specificity), and incorrect physician diagnoses were very low when reviewed by an expert panel (131). Another issue concerning our asthma definition and five-year follow-up period is that single outpatient physician visits for asthma in our study period are not counted because the confirmatory second visit needed to satisfy the definition isn't captured despite the fact that the date of diagnosis (from the first physician visit) does fall during our study period. This limitation may cause our incidence rate estimations and the association between RSV-hospitalization and asthma to be lower.

It is also important to note that the results from this study were based upon a cohort of NS-prematurely born infants and should be applied cautiously in other populations and geographic locations. The results are useful for public health decision makers in this Canadian province, but various environmental risk factors differ between other Canadian provinces and between other nations, which may impact the relationship between RSV hospitalizations and childhood asthma development.

6.3 Future Directions

Future studies investigating the relationship between RSV-hospitalization and childhood asthma development should include other important risk factors that may influence the relationship that weren't accounted for in our study. One variable in particular is atopy, commonly measured through proxy variables such as maternal history of asthma, which some studies have found to mediate the relationship between RSV hospitalization and asthma (115–117,160). A prospective, population-based study using validated definitions to accurately estimate the relationship between RSV-hospitalizations and asthma; especially amongst premature infants would help to clarify this association.

Future studies also should continue to examine the role of Pz-prophylaxis on childhood asthma development, to see if there are other unknown mechanisms of action to explain why no Pz-prophylaxed infants developed asthma in our study. These forthcoming studies should ensure adequate numbers of Pz-prophylaxed infants are recruited in order to have enough power to detect an effect size if present. To truly settle the debate between the role of preventing severe RSV infection with Pz-prophylaxis during infancy and the development of childhood asthma, results from a randomized controlled trial (25) currently underway are needed in order to overcome bias by indication and confounding issues inherent to observational studies.

Updated information concerning the burden of RSV-hospitalization and asthma in our preterm infant population provides valuable evidence to be used in public health policy and decision-making. Multiple systematic reviews have consistently found respiratory morbidity to result in reduced quality of life and increased health-care resource use (12). It was proposed by James et al., that 13% of asthma cases could be prevented by eliminating infant bronchiolitis during the RSV season based on their population-level study findings that 13% of asthma cases were associated with infant bronchiolitis during the RSV season (146). If upfront investment in Pz-prophylaxis for at-risk infants results in lower healthcare expenditure on asthma management in the long-term, changes to provincial Pz-prophylaxis programs should be considered.

The results of this study will be provided to the NS Utilization Management Program for RSV and will be apart of a larger report submitted to the Nova Scotia Department of Health. The results will also be disseminated in peer-reviewed literature with the purpose of providing evidence to advise public health decision-making in Nova Scotia, other Canadian provinces and other international health departments in RSV prevention and intervention.

7 Conclusions

Hospitalization for RSV among preterm infants continues to have a substantial burden on individuals and the healthcare system. The etiology of asthma continues to be elusive, and identifying potential preventative measures is important to address the substantial morbidity associated with the condition.

Our study used existing data from administrative datasets to retrospectively investigate the association of RSV-hospitalizations on subsequent asthma development in childhood. We began with quantifying the burden of RSV-hospitalizations during the infants first year of life, which yielded an incidence rate of 25/1000 infants. The incidence of asthma in our cohort was 37.1/1000 person-years, and when stratified on RSV-hospitalization, infants hospitalized for RSV had a higher incidence of asthma development (57.0/1000 person years) than non-hospitalized infants (36.7/1000 person years) Results from our Cox PH regression model found a significant association between RSV-hospitalization and asthma (HR 1.58 95%CI 1.03-2.41). The Cox proportional hazards regression model met the proportional hazards assumption. Our findings suggest an association between RSV-hospitalization and asthma development, but we cannot infer a causal relationship.

Multiple systematic reviews suggest an association between RSV-hospitalization during the first year of life and asthma, and our results support these findings. The association between the prevention of RSV hospitalizations through immunoprophylaxis and subsequent asthma development has only been briefly investigated. None of the Pz-prophylaxed kids in our cohort developed asthma during our study period, and results from the ongoing RCT (25) will prove interesting, and should continue to be explored.

The results from our study will be provided to the NS Utilization Management Program for RSV and the NS Department of Health to help aid decision-making and RSV prevention and intervention strategies. Our results provide evidence that long-term morbidities are associated with preceding RSV-hospitalizations, which may impact the eligibility criteria for Pz-prophylaxis in preterm infants.

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Appendix A

Variable	Objective	Rationale	Years of Data Required	Database
Month of birth	How many children are born at the beginning of the RSV season?	To determine if born at beginning of RSV season, beginning point for longitudinal 5-year follow-up	2000-2014	Atlee
Infant sex	Is male sex a risk factor for RSV illness and later onset of asthma?	Admission rates according to sex, male sex is known risk-factor for contracting RSV	2000-2014	Atlee
Gestational age	Does gestational age affect RSV infection rates?	Preterm infants are population of interest	2000-2014	Atlee
Birth weight for gestational age	Is low birth weight for gestational age a risk factor for RSV admission and later onset of asthma?	Known risk-factor for RSV infection	2000-2014	Atlee
Number of siblings <5 years old	Is the number of persons in the infant's home at daycare age a risk factor for RSV and later onset of asthma?	Opportunity for Community-acquired RSV infection	2000-2014	Atlee
Maternal Smoking i) Pre-pregnancy smoking ii) Smoking at 1st prenatal visit iii) Smoking at 20 weeks (prenatal visit) iv) Smoking at the time of admission	Is maternal smoking a risk factor for RSV infection and later onset of asthma	Known risk-factor for RSV infection in multivariate analysis	2000-2014	Atlee

Discharge data from birth admission	How much time in what season is the infant living in an area for RSV exposure risk?	Potentiality for increased risk in RSV infection if discharged around beginning of RSV season	2000-2014	Atlee
QAIPPE	Investigating potential effect of socioeconomic status proxy variable on RSV infection and later onset of asthma	Neighbourhood income level as a proxy for socioeconomic status risk-factor for RSV infection	2000-2014	Atlee
APGARs	Is low Apgar a risk factor for RSV associated illness and later onset of asthma in the first year of life?	Potential risk-factor for RSV infection	2000-2014	Atlee
Maternal Age	Is maternal age a risk factor for RSV infection and later onset of asthma in the first year of life?	Potential risk-factor for RSV-infection	2000-2014	Atlee
All cause mortality diagnostic codes	Is the cause of death RSV-associated?	Determine if mortality outcome is associated with RSV	2000-2014	NS Vital Statistics Database
Death Date	To determine the time to censor infants from the cohort	To provide temporal information about mortality outcome	2000-2014	NS Vital Statistics Database
Age at Death/Code+value	To describe age at which deaths from RSV occur	To determine if mortality occurred during RSV outbreak, and age that it occurred	2000-2014	NS Vital Statistics Database
Diagnostic codes 079.6 RSV		To identify outcome variable, asthma	2000-2014	CIHI Discharge Abstract

480.1 pneumonia due to RSV 466.1 Acute bronchiolitis due to RSV B97.4 RSV any diagnosis J12 viral pneumonia not otherwise specified J20.5 a b Acute bronchitis due to RSV J21.0 Acute bronchiolitis due to RSV J12.1 Sub code for RSV **Asthma Codes** 493.0 Extrinsic asthma 493.1 Intrinsic asthma 493.2 Chronic obstructive asthma 493.8 Other forms of asthma 493.9 Asthma unspecified J45.2x mild intermittent J45.3x mild persistent		and asthma-associated conditions		Database

J45.4x moderate persistent J45.5x severe persistent J45.90x x=0 Complicated x=1 With Exacerbation x=2 With Status **Asthma-related Condition Codes** **ICD-9** Acute bronchiolitis/bronchitis 466 Bronchitis not otherwise specified 490 Pneumonia 480-486 Acute Pharyngitis 462 464 Acute Laryngitis and Tracheitis 464 Acute Upper Respiratory Infections 465 **ICD-10** Bronchitis J40-42				

Pneumonia J12-18 Acute Pharyngitis J02 Acute Laryngitis and Tracheitis J04 Acute Upper Respiratory Infections J06				
Admission date	Admission with RSV, asthma or asthma-related illness	Aid in determining incidence of RSV infection in NS premature populations	2000-2014	CIHI Discharge Abstract Database
Diagnostic codes (ICD-9-CM)	RSV associated illness	Capture outcome variable	2000-2014	MSI (Physician Billing Database)
Hospital of birth	Linking variable	Linking variable	2000-2014	Atlee
Unit number	Linking variable	Linking variable	2000-2014	Atlee
Mother's name	Linking variable	Linking variable	2000-2014	Atlee
Mother's previous surname	Linking variable	Linking variable	2000-2014	Atlee
Postal code	Linking variable	Linking variable	2000-2014	Atlee
Address	Linking variable	Linking variable	2000-2014	Atlee
City	Linking variable	Linking variable	2000-2014	Atlee
Birth Weight	Linking variable	Linking variable	2000-2014	Atlee
Respiratory Disorder	Linking variable	Linking variable	2000-2014	Atlee
Health Card Number	Linking variable	Linking variable	2000-2014	Atlee, MSI, CIHI Discharge Abstract Database
Infant name	Linking variable	Linking variable	2000-2014	Nova Scotia Palivizumab utilization program (NSPUMP) and Blood Coordinating

				Program (previous Pz recording spreadsheet)
Infant Sex	Linking variable	Linking variable	2000-2014	NSPUMP
Infant date of birth	Linking variable	Linking variable	2000-2014	NSPUMP
429.2 (ICD-9) I25.10 (ICD-10) Congenital Heart Disease (CHD) Diagnoses	Are infants with CHD more likely to have severe RSV-LRTI	To identify CHD-diagnosed infants to be removed from the analysis	2000-2014	IWK Cardiology Database
770.7 (ICD-9) P27.1 Chronic Lung Disease/Bronchopulmonary Dysplasia	Infants at increased risk for severe RSV-LRTI	To identify CLD-diagnosed infants to be removed from the analysis	2000-2014	CIHI DAD, MSI Physician Billing
IWK "K" Number	Linking variable	Linking variable	2000-2014	Atlee, IWK Cardiology

Appendix B

Patient Initials:

|___|___|___|___|___|___|

PATIENT REFERENCE NO _____
(Determined by distributor)

INDICATION FOR USE Date of Birth (D/M/Y): ____/____/____ ☐Male ☐Female

(Please select appropriate indication)

☐Infants born prematurely at ≤ 32 weeks, 0 days gestation and aged ≤ 6 months WITH bronchopulmonary dysplasia/chronic lung disease i.e. must be born on or after June 1, 2015.

☐Infants born prematurely at ≤ 32 weeks, 0 days gestation and aged ≤ 6 months WITHOUT bronchopulmonary dysplasia/chronic lung disease i.e. must be born on or after June 1, 2015.

Please record the EXACT gestational age at birth of this infant:

weeks _____days _____

☐Children < 24 months of age with hemodynamically significant heart disease.

☐Pulmonary hypertension. PA pressure estimate: _____

☐Congestive heart failure. Medications: _____

☐Cyanotic CHD. Diagnosis: _____saturation %: _____

☐Other CHD. Indicate specific diagnosis (mandatory):_____

_____

Age: ☐ ≤ 1 year old ☐Between 1 and 2 years old

☐Children < 24 months of age with bronchopulmonary dysplasia/chronic lung disease AND who have required oxygen and/or medical therapy within the 6 months preceding the RSV season (June-November 2015).

Age: ☐≤ 1 year old ☐Between 1 and 2 years old

☐Infants 32 1/7 weeks – 35 6/7 weeks gestation and aged ≤ 6 months at the start of, or during, the local RSV season who are identified as high risk according to the scoring tool. (Refer to Table).

Please record the EXACT gestational age at birth of this infant: weeks _____days _____

Scoring tool (Complete only if the request is for a patient with gestational age 32 1/7 – 35 6/7 weeks without other risk factors)
Place an X in the "yes" column if the child has the risk factor.

Risk Factor	Yes	Value	No	Score
Small for gestational age (Birth weight < 10th percentile for GA)		12		
Sex is male		11		
Birth month in November, December or January		25		
Immediate family (mother,father,sibling) have a history without eczema (without eczema = Yes)		12		
Infant to attend daycare OR siblings attend daycare		17		
More than five individuals in the home including the infant (ie,six or more)		13		
Two or more smokers in the household		10		

Risk of RSV-Hospitalization	Score	Action	TOTAL SCORE	
Low Risk	0 - 48	Will not be approved	"Note: The overall risk of RSV-associated hospitalization(RSV-H) in the first year of life is ~1%. Moderately premature(32-35wk GA) infants have a RSV-H of ~ 3.5%."	
Moderate Risk	49 - 64	Case by case – With Evaluation		
High Risk	65 – 100	Approved		

IMPORTANT

Please fax all of this completed request form to: AbbVie Corporation at 1-888-703-6967
All RSV request forms submitted to AbbVie will be faxed back to the requesting physician's fax numbers (entered on forms) and also to the IWK Health Centre at 902-470-7846.

Form completed by : _____

Appendix C

Table 7.1: Sensitivity Analysis of Asthma Incidence by Preceding RSV-Hospitalization Status

RSV-Hospitalization Status	Asthma Cases	Rate per 1000 (95% CI)
RSV-Hospitalization	22	70.1 (46.16-106.47)
No RSV-Hospitalization	631	39.91 (37.27-43.99)
Total	655	41.15 (37.93-44.63)

* Risk Difference = 0.03 (95%CI 0.00-0.059), Rate ratio = 1.73 (95% CI 1.08-2.65)

Table 8.1: Sensitivity Analysis of Cox PH Bivariate Analysis of Possible Covariates for Asthma Development Excluding Asthma Diagnoses in First Year of Life

Predictive Variable	% Asthma	Hazard Ratio		P-Value
		Estimate	95% CI	
RSV-Hospitalization*				
Yes	22.9 (22/96)	1.71	1.12 – 2.62	**0.013**
No	17.2 (561/3,259)	1	-	-
Sex*				
Male	16.7 (349/2,098)	1.33	1.13 – 1.57	**0.001**
Female	12.9 (234/1,818)	1	-	-
Gestational Age*				
29 weeks + 0 days – 29 weeks + 6 days	7.8 (8/103)	0.49	0.24 – 0.98	**0.045**
30 weeks + 0 days – 30 weeks + 6 days	10.5 (16/152)	0.66	0.40 – 1.10	**0.113**
31 weeks + 0 days – 31 weeks + 6 days	11.0 (24/219)	0.70	0.46 – 1.06	**0.091**
32 weeks + 0 days – 32 weeks + 6 days	12.5 (43/344)	0.80	0.58 – 1.11	0.185
33 weeks + 0 days – 33 weeks + 6 days	17.3 (89/515)	1.14	0.90 – 1.46	0.266
34 weeks + 0 days – 34 weeks + 6 days	16.2 (149/922)	1.06	0.86 – 1.29	0.593
35 weeks + 0 days – 35 weeks + 6 days	15.3 (254/1,661)	1	-	-
Socioeconomic Status (SES)*				
Highest	16.6 (103/621)	1.00	0.78 – 1.30	0.968
Upper-Middle	12.3 (106/858)	0.74	0.57 – 0.96	**0.022**
Middle	14.1 (116/821)	0.85	0.66 – 1.09	0.195
Lower-Middle	15.5 (122/786)	0.95	0.74 – 1.21	0.676
Lowest	16.3 (130/795)	1	-	-
Siblings < 5 (Preschool Age)*				
$\geq$ 1 Sibling	13.6 (251/1,845)	0.84	0.71 – 0.99	**0.041**
0 Siblings	16.0 (332/2,071)	1	-	-
Siblings < 18				
$\geq$ 1 Sibling	14.5 (312/2,150)	0.95	0.81 – 1.12	0.541
0 Siblings	15.3 (271/1,766)	1	-	-
APGAR Score at 1 Minute*				
Low Score 0-6	16.3 (168/1,028)	1.15	0.96 – 1.37	**0.130**
Normal Score 7-10	14.4 (413/2,869)	1	-	-
APGAR Score at 5 Minutes				
Low Score 0-6	13.1 (23/175)	0.87	0.57 – 1.32	0.513
Normal Score 7-10	15.0 (557/3,717)	1	-	-
Mode of Delivery				
C-Section	14.4 (242/1,681)	0.94	0.80 – 1.11	0.470

Vaginal	15.3 (341/2,235)	1	-	-
Household Crowding (≥5 Individuals/Household)				
Yes	11.8 (25/211)	0.77	0.52 – 1.56	0.210
No	15.2 (539/3,549)	1	-	-
Birth weight for Gestational Age				
≤ 10^{th} Percentile	16.2 (59/365)	1.10	0.84 – 1.44	0.478
> 10^{th} Percentile	14.8 (524/3,537)	1	-	-
Smoke Exposure During Pregnancy*				
Yes	16.0 (169/1,055)	1.12	0.93 – 1.34	0.224
No	14.5 (403/2,778)	1	-	-
Pz-Prophylaxis				
Yes	0 (0/259)	$1.52x10^{-15}$	0	1.000
No	15.9 (583/3,657)	1	-	-

Note: Cohort includes 583 infants diagnosed with childhood asthma and 3333 who did not develop asthma

* Indicates significant variables (P<0.15 considered as covariates in the bivariate analysis to be tested in multivariable model

Appendix D

Table 7.2: Sensitivity Analysis of Asthma Incidence by Preceding RSV-Hospitalization Status After Removing Pz-Prophylaxed Infants

RSV-Hospitalization Status	Asthma Cases	Rate per 1000 (95% CI)
RSV-Hospitalization	22	57.9 (38.1-88.0)
No RSV-Hospitalization	631	39.6 (36.7-42.8)
Total	655	40.0 (37.1-43.2)

* Risk Difference = 0.018 (95%CI -0.006-0.043), Rate ratio = 1.46 (95% CI 0.91-2.23)

Table 8.2: Table 8.2: Sensitivity Analysis of Cox PH Bivariate Analysis of Possible Covariates for Asthma Development Excluding Pz-Prophylaxed Infants

Predictive Variable	% Asthma	Hazard Ratio		P-Value
		Estimate	95% CI	
RSV-Hospitalization*				
Yes	24.2 (22/91)	1.46	0.95 – 2.23	**0.081**
No	16.6 (633/3,566)	1	-	-
Sex*				
Male	20.3 (397/1,954)	1.39	1.19 – 1.63	**< 0.001**
Female	15.1 (258/1,703)	1	-	-
Gestational Age*				
29 weeks + 0 days – 29 weeks + 6 days	16.7 (9/54)	0.97	0.50 – 1.89	0.933
30 weeks + 0 days – 30 weeks + 6 days	18.6 (18/97)	1.10	0.68 – 1.78	0.685
31 weeks + 0 days – 31 weeks + 6 days	20.6 (29/141)	1.24	0.85 – 1.83	0.260
32 weeks + 0 days – 32 weeks + 6 days	17.8 (51/286)	1.06	0.79 – 1.43	0.355
33 weeks + 0 days – 33 weeks + 6 days	20.0 (100/501)	1.21	0.96 – 1.51	**0.108**
34 weeks + 0 days – 34 weeks + 6 days	18.1 (167/921)	1.08	0.89 – 1.31	0.424
35 weeks + 0 days – 35 weeks + 6 days	17.0 (281/1,657)	1	-	-
Socioeconomic Status (SES)*				
Highest	19.2 (113/588)	0.96	0.75 – 1.22	0.735
Upper-Middle	14.8 (118/796)	0.73	0.57 – 0.93	**0.011**
Middle	17.2 (130/757)	0.85	0.67 – 1.08	0.187
Lower-Middle	18.6 (137/735)	0.94	0.74 – 1.18	0.579
Lowest	19.8 (149/752)	1	-	-
Siblings < 5 (Preschool Age)*				
≥ 1 Sibling	17.0 (290/1,709)	0.90	0.78 – 1.06	0.201
0 Siblings	18.7 (365/1,948)	1	-	-
Siblings < 18				
≥ 1 Sibling	18.0 (358/1,992)	1.02	0.87 – 1.19	0.817
0 Siblings	17.8 (297/1,665)	1	-	-
APGAR Score at 1 Minute*				
Low Score 0-6	20.6 (187/908)	1.23	1.04 – 1.46	**0.016**
Normal Score 7-10	17.0 (465/2,732)	1	-	-
APGAR Score at 5 Minutes				
Low Score 0-6	18.3 (26/142)	1.04	0.70 – 1.54	0.848
Normal Score 7-10	17.9 (625/3,493)	1	-	-
Mode of Delivery				
C-Section	17.5 (269/1,537)	0.96	0.82 – 1.12	0.569

Vaginal	18.2 (386/2,120)	1	-	-
Household Crowding (≥5 Individuals/Household)				
Yes	16.8 (33/196)	0.95	0.67 – 1.34	0.755
No	18.0 (597/3,311)	1	-	-
Birth weight for Gestational Age				
≤ 10th Percentile	20.2 (68/337)	1.16	0.90 – 1.49	0.256
> 10th Percentile	17.7 (586/3,309)	1	-	-
Smoke Exposure During Pregnancy*				
Yes	19.6 (195/996)	1.15	0.97 – 1.36	**0.110**
No	21.0 (450/2,145)	1	-	-

Note: Cohort includes 655 infants diagnosed with childhood asthma and 3,002 who did not develop asthma

* Indicates significant variables (P<0.15 considered as covariates in the bivariate analysis to be tested in multivariable model

Appendix E

Table 8.2: Logistic Bivariate Analysis of Possible Covariates for Asthma Development

Predictive Variable	% Asthma	Odds Ratio		P-Value
		Estimate	95% CI	
RSV-Hospitalization*				
Yes	24.2 (22/91)	1.61	0.99 – 2.62	**0.056**
No	16.6 (633/3,823)	1	-	-
Sex*				
Male	18.9 (397/2,098)	1.41	1.19 – 1.67	**< 0.001**
Female	14.2 (258/1,818)	1	-	-
Gestational Age*				
29 weeks + 0 days – 29 weeks + 6 days	8.7 (9/103)	0.47	0.23 – 0.94	**0.034**
30 weeks + 0 days – 30 weeks + 6 days	11.8 (18/152)	0.66	0.40 – 1.10	**0.109**
31 weeks + 0 days – 31 weeks + 6 days	13.2 (29/219)	0.75	0.50 – 1.13	0.170
32 weeks + 0 days – 32 weeks + 6 days	14.8 (51/344)	0.85	0.62 – 1.18	0.342
33 weeks + 0 days – 33 weeks + 6 days	19.4 (100/515)	1.18	0.92 – 1.52	0.193
34 weeks + 0 days – 34 weeks + 6 days	18.1 (167/922)	1.08	0.88 – 1.34	0.442
35 weeks + 0 days – 35 weeks + 6 days	16.9 (281/1,661)	1	-	-
Socioeconomic Status (SES)*				
Highest	18.2 (113/621)	0.96	0.74 – 1.26	0.498
Upper-Middle	13.8 (118/858)	0.69	0.53 – 0.90	**0.006**
Middle	15.8 (130/821)	0.82	0.63 – 1.06	0.122
Lower-Middle	17.4 (137/786)	0.91	0.71 – 1.18	0.498
Lowest	18.7 (149/795)	1	-	-
Siblings < 5 (Preschool Age)*				
≥ 1 Sibling	15.7 (290/1,845)	0.87	0.74 – 1.03	**0.111**
0 Siblings	17.6 (365/2,071)	1	-	-
Siblings < 18				
≥ 1 Sibling	16.6 (358/2,150)	0.99	0.83 – 1.17	0.890
0 Siblings	16.8 (297/1,766)	1	-	-
APGAR Score at 1 Minute*				
Low Score 0-6	18.2 (187/1,028)	1.15	0.95 – 1.39	**0.144**
Normal Score 7-10	16.2 (465/2,869)	1	-	-
APGAR Score at 5 Minutes				
Low Score 0-6	14.9 (26/175)	0.86	0.56 – 1.32	0.480
Normal Score 7-10	16.8 (625/3,717)	1	-	-

Mode of Delivery				
C-Section	16.0 (269/1,681)	0.91	0.77 – 1.08	0.293
Vaginal	17.3 (386/2,235)	1	-	-
Household Crowding (≥5 Individuals/Household)				
Yes	15.6 (33/211)	0.92	0.63 – 1.34	0.655
No	16.8 (597/3,549)	1	-	-
Birth weight for Gestational Age				
≤ 10th Percentile	18.6 (68/365)	1.15	0.87 – 1.52	0.316
> 10th Percentile	16.6 (586/3,537)	1	-	-
Smoke Exposure During Pregnancy				
Yes	18.5 (195/1,055)	1.17	0.97 – 1.41	**0.091**
No	16.2 (450/2,778)	1	-	-

Note: Cohort includes 655 infants diagnosed with childhood asthma and 3261 who did not develop asthma

* Indicates significant variables (P<0.15 considered as covariates in the bivariate analysis to be tested in multivariable model