LOWER RESPIRATORY TRACT INFECTIONS IN MULTIPLE SUBGROUPS OF IMMUNOCOMPROMISED CHILDREN: A RETROSPECTIVE COHORT STUDY

by

Randy Aung

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TABLE OF CONTENTS

LIST OT TABLES

LIST OF FIGURES

ABSTRACT

Lower respiratory tract infections (LRTIs) are more likely to have severe impact on immunocompromised children. Hence, we determined among immunocompromised children (1) the incidence of LRTI hospitalizations, (2) microbiological etiology and clinical burden of LRTI hospitalizations, and (3) association between baseline characteristics and LRTI hospitalizations. A retrospective cohort study of children age < 16 years treated at IWK Health Center 2004-2014 for immunocompromising conditions was conducted. We followed them from date of diagnosis of immunocompromise until first LRTI hospitalization or death or end of study period or immunocompromised status. The incidence proportion and crude incidence of LRTI hospitalizations was 15.8% and 52.4 per 1,000 person-years. The incidence was relatively higher among immunology, oncology and hematology groups. Viruses were most common, followed by bacteria and fungi. Clinical burden was high among patients. Log-rank tests and hazard ratios were statistically significant for types of immunocompromising disorders, age at diagnosis, and gender.

LIST OF ABBREVIATIONS USED

AAP	American Academy of Pediatrics
ALC	Absolute lymphocyte counts
ALL	Acute lymphoblastic leukemia
ALC	Absolute lymphocyte counts
AML	Acute myeloid leukemia
ANC	Absolute neutrophil counts
ARI	Acute respiratory infection
BAL	Bronchoalveolar lavage
BPD	Bronchopulmonary dysplasia
CA	Community-acquired
CDC	Centers for Disease Control
CHD	Congenital heart disease
CI	Confidence interval
CLD	Chronic lung disease
CNS	Central nervous system
CPAP	Continuous positive airway pressure
CPS	Canadian Pediatric Society
CVID	Common variable immunodeficiency disorder
GVHD	Graft versus host disease
GI	Gastroenterology
Hib	*Haemophilus Influenzae* Type b
HR	Hazard ratio
hMPV	Human Metapneumovirus
HR	Hazard ratio
HSCT	Hematopoietic stem cell transplantation
IWK	Izaak Walton Killam Health Center
ICD-CM	International Classification of Diseases Clinical Modification
ICU	Intensive care unit
IVIG	Intravenous immunoglobulin
JIA	Juvenile idiopathic arthritis
LRTI	Lower respiratory tract infection
MeSH	Medical subject headings
N/n	Number
OR	Odds ratio
PCR	Polymerase chain reaction
PCV	Pneumococcal conjugate vaccine
PIV	Parainfluenza virus
RCT	Randomized controlled trials
RSV	Respiratory syncytial virus
RVP	Respiratory viral panel
SCID	Severe combined immunodeficiency disorder
SLE	Systemic lupus erythematosus
TBI	Total body irradiation
URTI	Upper respiratory tract infection
WHO	World Health Organization

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CHAPTER 1: INTRODUCTION

Acute respiratory infections (ARIs) are the leading causes of infection in the pediatric population. (1) ARIs can be broadly classified as upper respiratory tract infections (URTIs) or lower respiratory tract infections (LRTIs). (2) ARIs are most often limited to the upper respiratory tract, which comprise respiratory structures from nostrils to vocal cords and lead to URTIs. (3) URTIs (such as common cold and pharyngitis) typically present with mild fever, cough, runny nose, nasal congestion and sore throat. Although most URTIs are self-limiting in healthy children, many of them may progress to LRTIs. (4) LRTIs involve the respiratory structures below vocal cords. (3) LRTIs (such as bronchiolitis, pneumonia and influenza) typically present with fever, cough, hoarseness, tachypnea, wheezing, and respiratory distress. LRTIs can result in prolonged hospitalizations and life threatening conditions in immunocompromised children if they are not promptly treated. In many instances, severe bacterial LRTIs cause pulmonary complications such as pneumothorax, pleural effusion and acute respiratory failure that may necessitate mechanical ventilation and intensive care unit (ICU) admission. (5)

Viruses, bacteria and fungi can all cause LRTIs. However, viruses are the most common etiology of LRTIs in children under 5 years of age.(6) Some of the most common viruses that cause bronchiolitis and pneumonia are respiratory syncytial virus (RSV), influenza viruses, parainfluenza viruses (PIVs), rhinovirus, adenovirus and human metapneumovirus (hMPV).(6) Bacterial causes of LRTIs include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae*. The incidence of bacterial LRTIs has plummeted over the last decade in developed countries after the global implementation of routine childhood vaccination schedules (e.g. *Haemophilus Influenzae* Type b (Hib) vaccine and Pneumococcal conjugate (PCV13) vaccine). (7)

LRTIs are relatively self-limiting in healthy children if appropriate supportive care and treatment with antibiotics or antiviral drugs are initiated at early stages of infection. However, LRTIs are more likely to cause severe outcomes in the immunocompromised pediatric population. Immunocompromised children have weakened immune systems, which leads to an increased risk for developing frequent and

severe episodes of infections. Similarly, ARIs often progress to LRTIs, resulting in high morbidity and mortality in these populations.

Severe episodes of LRTIs could lead to prolonged delays and interruptions in life-saving immunosuppressive treatment of children with hematological, oncological, immunological, rheumatological and gastrointestinal disorders. In addition to standard preventative measures, the Canadian Immunization Guide by the Public Health Agency of Canada (PHAC) recommends the annual administration of seasonal influenza vaccine in immunocompromised children in addition to routine administration of Hib, PCV13 and pertussis vaccine. (8) However, vaccines could work less effectively in those with severe immunosuppression who are unable to mount antibody immune response after immunization. (9-11) Palivizumab (monoclonal antibody directed against RSV fusion protein) has been shown to be effective in the prevention of RSV-associated hospitalizations in high-risk infants under the age of 2 years. (12,13) Passive immunization with palivizumab is used in young children with severe immunocompromised status in many Canadian centers. (11) However, randomized controlled trials (RCTs) on the efficacy and cost-effectiveness of palivizumab in immunocompromised children are still lacking.

Treatment of viral ARIs mainly involves supportive care (such as hydration and respiratory support), but antiviral medications could be considered in immunocompromised children in order to prevent complications. Neuraminidase inhibitors (such as oseltamivir and zanamivir) may diminish severity of influenza when initiated early within 48 hours of symptoms onset. Ribavirin, IVIG and intravenous palivizumab were previously used by some centers for the treatment of viral LRTIs caused by RSV, PIV, hMPV and adenovirus in immunocompromised children but no definitive proof of efficacy is available for this population.

Our study aims to determine among immunocompromised children < 16 years in Nova Scotia: (1) the incidence of LRTI hospitalizations, (2) the microbiological etiology and clinical burden of LRTI hospitalizations, and (3) the association between baseline characteristics and LRTI hospitalizations.

1.1. Gaps in the Literature

Most studies in the literature investigated the clinical burden of virus-specific LRTIs (most often RSV and influenza viruses) rather than clinically diagnosed overall LRTIs. Also, newly emerged viruses such as hMPV and bocavirus that could have significant impact on immunocompromised children are often not included in previous studies. A study that examines the incidence and clinical burden of all LRTI hospitalizations regardless of microbiological etiology could provide a greater understanding of the scope and prevalence of different microbial pathogens leading to LRTI hospitalizations.

With regards to the target study population, most studies typically involved only one subgroup of immunocompromised children (most often cancer patients). A study that includes children with multiple subgroups of immunocompromising conditions has not been reported in the literature. Our study included immunocompromised children from hematology, oncology, immunology, rheumatology and gastroenterology services. This allowed comparison of the incidence, microbiological etiology and clinical burden of LRTI hospitalizations between different subgroups of immunocompromised children. This provided valuable information on the spectrum of the clinical burden of LRTIs that could result from the impairment of different components of the immune system associated with different immunocompromising conditions.

The clinical burden associated with LRTIs was previously examined in adult immunocompromised patients. (14,15,16) However, there is a paucity of evidence in the pediatric population, especially in Canada. We only found one Canadian study by Asner et al., which investigated the clinical burden and risk factors associated with community acquired and nosocomial RSV infections. (17) Our study was the first study in the literature to determine the incidence, clinical burden and baseline characteristics associated with LRTI hospitalizations in different subgroups of immunocompromised children.

We hope that our study lead to larger prospective studies to determine the risk factors associated with LRTI hospitalizations and RCTs to investigate early screening, diagnosis and treatment of viral LRTIs in immunocompromised children.

1.2. Format of the Thesis

The format of the thesis is as follows: (1) Introduction, (2) Background, (3) Objectives, (4) Methodology, (5) Results, (6) Discussion and (7) Conclusion. Chapter 2 provides an overview of the literature search strategy and current literature on the epidemiology, microbiological etiology, clinical burden, prevention and treatment associated with LRTIs in the immunocompromised pediatric population. Chapter 3 lists the study objectives. Chapter 4 describes the methodology that we used for our study. It begins by discussing an overview of the study design, study population, ethical considerations, data collection and sample size calculations. Next, primary outcome, secondary outcomes and baseline characteristic variable are outlined and statistical analyses are described. Chapter 5 outlines the study results. Chapter 6 provides the discussion of the results and also, the study implications, strengths and limitations of the study. Lastly, chapter 7 outlines the conclusion of the thesis.

CHAPTER 2: BACKGROUND

2.1. Literature Search

We conducted a literature search using the MEDLINE PubMed database (National Center for Biotechnology Information, U.S. National Library of Medicine; Bethesda, Maryland) to capture relevant studies in the literature. We used a comprehensive set of search terms for the following concepts: (1) lower respiratory tract infections, (2) immunocompromising conditions and (3) the pediatric population. We included both controlled words (MeSH terms) and free text words for each of our search terms combined with Boolean operators. The full literature search strategy and results are outlined in Appendix 1 and 2. To eliminate voluminous irrelevant studies, we restricted our search strategy to include epidemiological studies only. In addition to the PubMed search, more relevant studies were identified from the citations and reference lists of PubMed articles and were included in the literature review for the thesis.

2.2. Epidemiology of LRTIs in Pediatric Patients

ARIs are the most common types of infection in the pediatric population, comprising about 50% of all illnesses in children < 5 years and 30% in children ages 5-12 years.(1) ARIs are associated with high rates of morbidity and mortality worldwide, especially in developing countries. (18) The World Health Organization (WHO) reported that respiratory diseases comprising mainly ARIs were the second most significant cause of death for young children in 2010. (19)

ARIs commonly present as URTIs, but it is a challenge to estimate the incidence of URTIs because medical attention is not often sought. LRTIs are also largely diagnosed and associated with high morbidity and mortality in young children in both developing and developed countries. (20) It was previously reported that LRTIs were accountable for approximately 20% of all pediatric hospitalizations in the US, with 15% of them requiring ICU admission. (21) The two most common types of LRTIs are pneumonia and bronchiolitis. Pneumonia can either be caused by viruses or bacteria and is typically diagnosed by positive radiological findings of inflammatory infiltrates in lung

parenchyma. On the other hand, bronchiolitis is often caused by viruses and diagnosed clinically in children under the age of 2 years with lower respiratory tract (LRT) symptoms. However, they are usually not differentiated and grouped together as LRTIs in many instances due to the overlap of clinical signs and symptoms.

It was reported that pneumonia was diagnosed in approximately 120 million (95% CI: 60·8 - 277·0 million) children worldwide in 2010 and led to about 0.8 million (95% CI: 0·68 - 0·92 million) deaths in 2013. (22) Out of 120 million cases of pneumonia, over 14 million had severe outcomes and approximately 12 million required hospitalization. (22) In developed countries, the incidence of childhood pneumonia caused by bacterial agents has plummeted in the last decade after the implementation of childhood vaccination programs. The annual incidence of pneumonia among young children in developed countries is estimated to be approximately 33 per 10000 children. (23)

Bronchiolitis is most commonly caused by RSV in infants and young children. (4) Globally, it was estimated that RSV bronchiolitis was diagnosed in approximately 33·8 million (95% CI: 19·3 – 46·2 million) children < 5 years, with more than 3·4 million (95% CI: 2·8 – 4·3 million) of them requiring hospitalizations. (24) In Canada, approximately 12,000 children < 2 years are hospitalized with RSV bronchiolitis every year. (25) According to the Centers for Disease Control (CDC), RSV causes approximately 57,527 hospitalizations and 2.1 million ambulatory visits among young children annually in the US. (26)

Influenza is typically limited to the upper respiratory tract in adults, but it is the second most significant cause of LRTI hospitalizations after RSV in children. (3) On average, it was reported that influenza is diagnosed in 15% to 42% of young children, with mortality ranging from 0.05 to 0.38 per 100,000 children annually. (27) The clinical burden of influenza is higher in infants, with hospitalization rates ranging from 9 to 30 per 10,000 in infants < 6 months and 3 to 11 per 10,000 in infants ages 6-23 months, and many of them required ICU admission and mechanical ventilation. (27)

2.3. Pediatric Populations at Highest Risk for Severe LRTIs

Studies have suggested that some chronic medical conditions put pediatric patients at higher risk for recurrent and severe episodes of LRTIs. They include prematurity, chronic lung diseases, congenital heart diseases and also immunocompromising conditions. (28)

Prematurity is defined as the birth of an infant that occurs before 37 weeks of gestation. Premature infants have underdeveloped immune system and acquire insufficient transfer of transplacental immunoglobulin G, compared to full-term infants. (29) They also have underdeveloped respiratory system with immature bronchioles, surfactant deficiency, inadequate antioxidant mechanisms and impaired fluid clearance. Hence, they are more vulnerable to respiratory viruses such as RSV and influenza viruses leading to high rates of hospitalizations, pulmonary complications and deaths. (29-31) Dawood et al. suggested that 15% of children hospitalized with influenza had history of prematurity. (32) The Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) prospective study reported that RSV hospitalizations ranged from 5.0/1000 to 16.9/1000 among infants born before 33 weeks of gestation. (13) Moreover, it was suggested that mortality attributable to RSV LRTIs is more likely to occur in premature infants with low birth weight (< 1500 grams), compared to full term infants (OR 13.9; 95% CI 5.2 - 37.0). (13)

Bronchopulmonary dysplasia (BPD) results from lung injury due to prolonged oxygen supplementation and mechanical ventilation in infants with acute respiratory distress syndrome. (33) Chronic lung diseases (CLDs) such as BPD, asthma and cystic fibrosis are associated with abnormal lung structures, defective airway clearance mechanisms (such as cilia, coughing, and mucus production) and ventilation-perfusion mismatch. Consequently, they are more likely to be associated with respiratory failure, causing prolonged hospitalization, mechanical ventilation and ICU admission. (32,34) According to Neuzil et al. study, the incidence of influenza hospitalizations < 1 year and 1-3 years was 29/1000 and 9.7/1000 children respectively, which was approximately 2-4 times higher than healthy children. (34) Moreover, RSV LRTIs were associated with mortality rates as high as 8% in these populations. (35)

Congenital heart diseases (CHDs) are commonly associated with poor LRTI outcomes. According to a review of 260 children with CHDs admitted for RSV infections from 12 Canadian children's hospitals, 87 (33%) were admitted to ICU and 49 (19%) required mechanical ventilation. (36) With recent advances in intensive care, the clinical burden of RSV infections in children with CHDs have plummeted, but it is still significant compared to healthy children. (37) CHDs can be classified as cyanotic or acyanotic. Cyanotic CHDs (such as Tetralogy of Fallot, total anomalous pulmonary venous connection, persistent truncus arteriosus) involve shunting of deoxygenated blood via heart defects into the systemic circulation resulting in cyanosis. Acyanotic CHDs (such as atrial septal defect, ventricular septal defect, patent ductus arteriosus) involve shunting of oxygenated blood from left to right chambers of the heart, resulting in congestive heart failure. Cyanotic and acyanotic CHDs cause pulmonary under-circulation and over-circulation respectively. The abnormal pulmonary circulation and lack of effective collateral ventilation lead to ventilation-perfusion mismatch. As a result, these infants are unable to handle the extra respiratory stress caused by respiratory viruses, putting them at higher risk for LRTI complications. (37)

Immunocompromised children are a diverse group and include patients from hematology, oncology, immunology, rheumatology and gastroenterology services. Hematology and oncology patients are immunocompromised due to the malignancy itself or the antineoplastic treatments (such as radiotherapy and chemotherapy) that cause neutropenia, lymphopenia and destruction of the natural anatomical barriers of the skin and mucosal surfaces. Immunology patients have impaired humoral and/or cellular immune systems, which predispose them to frequent and severe infections. Rheumatology patients with autoimmune rheumatic disorders and gastroenterology patients with inflammatory bowel diseases are often immunocompromised due to treatment with high-dose systemic corticosteroids, biologic response modifiers (such as etanercept and infliximab) and other immunomodulators (such as methotrexate and corticosteroids). These immunocompromising conditions are found to be associated with significant morbidity and mortality attributable to LRTIs, which is described more in details in Section 2.8.

2.4. Epidemiology of LRTIs in Immunocompromised Children

Immunocompromised children are very commonly affected by ARIs due to their impaired immune systems. Among these patients, ARIs can present as a wide spectrum of clinical syndromes from mild URTIs to severe LRTIs and deaths. In a pediatric acute lymphoblastic leukemia (ALL) study, it was reported that respiratory infections were responsible for almost half all infections among children with ALL. (3)

The incidence of bacterial ARIs have greatly diminished after the worldwide implementation of childhood vaccination programs. Recent studies have shown that viruses are the leading cause of ARIs in young children, especially in the immunocompromised population. (38,39) Several studies suggested that respiratory viruses were detected in 50% to 75% of ARIs in pediatric cancer patients undergoing chemotherapy. (40,41) The most common viruses that cause ARIs in immunocompromised children include RSV, influenza viruses, PIVs, rhinovirus, adenovirus, coronavirus and hMPV. A summary of the prevalence of respiratory viruses in immunocompromised children in the current literature is outlined in Table 2-1.

Table 2-1: Prevalence of respiratory viruses in immunocompromised children

Study	**Prevalence**
Benites et al.	Rhinovirus (46.2%), RSV (17.4%), coronavirus (13.6%), influenza (11.6%), parainfluenza (6%), hMPV (5.8%)
Choi et al.	Rhinovirus (28.1%), RSV (25.8%), parainfluenza (24.7%), adenovirus (13.5%), coronavirus (11.2%), influenza (4.5%), hMPV (1.1%)
Lo et al.	RSV (42%), parainfluenza (26%), adenovirus (19%), influenza (12%)
Lujan-Zilbermann et al.	Parainfluenza (47%), influenza (20%), adenovirus (19%), influenza (17%), RSV (14%)
Mendoza-Sanchez et al.	RSV (43%), influenza (29.7%), adenovirus (13%), parainfluenza (13%)
Torres et al.	RSV (31%), rhinovirus (23%), parainfluenza (12%), influenza (11%), bocavirus (11%), hMPV (6%), adenovirus (5%), coronavirus (1%)

The prevalence of respiratory viruses in the abovementioned studies vary widely due to differences in the study population, geographic areas, types of diagnostic tests and study designs used in different studies. (39) In a Finnish prospective study of febrile leukemic children, respiratory viruses were detected in 44% subjects, with rhinovirus (22%) and RSV (11%) being the most common viruses. (42) However, Christensen et al. found that respiratory viruses were only responsible for 11% of ARIs in children with cancer, with rhinovirus and RSV again being the most common viruses. (43) Among pediatric HSCT recipients, several studies suggested that PIVs and adenovirus were the most frequently detected viral isolates. (44-46) It was found that most ARIs that occurred in children with solid tumors were also attributable to respiratory viruses, but they tend to have better outcomes and shorter hospitalizations. (43)

2.5. Microbiologic Etiology of LRTIs in Immunocompromised Children

2.5.1. Health-Care Associated LRTIs

Viral ARIs can be classified as health-care associated (i.e. nosocomial) or community-acquired ARIs. ARIs are usually considered nosocomial if the illness was not present or incubating at the time of admission, and thus respiratory symptoms begin more than 3-5 days after hospitalization. (17,47) In adult immunocompromised patients, Saad et al. suggested that the development of pneumonia due to influenza is more likely to be nosocomially transmitted rather than community-acquired (30.1% vs 3.2%, $p = 0.003$). (47) In a pediatric cancer study, it was reported that nosocomial RSV was more likely to be associated with the development of RSV LRTIs, compared to community acquired RSV (OR 7.80; 95% CI 1.65–36.7). (48) However, a Canadian study by Asner et al. found that nosocomial RSV infections in immunocompromised children were not associated with the development of pneumonia; instead community acquired RSV infections were found to be associated. (17) This might be because children with nosocomial RSV infection were diagnosed and treated at early stages provided that they were already under the medical attention at the time they developed LRTIs during hospitalization. Nevertheless, the same study showed that duration of hospitalization were longer in children with nosocomial RSV infections compared to community

acquired RSV infections (24 days vs 11.5 days, $p < 0.001$). (17) Overall, the current literature on the association between the source of infection acquisition and LRTI development is inconsistent.

2.5.2. Types of Microbial Pathogens

It has been previously established that ARIs are most commonly caused by viruses such as RSV, influenza, parainfluenza, adenovirus, and rhinovirus (see Table 2-1). (6) The importance of newly emerged viruses such as hMPV, human bocavirus, coronaviruses, and human polyomaviruses in the development of ARIs has become increasingly evident with the aid of molecular detection techniques. (49) Different types of respiratory viruses can cause distinctive clinical presentations and disease severity. A retrospective study by Lo et al. suggested that adenovirus had the highest morbidity and mortality rates compared to other viruses. (50) However, this could be confounded because adenoviral ARIs typically have delayed symptomatic presentations, resulting in delayed diagnosis and treatment. There is limited evidence in the current literature on the clinical burden of different types of respiratory viruses in immunocompromised children. It is unclear whether a specific type of respiratory virus could lead to the development of LRTIs with severe outcomes, compared to other viruses.

2.5.3. Microbial Co-Infections

Immunocompromised children could have more severe symptoms when they have co-infections with multiple viruses and bacteria. A prospective study by Fazekas et al. reported that viral co-infections were more often associated with severe LRTIs in immunocompromised children compared to immunocompetent children. In the study, 13 out of 25 (52%) children with leukemia, lymphoma and solid tumors and 3 out of 5 (60%) HSCT recipients with viral co-infections developed severe LRTIs, while none of the immunocompetent children with viral co-infections developed severe LRTIs ($P < 0.0001$). (51) In addition, Torres et al. suggested that mixed viral-bacterial infections were associated with more severe clinical outcomes, compared to sole viral ARIs and mixed viral ARIs. (52)

2.6. Clinical Burden of LRTIs in Immunocompromised Children

Viral ARIs typically result in LRTIs and respiratory failure among immunocompromised children especially during the period of immunosuppressive treatment. Several studies suggested that viral ARIs led to hospitalizations in 70% to 95% of children with and some patients required oxygen supplementation, mechanical ventilation and ICU admission. (50,62) In a Mendoza-Sanchez et al. study, 4 out of 19 children who were on antineoplastic treatment were admitted to ICU. (62) In pediatric HSCT and chemotherapy recipients, 28% to 40% of viral ARIs progress to LRTIs, with mortality rates as high as 10%. (40,50,56,62,63) Among pediatric allogeneic HSCT recipients, Verdeguer et al. suggested that the mortality related to viral infections was 9.7%, with respiratory viruses responsible for approximately 20% of deaths. (64)

Hall et al. was the first landmark study in 1986 that investigated the clinical burden of RSV infections in immunocompromised children who have congenital immunodeficiency disorders, were on chemotherapy medications for cancer and were on corticosteroids for non-malignant chronic conditions. (65) The study included 608 children < 5 years over 10 consecutive winters, who were hospitalized with RSV infections. All patients with immunodeficiency disorders and cancer developed RSV LRTIs during the study period, with a significant proportion of them (60% and 80% respectively) requiring intensive care, compared to healthy children (15%). (65) Among patients who died due to RSV LRTIs, 3 out of 20 (15%) were cancer patients on chemotherapy and 2 out of 5 (40%) patients had immunodeficiency disorders, whereas only 3 out of 502 (0.5%) were healthy children. (65)

Studies suggested that 24% to 40% of RSV infections progress to LRTIs, with mortality rates as high as 10%. (17,48,53,55,65,66) A Canadian retrospective chart review by the Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) reported prolonged durations of hospitalization, with a median of 39 days associated with RSV infections. (67) The PICNIC study reported that the duration of RSV hospitalizations was longer compared to other high-risk groups (OR 1.7; 95% CI 1.4 – 2.2). (68) In a Sung et al. study, RSV-related mortality was reported to be higher than 10%. (69) An infantile ALL study reported a significantly higher RSV mortality rate

of 60% during the induction phase of chemotherapy and 33% during the entire period of chemotherapy. (70)

Children with cancer are commonly affected by influenza viruses, occurring at 5.7 infections/1000 patients/year. (54) Immunocompromised children are more likely to suffer from higher rates of hospitalization and respiratory complications due to influenza. (38,54,71) In a pediatric ALL study, the incidence of influenza-related hospitalizations was 618.3 infections/100,000 person-months. (71) Influenza was also reported to be associated with high mortality in immunocompromised children. Among HSCT recipients, the influenza-related mortality was higher for children who developed LRTIs (28%), compared to those who developed URTIs (3%). (72)

The clinical burden associated with LRTIs among immunocompromised hosts may partly be due to their inability to inhibit the viral replication as well as prolonged viral shedding. (65,71) Hall et al. study reported that children with congenital immunodeficiency diseases as well as chemotherapy and steroids recipients had longer periods of RSV viral shedding, compared to healthy children. (65) In a case study by Cheng et al., lengthy RSV viral shedding period was reported in a 15-month-old boy with stage III neuroblastoma during the course of intensive chemotherapy. (73) Prolonged viral shedding is associated with higher rates of transmission in immunocompromised children. Knowledge of altered ability to limit viral replication in immunocompromised hosts is important when implementing isolation precautions among these children in the hospital.

2.7. The Role of the Underlying Diagnosis of Immunocompromising Conditions on LRTIs

There are no studies in the literature that involve different subgroups of immunocompromising conditions in a single study, so the role of the underlying diagnosis of immunocompromising conditions on the incidence and clinical burden of LRTIs have not been previously investigated. However, there were several studies that examined the role of underlying cancer diagnosis on the risk for LRTIs. Many found no significant differences in the development of LRTIs among patients with hematological malignancies, compared to solid tumors and HSCT. (53-55) In an El Saleeby et al. study,

there were higher proportion of HSCT recipients and acute myeloid leukemia (AML) patients (42%) that developed RSV LRTIs compared to ALL patients (9%), but the association did not reach statistical significance in the multivariate analysis. (48)

Hematology, oncology, immunology, rheumatology and gastroenterology patients who are on immunosuppressive treatment could have different degrees of immunosuppression. A retrospective adult hematology/oncology study by Saad et al. reported that more patients with LRTIs were found to have moderate to severe immunodeficiency compared to those with URTIs (71.2% versus 44.4%, $p < 0.0001$). (47) In the study, severe immunodeficiency was defined as having > 2 of the following criteria: absolute lymphocyte counts (ALCs) < 200 cells/mL, absolute neutrophil counts (ANCs) < 500 cells/mL and use of immunosuppressive drugs within 2 weeks of influenza infection. Moderate immunodeficiency was defined as having > 2 of the following criteria: ALCs 200-1000 cells/mL, ANCs 500-1000 cells/mL and use of immunosuppressive drugs within 1 month of influenza infection. Mild immunodeficiency was defined as having 1 criterion of moderate immunodeficiency. (47)

In the pediatric population, Lo et al. investigated whether the level of immunosuppression was a risk factor for LRTIs. (50) It was reported that more than 50% of LRTIs occurred in children with high immunosuppression. Despite not reaching statistical significance, it showed a trend towards worse LRTI outcomes in patients with high immunosuppression (pre-defined as <100 days since HSCT, <1 year since heart, lung or multivisceral transplantation, <6 months since kidney transplantation, active treatment for organ rejection, graft versus host disease (GVHD), induction phase chemotherapy, and history of severe combined immunodeficiency). (50)

HSCT is often necessary for multiple immunological and hematological disorders. HSCT can be classified as autologous or allogeneic. Autologous HSCT uses patient's own stem cells, which were extracted and stored prior to transplantation. Allogeneic HSCT uses matched donor's stem cells to replace patient's malignant cells. Due to the introduction of foreign cells, allogeneic HSCT recipients are more likely to experience rejection of the transplanted graft as well as GVHD. Despite a good match between the HLA genes, recipients usually require intensive conditioning regimens to prevent the rejection of transplanted graft. Conditioning regimens for HSCT have variable toxicity

and involve administration of cytotoxic chemotherapy drugs and radiotherapy. In consequence, viral ARIs could lead to severe LRTIs, respiratory failure and death among HSCT recipients. (74)

Lujan-Zilbermann et al. showed that allogeneic recipients had 5-fold higher rates of viral LRTIs compared to autologous recipients due to higher degree of immunosuppression secondary to conditioning regimens. (63) However, several studies found no statistically significant differences between autologous and allogeneic recipients, possibly due to small sample sizes. (53,55,56) Chemaly et al. also observed no association between the administration of cytotoxic chemotherapy and RSV LRTIs. (53) However, Kim et al. found that allogeneic patients receiving myeloablative conditioning regimens (combination of cytotoxic chemotherapy and radiotherapy, which may result in profound pancytopenia) were more likely to develop RSV LRTIs, compared to non-myeloablative conditioning regimen. (55) Kim et al. also suggested that high total body irradiation (TBI) dose (i.e. ≥ 1200 cGy) was a significant risk factor for RSV LRTIs. (55)

GVHD is a condition that can occur in allogeneic HSCT recipients in which white blood cells in the graft tissue recognize the host's cells as foreign, attacking the host's cells. Intravenous administration of corticosteroids is given to patients with GVHD in order to suppress the T-cell mediated immune response to host tissues. In conjunction, patients with grade 3-4 GVHD are also treated with rituximab (monoclonal antibody directed against the antigen CD20 on B cells), alemtuzumab (monoclonal antibody directed against the antigen CD52 on B and T cells, or etanercept (tumor necrosis factor inhibitor). Lujan-Zilbermann et al. suggested that allogeneic patients with grade 3-4 GVHD had a higher incidence of viral ARIs, compared to allogeneic patients with no or grade 1-2 GVHD. (63)

2.8. Baseline Sociodemographic Characteristics Associated with LRTIs in Immunocompromised Children

2.8.1. Age

Most studies in the literature suggested that young age is a significant risk factor associated with the development of LRTIs in immunocompromised children. A retrospective study of children with cancer and HSCT recipients by El Saleeby et al. reported that young age (i.e. < 2 years) is associated with the development of RSV LRTIs (adjusted OR 9.84; 95% CI 1.95 – 49.8) and mortality (unadjusted OR 12.3; 95% CI 1.26–120). (48) Another retrospective pediatric ALL study by Lee et al. suggested that the median age at admission was younger for influenza-related versus non-influenza hospitalizations (5.7 years versus 6.2 years; P = 0.04). (71) However, these findings were challenged by other smaller retrospective studies, which found no statistically significant association between age and the development of LRTIs in immunocompromised children. (50,53,54) Despite biological plausibility, the non-significance could be due to small sample sizes, flawed study designs and divergent study population.

2.8.2. Gender

Many studies did not show a significant association between gender and the development of LRTIs in immunocompromised children. (48,53-55) However, a retrospective study on children with cancer by Chemaly et al. reported a higher numbers of RSV LRTIs in males than females, although the association was not statistically significant (adjusted OR 2.57; 95% CI 0.86-7.62). (53)

2.8.3. Ethnicity

There were only two studies that examined the association of ethnicity and the development of LRTIs in immunocompromised children and neither showed a significant association. (48,54)

2.9. Predictive Factors Associated with LRTIs in Immunocompromised Children

2.9.1. Lymphopenia

The cytotoxic effects of radiotherapy and chemotherapy lack specificity and cause destruction of neoplastic cells as well as hosts immune cells such as lymphocytes. Lymphopenia is a common adverse effect of cytotoxic regimens. There are broad definitions of lymphopenia in the literature. Some studies defined lymphopenia as ALCs < 200 cells/mL, while other studies used a higher threshold criteria with ALCs < 500 cells/mL to define lymphopenia. (48,53,54,56)

Immunocompromised patients with lymphopenia have defective immune systems and are more susceptible to infections. The Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation identified lymphopenia as the most significant risk factor for RSV LRTIs in HSCT recipients (OR 3.04; 95% CI 1.26–7.35). (46) A retrospective study by El Saleeby et al. found that although the development of RSV LRTIs in children with cancer was not associated with mild lymphopenia (ALCs < 300 cells/mL) (OR 1.92; 95% CI 0.56 – 6.61), it was significantly associated with profound lymphopenia (ALCs < 100 cells/mL) (OR 5.70; 95% CI 1.34 – 24.2). (48) It also reported that profound lymphopenia was significantly associated with RSV-related mortality (OR 9.86; 95% CI 1.39 – 69.8). (48) Kim et al. suggested that lymphopenia was a significant risk factor associated with RSV LRTIs in pediatrics HSCT recipients. (55) Chemaly et al. showed trends of association between lymphopenia and RSV LRTIs, but there was no statistical significance. (53) However, several previous studies found no association between lymphopenia and the development of LRTIs. (38,54,56,57) It may be due to small sample sizes and inefficient power to detect statistically significant association.

2.9.2. Neutropenia

Cytotoxic effects of radiotherapy and chemotherapy also cause destruction and impairment of neutrophils. Neutropenia is a common and expected adverse effect of immunosuppressive regimens. Neutrophils are an important component of the innate

immune system, which are responsible for protecting against invasive pathogens as first line cellular inflammatory response. Paucity of neutrophils causes defective inflammatory response, allowing the invasion of host cells by pathogens. As a result, immunocompromised patients suffer from episodes of febrile neutropenia often caused by different infectious agents. Some of the other non-infectious causes of febrile neutropenia include tumor induced febrile response or blood transfusion reaction.

Based on absolute neutrophil count (ANC) levels, neutropenia is generally defined as mild (ANC 1000 – 1500 cells/mcL), moderate (ANC 500 – 1000 cells/mcL) and severe (ANC < 500 cells/mcL. (48,53,56) Many studies did not find an association between neutropenia and the development of viral LRTIs. (38,48,53,56,57) One study, Carr et al. suggested that pediatric cancer patients with neutropenia are more likely to require hospitalizations for influenza, compared to those without neutropenia (OR 4.16; 95% CI 1.85 – 11.07). (54) Children with neutropenia due to bone marrow suppression may also be lymphopenic simultaneously, which would compromise their ability to clear viral infections.

2.9.3. Influenza Vaccination Status

Influenza vaccination is a key component in the prevention influenza transmission. The CDC recommends influenza vaccine administration to high-risk individuals with chronic medical conditions and compromised immune systems. (58) Lower than expected vaccination rates were reported despite the recommendations made by multiple health organizations. There is limited data on the rate of influenza vaccination among immunocompromised children but one study reported that only one-third of Canadians received influenza vaccination in 2014. (59)

Immunocompromised children typically have severe influenza-related complications and it was often hypothesized that the administration of influenza vaccine lower the morbidity and mortality attributable to influenza. Although annual influenza vaccination is often deemed safe and efficacious in the prevention of influenza, previous studies found no significant effect on the length of hospitalization and respiratory complications. (54, 57)

2.9.4. Antiviral Drugs

There are limited antiviral drugs available for the treatment of viral LRTIs. In the current practice, neuraminidase inhibitors (such as oseltamivir and zanamivir) are used for treating influenza. Ribavirin was previously used to treat RSV infections but it has become obsolete due to the lack of evidence of significant clinical improvement leading to unavailability in the drug market.

A retrospective study by Saad et al. found that a smaller proportion of adult immunocompromised patients who developed influenza pneumonia received antiviral therapy within 48 hour of symptoms onset (45.0% vs 73.9%, $p < 0.0001$), compared to those who did not develop pneumonia. (47) However, the effectiveness of neuraminidase inhibitors in the treatment of LRTIs among immunocompromised chidren have not been investigated.

Several studies suggested that antiviral therapy with ribavirin leads to better RSV outcomes. (60,61) However, Chemaly et al. and Kim et al. reported that treatment with ribavirin at early stages did not prevent the RSV hospitalizations in immunocompromised children. (53,55) As a matter of fact, Lo et al. suggested that treatment for RSV infections with antiviral medications (OR 6.2; 95% CI 1.9 – 20.4; p-value = 0.003) and IVIG (OR 12.1; 95% CI 3.9 – 37.2; p-value < 0.001) were associated with worse clinical outcomes during RSV hospitalizations. (50) The authors believed that it was most likely confounded by the fact that patients who were treated with antiviral drugs and IVIG had more severe infections.

2.9.5. Passive Immunization

Passive immunization such as palivizumab or IVIG could be administered to prevent the development of LRTIs in immunocompromised children. Immunoprophylaxis with palivizumab was previously shown to be effective in preventing RSV hospitalizations in certain high-risk populations. However, there are no current recommendations by the American Academy of Pediatrics (AAP) and Canadian Pediatric Society (CPS) for the routine administration of palivizumab immunoprophylaxis to prevent RSV hospitalizations in immunocompromised children due to lack of availability of RCTs in this population. There are no studies in the current literature that examine the

effectiveness of passive immunization on LRTI hospitalizations in immunocompromised children.

2.10. Prevention and Treatment of LRTIs

Nosocomial ARIs are getting increasingly common and responsible for approximately one-third of all ARIs. Nosocomial RSV infections tend to cause longer duration of hospitalization, compared to community acquired RSV infections. (17) Hence, it is prudent to take strict isolation measures to prevent the transmission of viruses to susceptible immunocompromised patients in the hospital. Droplet and contact precautions are the most important measures to prevent nosocomial transmission of respiratory viruses. It was reported that appropriate initiation and adherence to isolation measures was associated with reduction in the incidence of nosocomial transmission of ARIs. (75) Isolation measures were recommended to be implemented for longer periods of time for immunocompromised patients due to their association with prolonged viral shedding. (65)

Both AAP and CPS recommend the administration of annual seasonal influenza vaccine in immunocompromised children. (9,10) Studies showed that children with ALL and solid tumors who had seasonal influenza vaccine during the induction phase of chemotherapy had protective response rates of approximately 57% to 85% and 60% to 84% respectively. (76,77) Currently, RSV vaccine is not available. The challenges of developing RSV vaccine include insufficient attenuation of live viruses and the reluctance to use inactivated vaccine after the series of adverse events that arose during clinical trials of formalin-inactivated RSV vaccine in the 1960s. (13)

Due to high costs and monthly intravenous delivery schedule, it is not feasible to deliver passive immunization with palivizumab to the general pediatric population. Palivizumab is found to be effective in preventing RSV hospitalizations in high-risk infants. (13) IMpact-RSV Trial is a randomized, double blinded, placebo controlled multicenter study that demonstrated the safety and efficacy of palivizumab immunoprophylaxis to prevent RSV hospitalizations among infants. (12) However, the study included only a subset of high-risk premature infants with chronic lung diseases. Based on the current evidence, AAP and CPS both recommend the administration of

palivizumab among premature infants with chronic lung diseases and infants with hemodynamically significant CHDs. (9,10) However, there are no clear recommendations on the use of palivizumab among special populations with cystic fibrosis, Down syndrome, neuromuscular and immunocompromising conditions most likely due to lack of high quality evidence of efficacy.

Treatment of viral LRTIs is mainly supportive and antiviral drugs are often not given in healthy children. Patients usually receive symptomatic treatment such as antipyretics, intravenous hydration, and respiratory support with oxygen supplementation or positive pressure ventilation. However, it is prudent to initiate antiviral drugs early in immunocompromised children because they are more at risk for severe respiratory complications. Neuraminidase inhibitors such as oseltamivir and zanamivir are found to be effective in reducing the severity of influenza complications when administered within 48 hours of symptoms onset. Treat with ribavirin alone or together with other immunomodulators such as IVIG or intravenous palivizumab was demonstrated to prevent progression to LRTIs and deaths in adults. (78) These interventions were previously used for treatment of RSV, parainfluenza, hMPV and adenovirus LRTIs in immunocompromised adults. However, the effectiveness of ribavirin in the treatment of RSV LRTIs among immunocompromised children was only experimented in case series, and a RCT is yet to be completed. Hence, there is insufficient evidence to recommend use of ribavirin, IVIG, or intravenous palivizumab for viral ARIs in immunocompromised children.

CHAPTER 3: OBJECTIVES

The general objective of this study is to provide data that could be used to improve the understanding of the epidemiology of lower respiratory tract infections (LRTIs that could aid in the diagnosis, prevention and management of LRTI hospitalizations in immunocompromised children.

The specific objectives of this study are:

(1) To determine the incidence of LRTI hospitalizations in immunocompromised children.
(2) To describe the microbiological etiologies and clinical burden (i.e. mortality and morbidity such as ICU admission, oxygen supplementation, and mechanical ventilation) of LRTI hospitalizations in immunocompromised children.
(3) To determine the association between the baseline characteristics and LRTI hospitalizations in immunocompromised children.

CHAPTER 4: METHODOLOGY

4.1. Overview of Study Design

We conducted a retrospective cohort study of immunocompromised children age < 16 years who resided in Nova Scotia and were treated at the IWK Health Center between 2004 and 2014. They were followed from the date of diagnosis with an immunocompromising condition until the first LRTI hospitalization, death, end of study period or end of immunocompromised status. The study population was identified from the IWK Decision Support Services for potentially eligible patients using codes from the International Classification of Disease Clinical Modification (ICD-9-CM and ICD-10-CM) diagnosis and procedure code-based classification system for hematological, oncological, immunological, rheumatological and gastrointestinal disorders. References to the IWK hematology/oncology and rheumatology database were also made. From the databases, a list of immunocompromised children followed by IWK hematology/oncology and rheumatology services were generated to make cross-reference to the list of immunocompromised children generated by the IWK Decision Support Services. This was to ensure all patients with relevant hematological, oncological and rheumatological disorders were identified. Health records of the eligible patients were retrieved either electronically or in hard copy, and data was collected using a standardized data collection form to record the primary outcome, secondary outcomes and baseline characteristics. The primary outcome was LRTI hospitalization, which was defined as hospital admission with lower respiratory symptoms and positive radiological findings. Descriptive analyses such as percentages, means, medians and ranges were performed to describe the incidence, microbiological etiology, and clinical burden of LRTI hospitalizations. The baseline sociodemographic characteristics and underlying diagnoses of immunocompromising conditions were documented to describe the cohort. A survival analysis was conducted to compare time to LRTI hospitalizations for different subgroups classified by the baseline characteristics and underlying diagnosis of immunocompromising conditions.

4.2. Study Population

4.2.1. Inclusion Criteria

We included children age < 16 years from Nova Scotia, who were diagnosed with the following immunocompromising conditions from January 1st, 2004 to December 31st, 2014: (1) hematological disorders, (2) oncological disorders, (3) immunological disorders, (4) rheumatological disorders and (5) gastrointestinal disorders necessitating immunosuppressive therapy. Included patients were diagnosed and followed for their immunocompromising conditions at the IWK Health Center between 2004 and 2014.

If multiple immunocompromising conditions developed over the study period, subjects were only included once in the study for their first diagnosed immunocompromising condition. For example, a patient who developed a relapse or a new immunocompromising condition was not included in the study as a different subject. This is because multiple immunocompromising conditions that developed in the same patient could not be considered independent and could lead to biased results. Therefore, patients were used as units of analysis for univariate analyses, instead of immunocompromising conditions.

4.2.2. Exclusion Criteria

Healthy children without the aforementioned immunocompromising conditions were excluded. We also excluded children with certain ongoing pre-existing conditions, which were known to increase the risk for LRTI hospitalizations, regardless of whether they were immunocompromised or not. These conditions included prematurity, hemodynamically significant CHDs and CLDs (such as BPD and cystic fibrosis). Prematurity was defined as the birth of an infant that occurred before 37 weeks of gestation. Only premature infants that were in their first two years of life at the diagnosis of immunocompromising condition were excluded. These underlying conditions could potentially contribute confounding effects to LRTI hospitalizations.

4.2.3. Follow-Up Criteria

The study population was followed from the date of diagnosis with an immunocompromising condition until the first of LRTI hospitalization, death, end of study period or end of immunocompromised status. Hematology and oncology patients were considered immunocompromised if they had active malignancies, abnormalities of immune cells (e.g. aplastic anemia, bone marrow failure syndromes), or had ongoing treatment with radiotherapy or chemotherapy. Oncology patients were considered immunocompromised up to 2 years after the maintenance therapy or hematopoietic stem cell transplant was completed. Studies showed that it takes 2 years or longer for the adaptive immune system to fully recover after stem cell transplantation. (87) As all oncology patients were grouped together (radiotherapy, chemotherapy and HSCT recipients), the maximum immunocompromised duration of 2 years was chosen as the follow up period as a conservative estimate. All immunology patients were considered immunocompromised unless they underwent curative therapy (e.g. hematopoietic stem cell transplant). Rheumatology and gastroenterology patients were considered immunocompromised if they were on treatment with immunosuppressive medications such as biologic modifiers, methotrexate or high dose systemic corticosteroids.

If an LRTI hospitalization occurred during the study period and period of immunosuppression, it was captured as an outcome or survival event. When the information about the survival time was not complete, observations were right-censored in survival analysis. Subjects who did not develop LRTI hospitalizations were right-censored at the end of study period or when they were no longer considered immunocompromised. Subjects who died or were lost to follow-up were also right-censored.

4.3. Outcome Measures

The principal objective of our study was to determine the incidence, microbiological etiology, clinical burden and baseline characteristics associated with LRTI hospitalizations in immunocompromised children. The primary outcome was LRTI hospitalization. The secondary outcomes were the microbiological etiology and clinical burden of LRTIs hospitalizations. The baseline characteristics and underlying diagnosis

of immunocompromising conditions were collected to describe the overall study cohort and different subgroups.

4.3.1. Primary Outcome

LRTIs affect the respiratory structures below vocal cords such as trachea, bronchi and bronchioles. LRTIs were broadly defined as clinical syndromes, with URT symptoms (such as rhinorrhea, cough, and sore throat) and LRT symptoms (such as tachypnea, intercostal retractions, stridor, wheezing, crackles and hypoxia) in association with positive radiological findings (such as interstitial or alveolar inflammatory infiltrates, peribronchial thickening, and consolidation). (50)

The primary outcome of the study was LRTI hospitalization. The case definition of LRTI hospitalization for our study was any hospital admission with LRTI as a primary admission diagnosis or the development of LRTI during a non-LRTI hospitalization (i.e. nosocomial LRTI). For both scenarios, it was captured as an outcome event of definite LRTI if there were: (1) presence of 2 or more LRT symptoms and (2) presence of at least 1 positive radiological finding. It was captured as possible LRTI if patient was hospitalized with 2 or more LRT symptoms in the absence of pertinent radiological findings. Since we assumed that viral diagnostic tests were not routinely ordered for all patients hospitalized with LRT symptoms, we did not include specific microbiological diagnosis in the case definition. A summary of the case definition of LRTI hospitalization is outlined in Table 4-1.

Table 4-1: Case definition of LRTI hospitalizations

LRTI hospitalization included (1) any hospitalization with LRTI as a primary admission diagnosis or (2) development of LRTI during a non- LRTI hospitalization	**Case definitions** (A) Presence of 2 or more of the following LRT signs and symptoms: tachypnea, intercostal retractions, stridor, wheezing, crackles or hypoxia, and (B) Presence of 1 or more of the following radiological findings: interstitial or alveolar inflammatory infiltrate, peribronchial thickening, or consolidation.	**LRTI hospitalizations** **Definite LRTI:** (A) + (B) Presence of LRTI symptoms and radiological findings **Possible LRTI:** (A) Presence of LRTI symptoms without radiological findings	**Treatment of the primary outcome variable** Dichotomized: Yes or No

LRTI = Lower respiratory tract infection, LRT = Lower respiratory tract

To address the study objectives, only the first episode of LRTI hospitalization was captured as an outcome event. Subsequent LRTI hospitalizations were not considered for analyses. The clinical burden of LRTI hospitalizations that occurred in the same immunocompromised patient could be similar and hence it could not be considered independent. The baseline characteristics associated with LRTI hospitalizations that developed in the same child would also be identical, leading to confounding effects in the analyses.

4.3.2. Secondary Outcomes

Ascertainment of the microbiological etiology of LRTIs could be challenging because lower respiratory tract specimens could not easily be acquired in young children. Specific microbiological diagnosis could sometimes be made by specimens from upper respiratory tract (e.g. nasopharyngeal aspirate) or laboratory evaluations of blood cultures. We investigated and the following microbiological etiology of LRTI hospitalizations: (1) health-care associated LRTIs, (2) types of microbial pathogens, and

(3) microbial co-infections. Descriptions of the variables related to the microbiological etiology of LRTI hospitalizations are outlined in Table 4-2.

The clinical burden of LRTI hospitalizations was defined as morbidity and mortality attributable to LRTIs during hospitalization. The outcomes were restricted to specific pulmonary outcomes in order to minimize confounding effects of existing immunocompromising conditions or other comorbidities on the clinical burden. They included: (1) duration of hospitalization, (2) duration of oxygen supplementation, (3) mechanical ventilation, (4) duration of mechanical ventilation (5) ICU admission, and (6) mortality attributable to LRTIs. Descriptions of the secondary outcomes related to the clinical burden of LRTI hospitalizations are outlined in Table 4-3.

Table 4-2: Descriptions of the variables related to the microbiological etiology of LRTI hospitalizations

Secondary outcome variables		**Treatment of variables included in the study**
Variables	**Description**	
Health-care associated LRTIs	Classification of LRTIs by the source of infection acquisition (i.e. nosocomial vs. community acquired)	Dichotomized: Yes or No
Types of microbial pathogens	Laboratory diagnosis of causative microbial pathogens (by PCR, viral culture, etc.)	Grouped into seven categories: [Bacteria, Viruses (including RSV, rhinovirus, influenza, parainfluenza, adenovirus, others), Fungi]
Microbial co-infections	Presence of coinfections by 2 or more microbial pathogens in a particular episode of LRTI hospitalization	Dichotomized: Yes (Viral, Viral-bacterial, Bacterial) or No

LRTI = Lower respiratory tract infection, PCR = Polymerase chain reaction

Table 4-3: Descriptions of the secondary outcomes related to clinical burden of LRTI hospitalizations in the study

Secondary outcome variables		Treatment of variables included in the study
Variables	**Description**	
Oxygen supplementation	Need for supplemental oxygen due to LRTIs	Dichotomized: Yes or No
CPAP use	Duration of CPAP use in days	Maintained as continuous variable
ICU admission	Intensive care unit admission attributable to LRTIs	Dichotomized: Yes or No
Mechanical ventilation	Requirement of mechanical ventilation	Dichotomized: Yes or No
Mortality attributable to LRTIs	Deaths within two weeks of onset of LRTIs	Dichotomized: Yes or No
Duration of hospitalization	Number of days hospitalized with URT and LRT symptoms	Maintained as continuous variable
Duration of oxygen supplementation	Duration of oxygen supplementation if given, in days	Maintained as continuous variable
Duration of ICU admission	Number of days hospitalized in ICU due to LRTIs	Maintained as continuous variable
Duration of mechanical ventilation	Duration of mechanical ventilation if indicated, in days	Maintained as continuous variable

LRTI = Lower respiratory tract infection, CPAP = Continuous positive airway pressure, ICU = Intensive care unit, URT = Upper respiratory tract, LRT = lower respiratory tract

4.3.3. *Baseline Characteristics of the Study Population at Diagnosis with Immunocompromising Condition*

The literature portrayed several baseline characteristics associated with LRTI hospitalizations in immunocompromised children (Section 2.6). The role of underlying diagnosis of different immunocompromising conditions on the risk for LRTI hospitalizations had not previously been investigated. We assessed the following baseline characteristics of the target population at diagnosis with immunocompromising conditions: (1) age at diagnosis with immunocompromising condition, (2) gender, (3) ethnicity, (4) status of household crowding, (5) passive smoking exposure, and (6) underlying diagnosis of immunocompromising condition. Description of the baseline

characteristics of the study population at diagnosis with immunocompromising condition is outlined in Table 4-4.

Table 4-4: Descriptions of the baseline characteristics of the study population at diagnosis with immunocompromising condition

Independent Variables		**Treatment of Variables included in the Study**
Variable	**Description**	
Age	Age at diagnosis of immunocompromising conditions	Maintained as continuous variable
Gender	Male or female	Dichotomized: Male and Female
Ethnicity	-	Grouped into five categories: (White, Asian, Black, Indigenous, Others)
Household crowding	Household crowding is defined as the presence of ≥ 5 members in one household	Grouped into three categories: (Yes, No, Unknown)
Passive smoking exposure	Passive smoking exposure from household members	Grouped into three categories: (Yes, No, Unknown)
Underlying diagnosis of immunocompromising condition	The initial diagnosis of an immunocompromising condition made by a clinician	Grouped into five categories: (Hematological disorders, Oncological disorders, Immunological disorders, Rheumatological disorders, and Gastrointestinal disorders)

ALL = Acute lymphoblastic leukemia, HSCT = Hematopoietic stem cell transplantation

4.4. Ethical Considerations

Being an observational study in nature, our study imposed minimal risk to study participants because there was no direct patient contact and patient care was not altered or intervened in any way. All information and data for the study were collected as part of a routine patient care. Due to the large sample size making obtaining individual consent impractical and there was minimal potential risk associated with the study, it was deemed that individual consent from participants was not required to conduct the study.

The main privacy risk was the potential loss of confidentiality during data collection and analysis. Several measures were taken to ensure the security of data

acquired. Patient identifiers were not included in data collection forms. Instead, unique study identification numbers were assigned. A separate list containing both unique study identification numbers and patient identifiers were created so that reference could be made back to the health records if necessary. Only the study researchers had access to health records and data collection forms from password-protected IWK servers. All printed documents were securely stored in a locked room at the Center for Vaccinology. All data collection and analyses were conducted using password-protected IWK computers.

4.5. Data Collection

The study population was identified from the IWK Decision Support Services which found potentially eligible patients using ICD codes of immunocompromising conditions, supplied by the Principal Investigator. Reference to the IWK hematology/oncology and rheumatology database were also made. From the IWK hematology/oncology and rheumatology database, a list of immunocompromised children followed by IWK hematology/oncology and rheumatology services were generated in order to make cross-reference to the list of immunocompromised children generated by the IWK Decision Support Services. This was to ensure all patients with relevant hematological, oncological and rheumatological disorders were identified. The IWK hematology/oncology database consisted of every patient with hematological and oncological disorders who were treated at the IWK Health Center. The IWK rheumatology database consisted of every patient with rheumatological disorders who were treated at the IWK Health Center from 2008 onwards. The investigators consulted with members of these subspecialties (i.e. immunology, rheumatology, and oncology services) to determine the ICD codes for hematological, oncological, immunological, rheumatological and gastrointestinal disorders. Appendix 3 outlines the thus-validated ICD-9-CM and ICD-10-CM codes that were used to identify the cohort of immunocompromised children in our study.

Once the study was approved by the IWK Research Ethics Board, the list of relevant ICD codes were submitted to IWK Decision Support Services to retrieve the K numbers (identification number used at the IWK) of the study population. Using K

numbers, health records were retrieved electronically or in hard copy (for information before the electronic medical record system was introduced at the IWK Health Center). A standardized paper data collection form was used to collect the data (Appendix 4). The data was entered into a Microsoft Access Database Management System on an IWK-based server at the Canadian Center for Vaccinology. The database was imported into STATA/SE14 for data analysis via text file. Data storage was described in "Ethical considerations".

4.6. Sample Size Calculations

Sample size calculations were based on Objectives 1 and 2: (1) to determine the incidence of LRTI hospitalizations and (2) to determine the microbiological etiology and clinical burden of LRTI hospitalizations in immunocompromised children.

The National Longitudinal Survey of Children and Youth (NLSCY) reported that the prevalence of acute respiratory infections in Atlantic Canada ranged from 16.8% to 20.3%. (80) For this study, we assumed that the rate of LRTI hospitalizations among immunocompromised children in Nova Scotia was 20%. For objective 1, we would need approximately 250 subjects in order to be 95% confident that the true incidence of LRTI hospitalizations was no more than 5% greater or less than the value estimated from our study. Requirement of mechanical ventilation and ICU admission were two of the most clinically significant clinical burden of LRTI hospitalizations. Several studies suggested that approximately 10% of immunocompromised children required mechanical ventilation and ICU admission during the course of their LRTI hospitalizations. (47,53,56,57,71) For objective 2, we would need approximately 138 subjects in order to be 95% confident that the true proportion was no more than 5% greater or less than the value estimated from our study.

We estimated that we would need greater than 250 subjects with LRTI hospitalizations to address both Objective 1 and 2.

4.7. Statistical Analysis

4.7.1. Overview

For this study, the primary outcome was the incidence of LRTI hospitalizations in the overall and different subgroups of immunocompromised children. The secondary outcomes were the microbiological etiology and clinical burden of LRTI hospitalizations. The baseline sociodemographic characteristics and underlying diagnosis of immunocompromising conditions were described in the inception cohort. Table 4-1, 4-2, 4-3 and 4-4 outline the treatment of the following variables included for analyses: primary outcome, secondary outcomes related to the microbiological etiology and clinical burden of LRTI hospitalizations and the baseline characteristics of the study population at diagnosis with immunocompromising conditions. After analyses, any cell sizes less than 5 would not be reported for the purpose of protecting the confidentiality of study patients.

All statistical analyses were performed using STATA/SE 14 (StataCorp LP, College Station, Texas). Statistical significance for all analyses were set at the 2-sided $P < 0.05$.

4.7.2. Analyses

Prevalence measures the existing cases of a disease in a population at risk. Since LRTIs generally have acute onset and course of disease, the incidence rates of LRTI hospitalizations for the overall and different subgroups of the immunocompromised pediatric population were determined. Incidence is defined as the number of new cases of a disease diagnosed in a study population at risk at a particular period of time.

For Objective 1, we calculated incidence proportions of LRTI hospitalizations by using new cases of LRTI hospitalizations as numerator and the total number of immunocompromised children in the study as the denominator. However, the inception cohort of our study resulted in a dynamic population, where study participants entered and left the study at different times. The participants were at risk for varying length of time. Hence, it was not entirely appropriate to solely use incidence proportions, where new cases were expressed as a proportion of the entire study population at risk. In addition, we also calculated crude incidence rates, which took into account of the sum of

the time each immunocompromised child remained in the study before developing LRTI hospitalizations, instead of the total number of immunocompromised children at the beginning of the study. New cases of LRTI hospitalizations in immunocompromised children were used as the numerator. The denominator was the person-time estimate, which was calculated by the cumulative amount of time from diagnosis with immunocompromising conditions till the development of LRTI hospitalizations contributed by all study subjects.

For Objective 2, standard descriptive analytic statistics such as percentages, means, medians and ranges were used to describe the microbiological etiology and clinical burden associated with LRTI hospitalizations. Categorical variables such as mechanical ventilation, ICU admission, CPAP use and mortality were described using frequencies and percentages. The proportion of immunocompromised children who required mechanical ventilation, ICU admission and CPAP were determined for the overall and different subgroups of immunocompromised children. Similarly, continuous variables such as duration of hospitalization, oxygen supplementation and mechanical ventilation were described using means with 95% confidence intervals or medians with interquartile ranges for the overall and different subgroups of immunocompromised children.

Survival analysis was used to describe the onset of primary outcome over time for the overall and different subgroups of immunocompromised children. It was appropriate for our study due to different start times and follow up periods. LRTI hospitalizations could occur any time after diagnosis with an immunocompromising condition, so a fixed follow-up period was not feasible. Moreover, survival analysis would typically focus on non-recurrent events. Since this study only captured the first episode of LRTI hospitalization, the outcome was non-recurrent. Hence, survival analysis was most appropriate to determine the association between baseline characteristics present at diagnosis and LRTI hospitalizations.

Log-rank tests are often used in observational studies to establish the association of exposure variables to an outcome event when the measurement is the time from initial exposure to an outcome event. It is most appropriate to use log-rank tests when the data is right-censored. Log-rank tests were performed on the baseline characteristics and

different subgroups of immunocompromising conditions to compare the incidence of LRTI hospitalizations between each category.

Also, Kaplan-Meier method was used to describe time to LRTI hospitalizations for the baseline characteristics and different subgroups of immunocompromising conditions. Kaplan-Meier estimators were used to estimate the survival probability of patients in a cohort from an outcome event over time, especially in a study where patients tend to drop out or are followed along different periods of time during the study. Hence, it estimates the proportion of patients free from the outcome event at any point in time during the study (i.e. the number of patients surviving over total number of patients at risk). The estimator is plotted over time and portrayed as the Kaplan-Meier curve, which is a series of horizontal declining steps that approaches the true survival function of the study population over time. Stratified Kaplan-Meier curves were generated for each variable to estimate and compare the time to LRTI hospitalizations between different strata. They were also used to determine if the risk for LRTI hospitalizations was constant or changed over time.

Cox proportional hazard model is a regression analysis used to investigate the association between the survival time of study subjects and one or more of their independent variables. The hazard ratio is the ratio of two hazard rates, which indicates the hazard of an outcome event in one independent group in comparison to the other. In order to determine the association of the baseline characteristics and types of immunocompromising conditions, Cox proportional hazard model was used to calculate the univariate hazard ratios with 95% confidence intervals for LRTI hospitalizations. A backward elimination method was used to develop the final multivariate Cox proportional hazard model.

For both log-rank tests and Cox proportional hazard models, we assumed that the effect of risk factors and hazard ratios were constant and proportional over time. We used several statistical graphical analyses methods (*stphplot* and *stcoxkm*) in order to assess if there were any violations of the proportional hazard model assumptions. *Stphplot* (also known as log-log plot) graphs –ln {–ln(survival)} curves for each category of baseline characteristics variables against ln (time). If there was parallelism between the plotted curves, we could assume the proportionality of hazard ratios. *Stcoxkm* is a graphical

method which plots the Kaplan-Meier observed curves in comparison with the Cox predicted curves for the baseline characteristics variables. If the observed and predicted curves are in proximity of each other, the assumption of proportionality was not violated.

CHAPTER 5: RESULTS

5.1. Description of the Baseline Characteristics of the Study Population

We identified 695 patients from the IWK Decision Support Services using the ICD-10 codes for all abovementioned immunocompromising conditions. Appendix 3 reports the full list of ICD-10 codes that were used to identify immunocompromised children who were treated and followed at the IWK Health Center during the study period. Additionally, we identified 322 and 181 patients from the IWK hematology/oncology and rheumatology databases respectively. After the elimination of duplicate patients from different lists and exclusion of 21 patients as per our exclusion criteria, a total of 640 children were included in the study. Figure 5-1-1 illustrates how the aggregate number of the study patients were identified by our search strategy via the IWK Decision Support Services and also the IWK hematology/oncology and rheumatology databases.

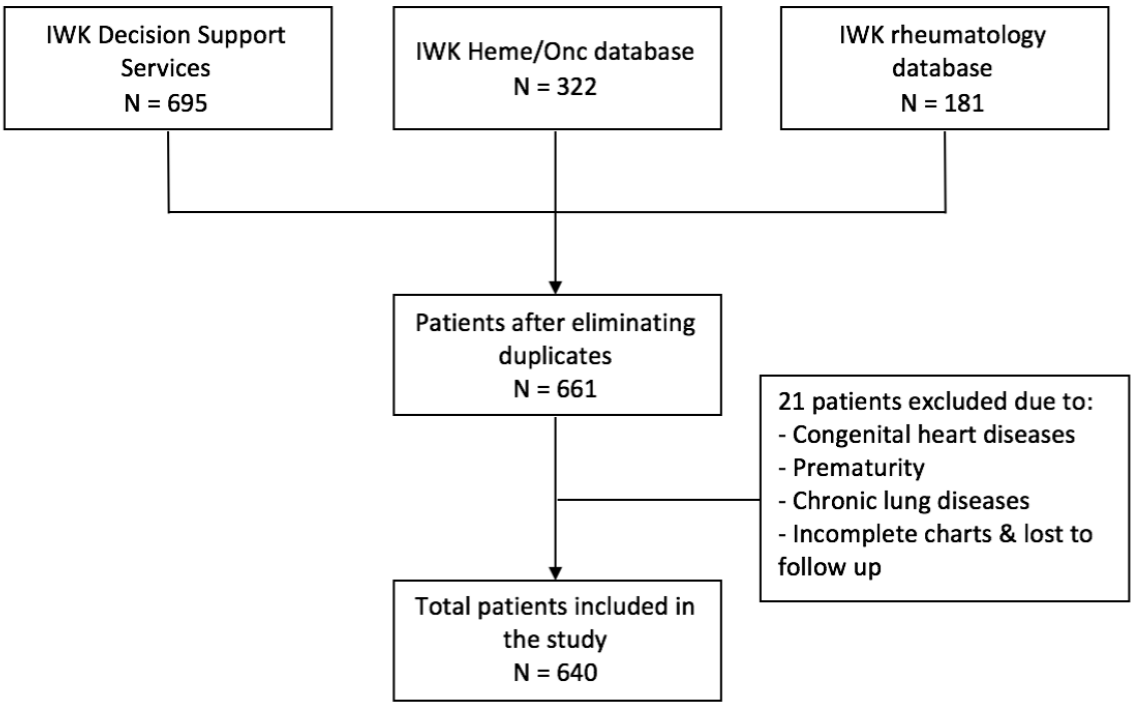


Figure 5-1-1: Study patient flow diagram

Table 5-1-1 shows detailed description of the baseline characteristics of the overall study population at the time of diagnosis with immunocompromising conditions. The mean age at diagnosis with all immunocompromising conditions was 7.7 years. Of all immunocompromising conditions, hematological conditions were diagnosed at the youngest ages with the mean age at diagnosis of 3.2 years, whereas gastrointestinal conditions were diagnosed at oldest ages with the mean age at diagnosis of 11 years. The mean age at diagnosis with the remaining disorders range from 5.1 years to 9 years. We did not identify major differences in the gender distribution of the overall study population. Additionally, we found that approximately one-fifth of all immunocompromised children in our study reside in a crowded household (i.e. 5 or more people). However, we were not able to retrieve information on the status of household crowding for 14.8% of study patients. There were also significant numbers of missing values in several variables such as ethnicity and status of passive smoking, for which information was missing in 92.5% and 80.8% of the charts.

Table 5-1-1: Baseline characteristics of the overall study cohort at the time of diagnosis with immunocompromising conditions

Baseline characteristics	**Overall** (n=640)	**Heme** (n=31)	**Onc** (n=279)	**Immuno** (n=75)	**Rheum** (n=149)	**GI** (n=106)
Age at diagnosis (years)	7.7 ± 5	3.2 ± 3.6	6.9 ± 5	5.1 ± 4.2	9 ± 4.6	11.4 ± 3.4
Gender (n,%)						
Male	319 (49.8%)	17 (54.8%)	146 (52.3%)	44 (58.7%)	52 (34.9%)	60 (56.6%)
Female	319 (49.8%)	14 (45.2%)	133 (47.7%)	31 (41.3%)	97 (65.1%)	46 (43.4%)
Ethnicity (n,%)						
White	16 (2.5%)	*	5 (1.8%)	*	*	*
Black	*	-	*	-	-	-
Asian	13 (2%)	*	6 (2.2%)	*	*	*
Indigenous	8 (1.3%)	-	*	*	*	-
Mixed	9 (1.4%)	-	5 (1.8%)	-	*	*
Unknown	592 (92.5%)	28 (90.3%)	258 (92.5%)	69 (92%)	136 (91.3%)	101 (95.3%)
Household crowding (n,%)						
Yes	141 (22%)	*	58 (20.8%)	13 (17.3%)	41 (27.5%)	25 (23.6%)
No	404 (63.1%)	24 (77.4%)	172 (61.7%)	57 (76%)	91 (61.1%)	60 (56.6%)
Unknown	95 (14.8%)	*	49 (17.6%)	5 (6.7%)	17 (11.4%)	21 (19.8%)
Passive smoking (n,%)						
Yes	55 (8.6%)	8 (25.8%)	27 (9.7%)	6 (8%)	11 (7.4%)	*
No	68 (10.6%)	*	15 (5.4%)	21 (28%)	17 (11.4%)	12 (11.3%)
Unknown	517 (80.8%)	20 (64.5%)	237 (84.9%)	48 (64%)	121 (81.2%)	91 (85.9%)
Year of diagnosis						
2004	59 (9.2%)	*	30 (10.8%)	*	12 (8.1%)	11 (10.4%)
2005	53 (8.3%)	*	22 (7.9%)	*	17 (11.4%)	10 (9.4%)
2006	52 (8.1%)	*	22 (7.9%)	6 (8%)	15 (10.1%)	6 (5.7%)
2007	59 (9.2%)	*	23 (8.2%)	5 (6.7%)	15 (10.1%)	14 (13.2%)
2008	45 (7%)	*	27 (9.7%)	*	8 (5.4%)	5 (4.7%)
2009	56 (8.8%)	*	25 (9%)	7 (9.3%)	11 (7.4%)	10 (9.4%)
2010	55 (8.6%)	*	17 (6.1%)	6 (8%)	15 (10.1%)	14 (13.2%)
2011	61 (9.5%)	-	25 (9%)	10 (13.3%)	17 (11.4%)	9 (8.5%)
2012	58 (9.1%)	*	32 (11.5%)	*	12 (8.4%)	6 (5.7%)
2013	72 (11.3%)	*	32 (11.5%)	16 (21.3%)	10 (6.7%)	10 (9.4%)
2014	70 (10.9%)	5 (16.1%)	24 (8.6%)	13 (17.3%)	17 (11.4%)	11 (10.4%)

* denotes cell size < 5
- denotes nil value

Table 5-1-2 and 5-1-3 report the baseline characteristics of the study cohort that were later hospitalized with definite LRTIs and possible LRTIs respectively. The mean ages at diagnosis with immunocompromising conditions amongst children who were later hospitalized with definite and possible LRTIs were 4.8 years and 5.5 years respectively, which were less than that of overall study patients (7.7 years). Also, the mean age at diagnosis with oncological and immunological disorders were generally younger among children who were later hospitalized definite or possible LRTIs. Among patients who were later hospitalized with definite LRTIs, hematological disorders were diagnosed at the youngest ages (not shown in Table 5-1-2 due to hematology groups having cell size < 5) while rheumatological disorders were diagnosed the latest in life (6.2 years).

In both cohorts that were later hospitalized with definite or possible LRTIs, there were more males than female in comparison to the overall cohort where the gender proportion was almost equivalent. The status of household crowding with 5 or more individuals was similar in both cohorts that later developed definite or possible LRTIs and the overall study cohort. There were large numbers of missing values for ethnicity and passive smoking in both cohorts who later developed definite or possible LRTIs.

Table 5-1-2: Baseline characteristics of the cohort that were hospitalized with definite LRTIs at the time of diagnosis with immunocompromising conditions

Baseline characteristics	**Overall** (n=101)	**Onc** (n=62)	**Immuno** (n=22)	**Rheum** (n=12)
Age at diagnosis (years)	4.5 ± 4.2	5 ± 4.1	2.3 ± 3	6.2 ± 4.7
Gender (n,%)				
Male	61 (60.4%)	42 (67.7%)	13 (59.1%)	*
Female	40 (39.6%)	20 (32.3%)	9 (40.9%)	8 (66.7%)
Ethnicity (n,%)				
White	*	*	*	-
Black	*	*	-	-
Asian	*	*	*	-
Indigenous	*	*	*	-
Mixed	*	*	-	*
Unknown	91 (90.1%)	58 (93.6%)	18 (81.8%)	11 (91.7%)
Household crowding (n,%)				
Yes	22 (21.8%)	14 (22.6%)	*	*
No	72 (71.3%)	42 (67.7%)	18 (81.8%)	8 (66.7%)
Unknown	7 (6.9%)	6 (9.7%)	-	*
Passive smoking (n,%)				
Yes	11 (10.9%)	6 (9.7%)	*	*
No	14 (13.9%)	5 (8.1%)	5 (22.7%)	*
Unknown	76 (75.2%)	51 (82.3%)	15 (68.2%)	8 (66.7%)

* denotes cell size < 5
Note: Hematology and GI groups were omitted from the table due to cell size < 5

Table 5-1-3: Baseline characteristics of the cohort that were later hospitalized with possible LRTIs at the time of diagnosis with immunocompromising conditions

Baseline characteristics	**Overall** (n=21)	**Onc** (n=13)
Age at diagnosis (years)	5.5 ± 4.3	5.4 ± 4.1
Gender (n,%)		
Male	12 (57.1%)	7 (53.9%)
Female	9 (42.9%)	6 (46.1%)
Ethnicity (n,%)		
White	*	-
Black	-	-
Asian	*	*
Indigenous	-	-
Mixed	-	-
Unknown	18 (85.7%)	11 (84.6%)
Household crowding (n,%)		
Yes	6 (28.6%)	*
No	13 (61.9%)	8 (61.5%)
Unknown	*	*
Passive smoking (n,%)		
Yes	*	*
No	*	-
Unknown	18 (85.7%)	12 (92.3%)

* denotes cell size < 5
Note: Hematology, immunology, rheumatology and GI groups were omitted from the table due to cell size < 5

Table 5-1-4 reports the composition of different types of immunocompromising conditions of the overall study cohort. Table 5-1-5 reports the composition of different type of immunocompromising conditions of children that later developed definite and possible LRTIs. Figure 5-1-2 reports the proportion of children with different type of immunocompromising conditions that later developed definite and possible LRTIs.

Table 5-1-4: Types of immunocompromising conditions of the overall study cohort

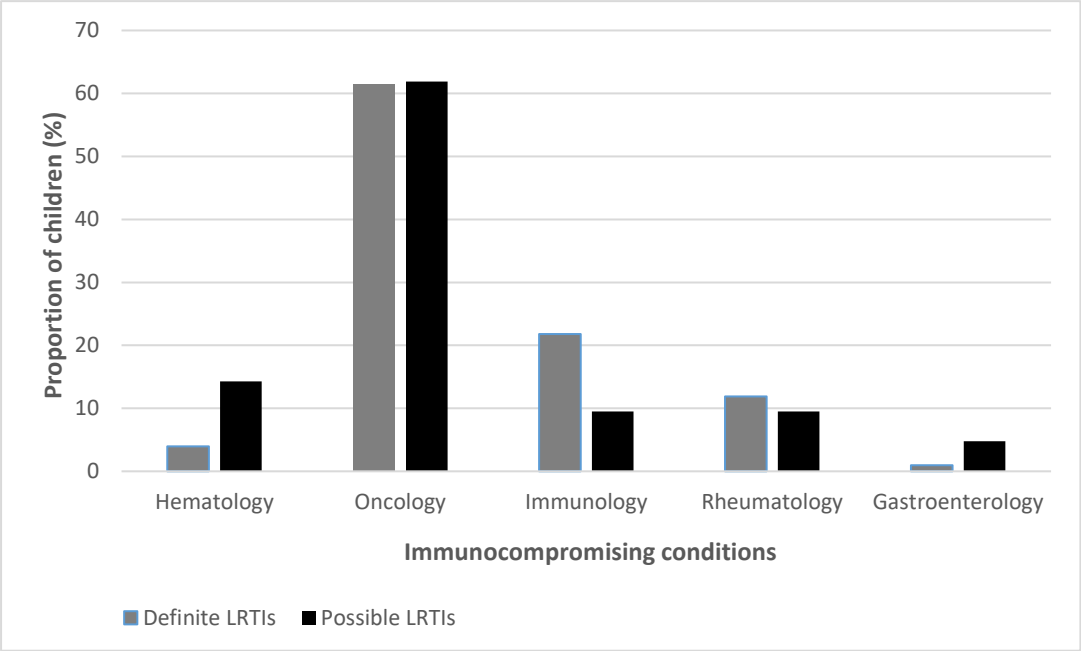
Immunocompromising conditions	**[n = 640] (%)**
Hematology [Total 31 (4.8%)]	
Aplastic anemia	5 (16.1%)
Neutropenia	19 (61.3%)
Other hematologic disorders	7 (22.6%)
Oncology [Total 279 (43.6%)]	
Hodgkin's lymphoma	14 (5%)
Non-Hodgkin's lymphoma	18 (6.5%)
AML	11 (3.9%)
ALL	83 (29.7%)
Other hematologic malignancies	*
CNS tumors	48 (17.2%)
Neuroblastoma	21 (7.5%)
Wilm's tumors	15 (5.4%)
Rhabdomyosarcoma	10 (3.6%)
Retinoblastoma	9 (3.2%)
Bone tumors	17 (6.1%)
Other oncologic disorders	31 (11.1%)
Immunology [Total 75 (11.7%)]	
White blood cell disorders	*
Severe combined immunodeficiency	7 (9.3%)
Common variable immunodeficiency	12 (16%)
Immunodeficiency with antibody defects	47 (62.7%)
Other primary immunodeficiency disorders	6 (8%)
Rheumatology [Total 149 (23.3%)]	
Juvenile idiopathic arthritis	96 (64.4%)
Enthesitis related arthritis	13 (8.7%)
Psoriatic arthritis	10 (6.7%)
Systematic lupus erythematosus	*
Juvenile dermatomyositis	16 (10.7%)
Other rheumatologic disorders	10 (6.7%)
Gastroenterology [Total 106 (16.6%)]	
Crohn's disease	69 (65.1%)
Ulcerative colitis	37 (34.9%)

* denotes cell size < 5

Table 5-1-5: Types of immunocompromising conditions of the cohort that developed definite LRTIs and possible LRTIs

Immunocompromising conditions	**Definite LRTIs** n (%)	**Possible LRTIs** n (%)
Hematology	*	*
Aplastic anemia	-	*
Neutropenia	*	*
Other hematologic disorders	*	-
Oncology	**62 (61.4%)**	**13 (61.9%)**
Hodgkin's lymphoma	*	-
Non-Hodgkin's lymphoma	*	-
AML	*	-
ALL	33 (32.67%)	10 (47.6%)
Other hematologic malignancies	*	*
CNS tumors	*	-
Neuroblastoma	*	*
Wilm's tumors	*	-
Rhabdomyosarcoma	*	-
Retinoblastoma	*	-
Bone tumors	*	-
Other oncologic disorders	*	-
Immunology	**22 (21.8%)**	*
White blood cell disorders	*	-
Severe combined immunodeficiency	6 (5.9%)	*
Common variable immunodeficiency	*	-
Immunodeficiency with antibody defects	11 (10.9%)	-
Other primary immunodeficiency disorders	-	*
Rheumatology	**12 (11.9%)**	*
Juvenile idiopathic arthritis	7 (6.9%)	*
Enthesitis related arthritis	-	-
Psoriatic arthritis	-	-
Systematic lupus erythematosus	-	*
Juvenile dermatomyositis	*	-
Other rheumatologic disorders	*	-
Gastroenterology	*	*
Crohn's disease	-	*
Ulcerative colitis	*	-

* denotes cell size < 5
- denotes nil value



LRTI = Lower respiratory tract infection

Figure 5-1-2: Proportion of children with different type of immunocompromising conditions that developed definite and possible LRTI hospitalizations

Most study patients were diagnosed with oncological disorders, followed by rheumatological, gastrointestinal, immunological and hematological disorders. Overall, there were 279 patients with oncological disorders and the three most common ones were ALL, CNS tumors, and neuroblastoma. The remaining oncological disorders in the study include AML, lymphoma (Hodgkin's and Non-Hodgkin's), Wilm's tumor, rhabdomyosarcoma, retinoblastoma, and bone tumors. The study also involved 149 children with rheumatological disorders such as juvenile idiopathic arthritis, enthesitis-related arthritis, psoriatic arthritis and systemic lupus erythematosus. Additionally, we included 106 children with Crohn's disease and ulcerative colitis. There were 75 patients with immunological disorders and the most common ones were immunodeficiency with antibody defects (i.e. abnormal or low immunoglobulin levels of IgG, IgA, and/or IgM), common variable immunodeficiency and severe combine immunodeficiency. There were 31 children with hematological disorders and a majority of them were diagnosed with

neutropenia and aplastic anemia. Other hematological disorders include lymphohistocytosis, bone marrow failure syndromes and dyskeratosis congenital.

Among study patients later hospitalized with definite LRTIs, oncological disorders were the common types of immunocompromising conditions followed by immunological, rheumatological, hematological and gastrointestinal disorders. Among immunocompromised patients later hospitalized with possible LRTIs, oncological disorders were again the common types of immunocompromising conditions followed by hematological, immunological, rheumatological and gastrointestinal disorders.

5.2. Objective 1: To Determine the Incidence of LRTI Hospitalizations in Immunocompromised Children

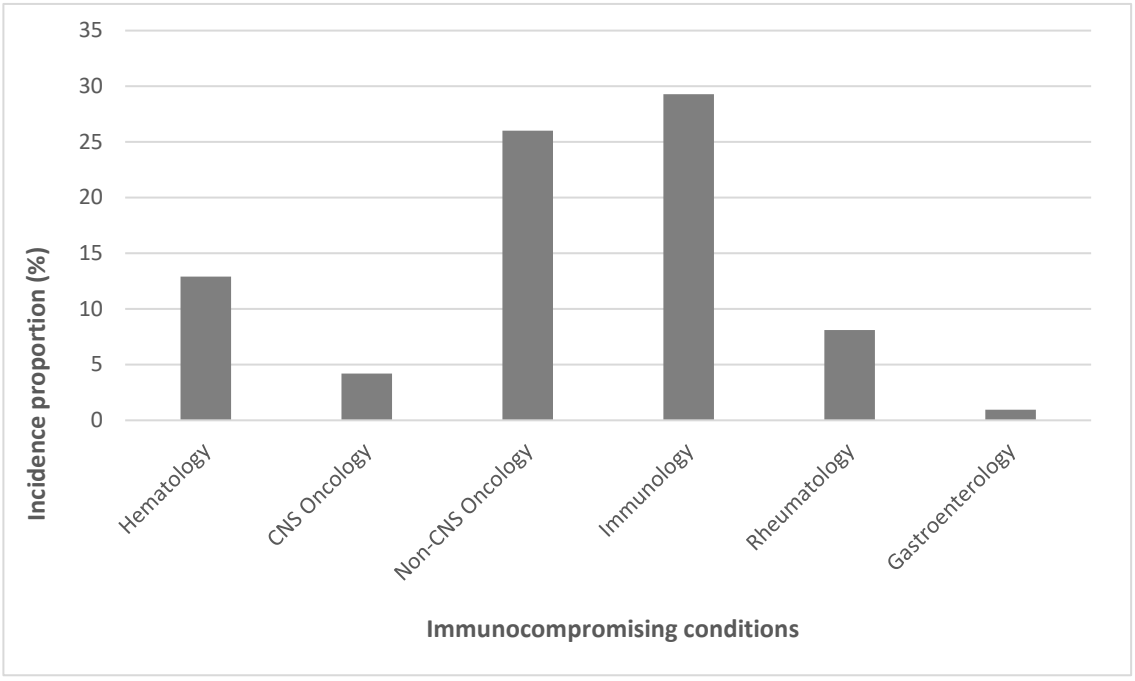
We determined the incidence of definite LRTI hospitalizations in immunocompromised children. Table 5-2-1 reports the incidence of hospitalizations due to definite LRTIs among different subgroups of children with different immunocompromising conditions in addition to the overall study cohort.

Table 5-2-1: Incidence rates of definite LRTI hospitalizations

Immunocompromising conditions	Total # LRTI Hosp	Total # children	Total person-years	Incidence proportion (%)	Crude Incidence per 1,000 person-years (95% CI)
Hematology	*	*	*	**12.9**	**47.1** (17.7 - 125.4)
Oncology	62	279	600.3	**22.2**	**103.3** (80.5 - 132.5)
CNS tumors	*	*	*	**4.2**	**14.8** (3.7 - 59.1)
Without CNS tumors	60	231	465.1	**26**	**129.0** (100.2 - 166.2)
Immunology	22	75	249.3	**29.3**	**88.3** (58.1 - 134)
Rheumatology	12	149	623.9	**8.1**	**19.2** (10.9 - 33.9)
Gastroenterology	*	*	*	**0.9**	**2.7** (0.4 - 19.3)
Overall cohort	101	640	1926	**15.8**	**52.4** (43.1 - 63.7)

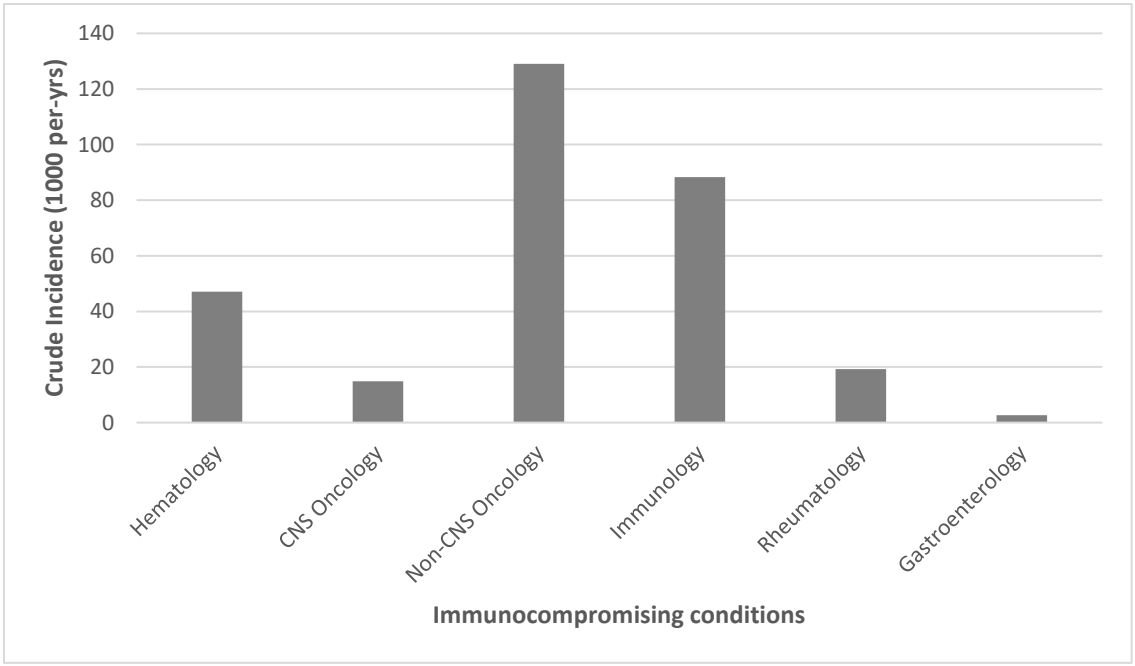
* denotes cell size < 5
CI = confidence interval

A total of 101 patients developed definite LRTI hospitalizations out of 640 immunocompromised patients during the study period. As a result, the incidence proportion of definite LRTI hospitalizations for the overall study cohort was calculated as 15.8%. On subgroup analysis, the incidence proportion was the highest among children with immunological disorders (29.3%), followed by oncological disorders (22.2%), hematological disorders (12.9%), rheumatological disorders (8.1%) and gastrointestinal disorders (0.9%), as shown in Table 5-2-1.



CNS = Central nervous system

Figure 5-2-1: Incidence proportion of definite LRTI hospitalizations by type of immunocompromising conditions



CNS = Central nervous system

Figure 5-2-2: Crude incidence of definite LRTI hospitalizations by type of immunocompromising conditions

To calculate crude incidence rate of definite LRTI hospitalizations, we used the total number of definite LRTI hospitalizations (101 events) as the numerator and the total person-time estimate of the study cohort (1926 person-years) as the denominator. The crude incidence rate of definite LRTI hospitalizations for the overall cohort was calculated as 52.4 per 1,000 person-years. On subgroup analysis, the crude incidence rate was the highest among children with overall oncological disorders (103.0 per 1,000 person-years). Post-hoc analysis showed that it was even higher among children with oncological disorders exclusive of CNS tumors (129.0 per 1,000 person-year). On the other hand, we found that the crude incidence rate among children with CNS tumors (14.8 per 1,000 person-years) was very much lower. The crude incidence rate was the lowest among children with gastrointestinal disorders (2.7 per 1,000 person-years). The crude incidence rates for the remaining immunocompromising conditions such as immunological, hematological and rheumatological disorders were 88.3, 47.1 and 19.2 per 1,000 person-years respectively.

Table 5-2-2 reports the incidence of definite LRTI hospitalizations in the study cohort categorized by age at diagnosis and type of immunocompromising conditions.

Table 5-2-2: Incidence rates of definite LRTI hospitalizations by age at diagnosis and type of immunocompromising conditions

Age	Total # LRTI Hosp	Total # children	Total person-years	Incidence proportion (%)	Crude Incidence per 1,000 person-years (95% CI)
Overall					
< 5 years	68	263	878.8	**25.9**	**77.4** (61 - 98.1)
5-15 years	33	377	1047.4	**8.8**	**31.5** (22.3 - 44.3)
Hematology					
< 5 years	*	*	*	**16**	**57.2** (21.5 - 152.4)
5-15 years	0	6	15.1	**0**	0
Oncology					
< 5 years	38	137	316.6	**22.7**	**120** (87.3 - 165)
5-15 years	24	142	283.8	**16.9**	**84.6** (56.7 - 126.2)
Immunology					
< 5 years	18	46	141	**39.1**	**127.7** (80.4 - 202.7)
5-15 years	*	*	*	**13.8**	**36.9** (13.9 -98.4)
Rheumatology					
< 5 years	8	46	302.2	**17.4**	**26.5** (13.2 - 52.9)
5-15 years	*	103	321.8	**3.9**	**12.4** (4.7 - 33.1)
GI					
< 5 years	0	9	49.2	**0**	0
5-15 years	*	*	*	**1.03**	**3.1** (0.4 - 22.3)

* denotes cell size < 5
CI = Confidence interval, GI = Gastroenterology

36.9 (13.9 - 98.4)

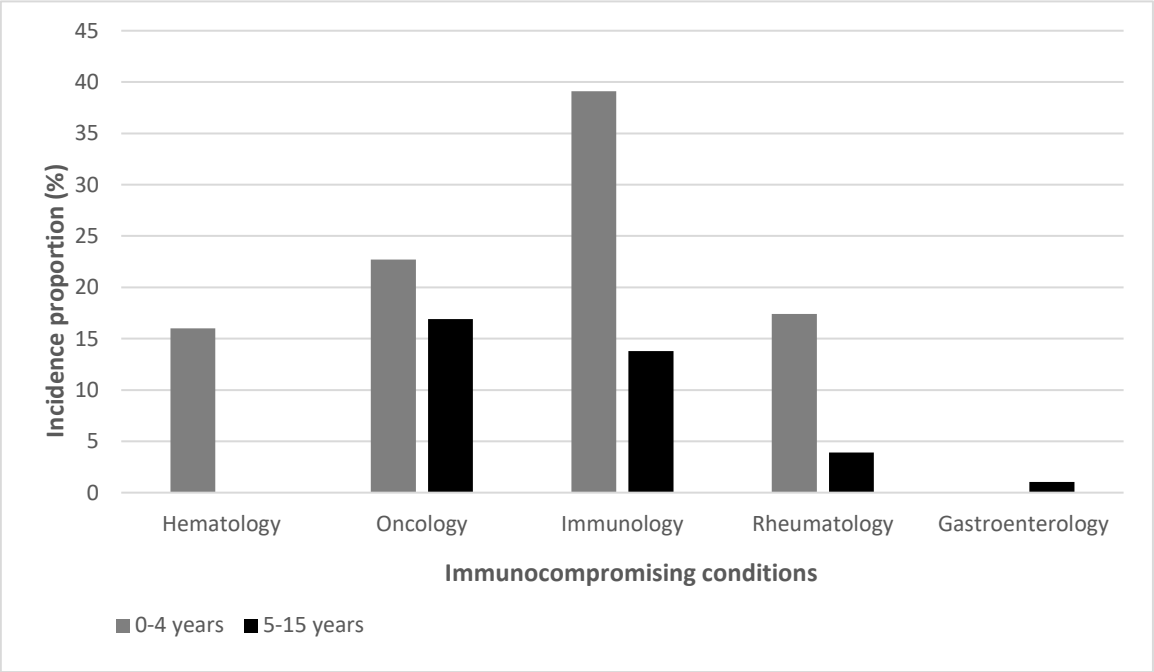


Figure 5-2-3: Incidence proportion of definite LRTI hospitalizations by age at diagnosis and type of different immunocompromising conditions

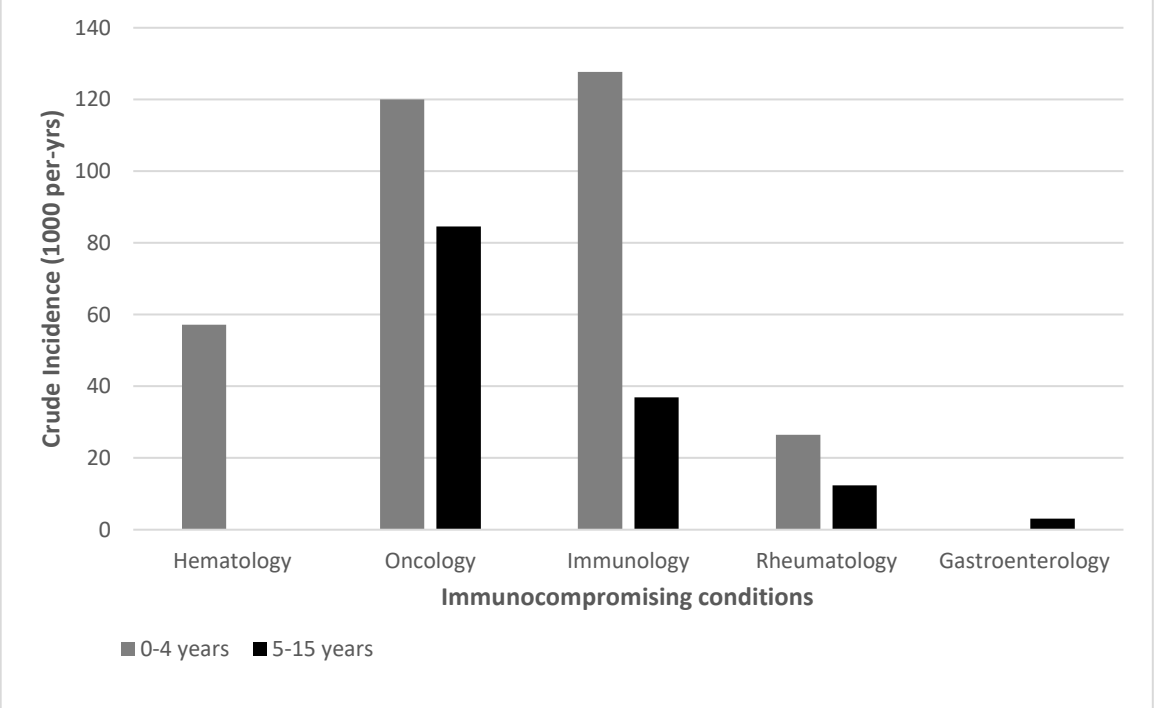


Figure 5-2-4: Crude incidence of definite LRTI hospitalizations by age at diagnosis and type of different immunocompromising conditions

The incidence proportion of definite LRTI hospitalizations for the overall study cohort was relatively higher in the younger group of children < 5 years (25.9%) compared to the older group (8.8%). There was also a similar trend of relatively higher incidence proportions in children < 5 years across all subgroups of immunocompromising conditions.

The crude incidence rates of definite LRTI hospitalizations among all immunocompromised children at ages < 5 years and 5-15 years were 77.4 and 31.5 per 1,000 person-years respectively. On subgroup analysis by age and type of immunocompromising conditions, we found that crude incidence rates were similarly higher among younger children < 5 years, compared to the older group in all subgroups except immunological disorders. Among children with immunological disorders, the crude incidence rate was 36.9 per 1,000 person-years in the younger group, versus 127.7 per 1,000 person-years in the older group. We found that immunology patients in the older category had the highest crude incidence of LRTI hospitalizations, whereas, oncology patients had the highest crude incidence in the younger category (120.0 per 1,000 person-years). The crude incidence rate was the lowest among gastrointestinal patients in both younger and older age groups, compared to other subgroups.

Table 5-2-3 reports the incidence of definite LRTI hospitalizations in the study cohort categorized by gender and type of immunocompromising conditions.

Table 5-2-3: Incidence rates of definite LRTI hospitalizations by gender and type of immunocompromising conditions

Gender	Total # LRTI Hosp	Total # children	Total person-years	Incidence proportion (%)	Crude Incidence per 1,000 person-years (95% CI)
Overall					
Male	61	319	932.4	**19.1**	**65.4** (50.9 - 84.1)
Female	40	321	993.8	**12.5**	**40.2** (29.5 - 54.9)
Hematology					
Male	*	*	*	**11.8**	**44.0** (11.1 - 17.6)
Female	*	*	*	**14.3**	**50.5** (12.6 - 202.0)
Oncology					
Male	42	146	298	**28.8**	**140.9** (104.2 - 190.7)
Female	20	133	302.3	**15**	**66.2** (42.7 - 102.5)
Immunology					
Male	13	44	141.6	**29.6**	**91.8** (53.3 - 158.1)
Female	9	31	107.7	**29**	**83.6** (43.5 - 160.7)
Rheumatology					
Male	4	52	230.8	**7.7**	**17.3** (6.5 - 46.2)
Female	8	7	393.2	**8**	**20.3** (10.2 - 40.7)
GI					
Male	0	60	216.7	**0**	**0**
Female	*	*	*	**2.2**	**6.6** (0.9 - 47.0)

* denotes cell size < 5
CI = Confidence interval, GI = Gastroenterology

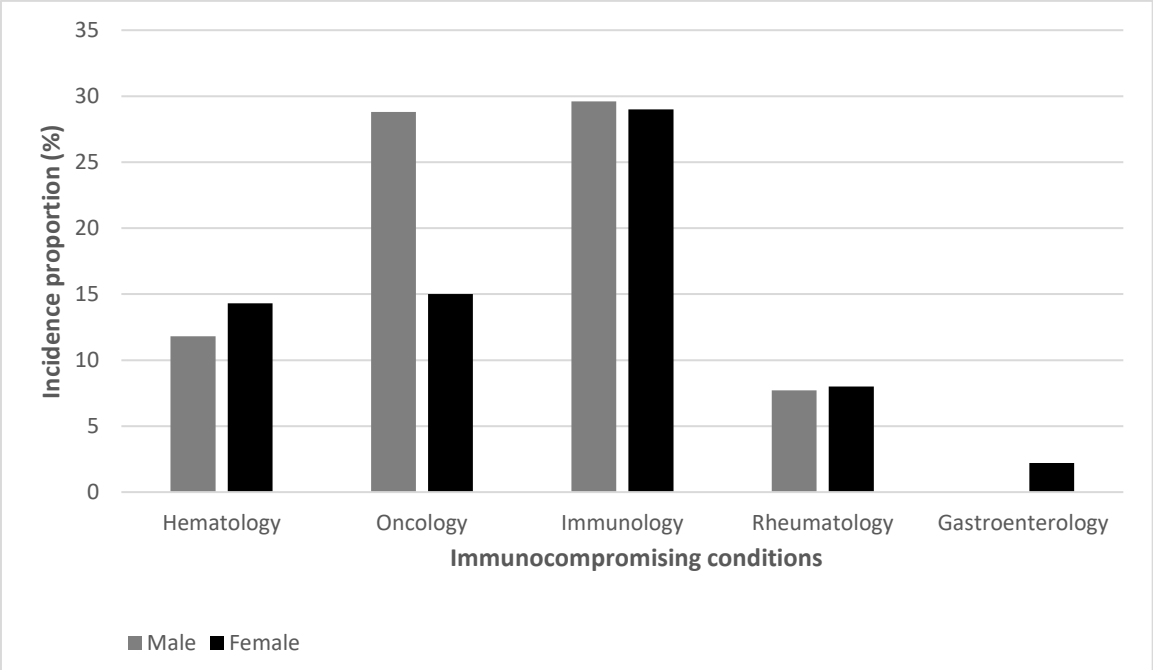


Figure 5-2-5: Incidence proportion of definite LRTI hospitalizations by gender and type of different immunocompromising conditions

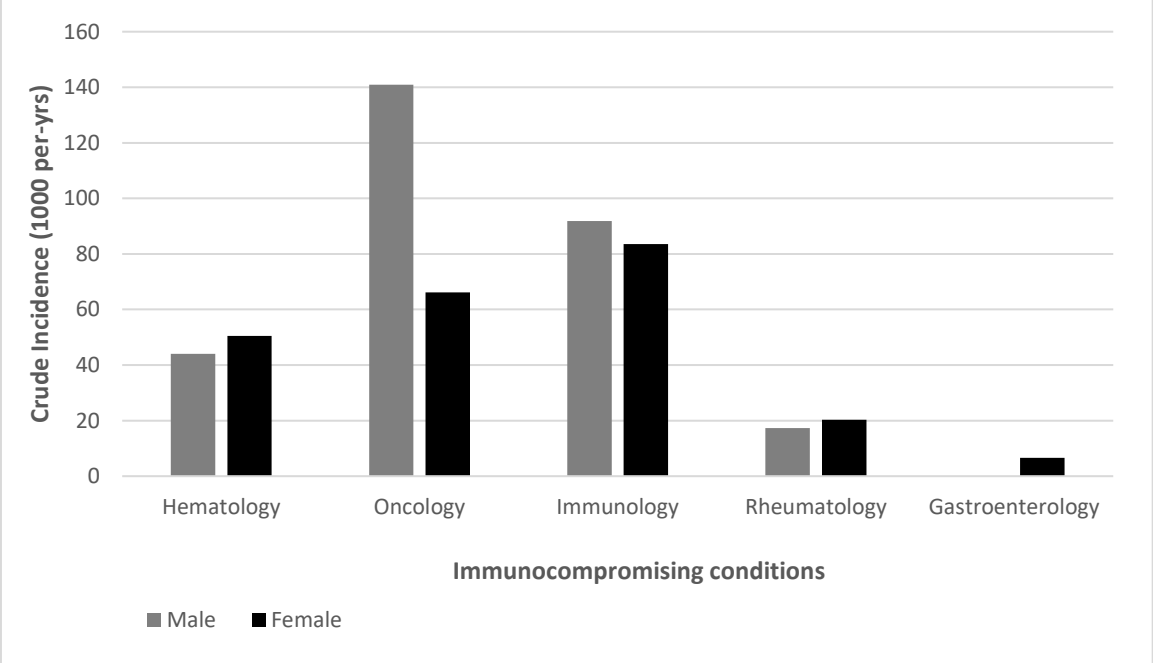


Figure 5-2-6: Crude incidence of definite LRTI hospitalizations by gender and type of different immunocompromising conditions

The incidence proportion of definite LRTI hospitalizations for the overall study cohort was higher in males (19.1%) compared to females (12.5%). On subgroup analysis, we found that the incidence proportion was approximately two times higher in males than females among children with oncological disorders. However, the incidence proportion was higher in females among children with hematological, rheumatological and gastrointestinal disorders. Similarly, we found that the crude incidence for definite LRTI hospitalizations was higher in males than females in the overall study cohort (65.4 vs 40.2 per 1,000 person-years) although there was an overlap in the confidence interval between the two groups. On subgroup analysis, the crude incidence rates were also higher in males for oncological disorders with no overlap of confidence intervals. However, we found that the crude incidence rates were generally higher in females for the remaining groups of hematological, rheumatological and gastrointestinal disorders with an overlap in confidence interval.

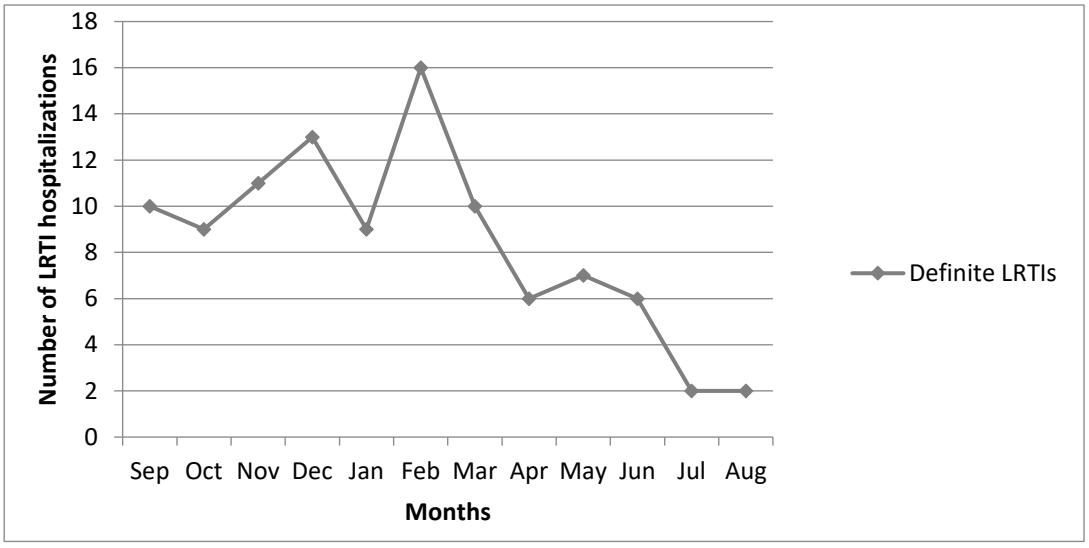
Table 5-2-4 shows the proportion of nosocomially acquired LRTI hospitalizations in immunocompromised children in our study. We found that a majority of LRTI hospitalizations among immunocompromised children were due to community acquired infections (80.2%), while the remaining LRTIs were nosocomially acquired. On subgroup analysis, nosocomial LRTIs were found in only 19.4% and 13.6% of oncology and immunology patients respectively. There were minimal cases of nosocomial LRTIs in each of the rheumatology and gastroenterology group, while there was none in the hematology group. There were missing information about health-care associated LRTI hospitalizations in 4 study patients.

Table 5-2-4: Nosocomially acquired definite LRTI hospitalizations in immunocompromised children

	Overall	Heme	Onc	Immuno	Rheum	GI
Health-care associated LRTIs						
Yes	16 (15.8%)	*	12 (19.4%)	*	*	*
No	81 (80.2%)	*	48 (77.4%)	19 (86.4%)	10 (83.3%)	*
Unknown	*	*	*	*	*	*

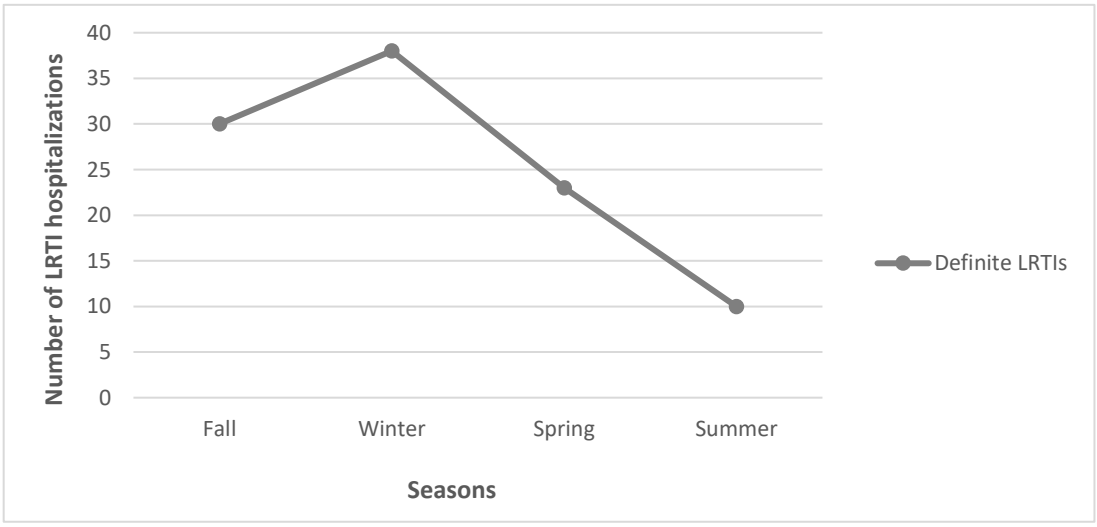
* denotes cell size < 5
LRTI = Lower respiratory tract infection, GI = Gastroenterology

Figure 5-2-6 and Figure 5-2-7 illustrate the seasonality of definite LRTI hospitalizations amongst immunocompromised children by month and season respectively. We found that there were relatively higher numbers of definite LRTI hospitalizations among immunocompromised children in the fall and winter seasons (between November and March), peaking in the month of February.



LRTI = Lower respiratory tract infection

Figure 5-2-7: Seasonality of definite LRTI hospitalizations (by month), 2004-2014



LRTI = Lower respiratory tract infection

Figure 5-2-8: Seasonality of definite LRTI hospitalizations (by season), 2004-2014

5.3. Objective 2: To Describe the Microbiological Etiologies and Clinical burden of LRTI Hospitalizations in Immunocompromised Children

Specimens were typically collected among immunocompromised pediatric patients during LRTI hospitalizations to conduct laboratory tests such as respiratory viral panels, blood and body fluid cultures and biopsies. We reported the microbiological etiology of definite LRTI hospitalizations in immunocompromised children. We found that 94.1% of the study cohort who were hospitalized with LRTIs had specimens collected for laboratory tests to determine the microbiological etiology. Table 5-3-1 reports the microbiological etiology of definite LRTI hospitalizations in all immunocompromised children in the study.

Among 95 completed microbiological tests, 48.5% were positive for microbiological pathogens. A majority of the microbiological tests were positive for respiratory viruses in 36 patients, followed by bacteria and fungi. Among 36 children detected with respiratory viruses, RSV was the most common, followed by influenza viruses, rhinovirus, parainfluenza viruses, human metapneumovirus, bocavirus and coronavirus. Bacterial pathogens led to definite LRTI hospitalizations among 13 study subjects and the most common ones were as follows in descending order: *Mycoplasma pneumoniae, Staphylococcus aureus, Haemophilus influenzae* and *Streptococcus pneumoniae*. There were 5 patients in the study who were positive for fungal agents namely Candida albicans and Pneumocystic jiroveci.

We also explored the microbiological etiology of definite LRTI hospitalizations in different subgroups immunocompromising conditions, and we found similar trends as the overall cohort. The proportion of positive microbiological tests among children with hematological, oncological, rheumatological and immunological disorders were 25%, 40.3%, 58.3% and 68.2% respectively. Most of the patients with oncological and immunological disorders were also found to be tested positive for respiratory viruses especially RSV and influenza viruses. Of note, all 5 cases of respiratory viruses among rheumatology patients were influenza viruses but not RSV. The most common bacterial agents detected in oncology patients who had LRTI hospitalizations were *Mycoplasma pneumoniae* and *Staphylococcus aureus.* We also found that a majority of fungal

pathogens such as Candida albicans and Pneumocystic jiroveci were detected in immunology patients. The only patient with gastrointestinal disorder who developed LRTI hospitalization was tested positive for *Mycoplasma pneumoniae*.

There were co-infections with multiple microbiological pathogens in 13.9% of the study cohort hospitalized with definite LRTIs, most of whom were immunology and oncology patients. In our study, there were less than 5 children in each category of viral-viral, viral-bacterial and bacteria-fungal co-infections. A majority of the microbiological co-infections occurred in children with oncological and immunological disorders. On subgroup analysis, co-infections were found in only 8% of oncology patients. On the other hand, we found relatively high proportions of co-infections (9.2%) among immunology patients. There were minimal co-infections in the rheumatology group and none among the hematology and gastroenterology groups hospitalized with definite LRTIs. We could not find information about co-infections in the charts of 6 patients who had definite LRTI hospitalizations.

Table 5-3-1: Microbiological etiology of definite LRTI hospitalizations

	Overall (n=101)	**Heme** (n=*)	**Onc** (n=62)	**Immuno** (n=22)	**Rheum** (n=12)	**GI** (n=*)
Microbiological tests						
Positive	49 (48.5%)	*	25 (40.3%)	15 (68.2%)	7 (58.3%)	*
Viruses [a]	36	*	18 (72%)	12 (80%)	5 (71.4%)	-
RSV	16	*	9	6	-	-
Influenza	13	-	5	*	5	-
Parainfluenza	*	-	-	*	-	-
Rhinovirus	5	-	*	*	-	-
H. metapneumovirus	*	-	*	-	-	-
Bocavirus	*	-	*	-	-	-
Coronavirus	*	-	-	*	-	-
Bacteria[a]	13	-	8	*	*	*
Strep. Pneumoniae	*	-	-	*	-	-
H. influenzae	*	-	-	*	*	-
M. pneumoniae	6	-	*	-	*	*
Staph aureus	*	-	*	-	-	-
Others	*	-	*	-	-	-
Fungi[a]	5	-	*	*	-	-
Candida albicans	*	-	*	*	-	-
P. jiroveci	*	-	-	*	-	-
Negative	46 (45.5%)	*	33 (53.2%)	7 (31.8%)	*	-
Not completed	6 (5.9%)	*	*	-	*	-
Coinfections						
Not completed	87 (86.1%)	*	53 (85.5%)	20 (90.9%)	10 (83.3%)	*
Viral-viral	*	-	*	*	-	-
Viral-bacterial	*	-	*	*	*	-
Bacterial-fungal	*	-	*	-	-	-
Unknown	6 (5.9%)	*	*	-	*	-

* denotes cell size < 5

- nil value

[a] multiple microbial pathogens detected in several patients

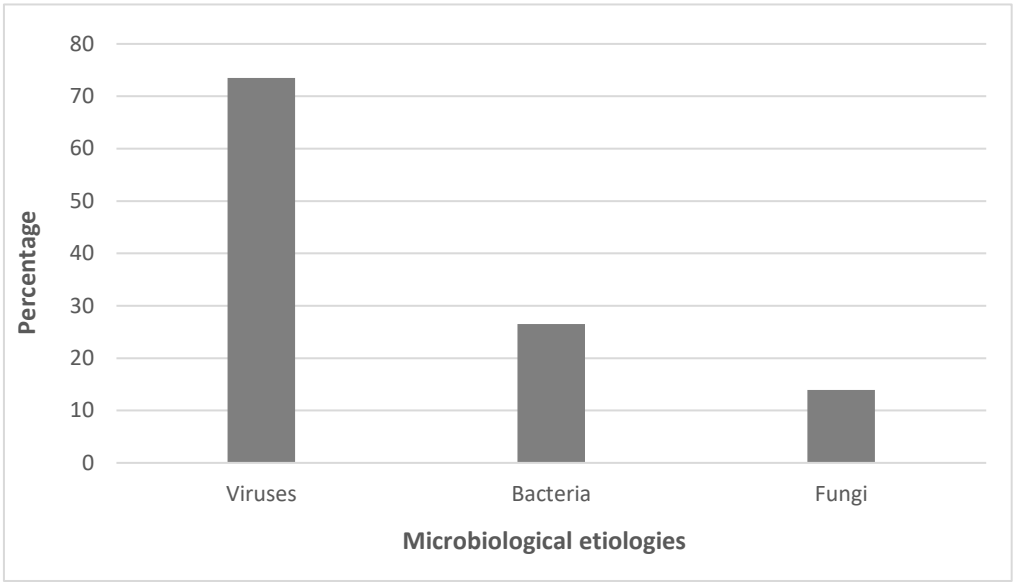
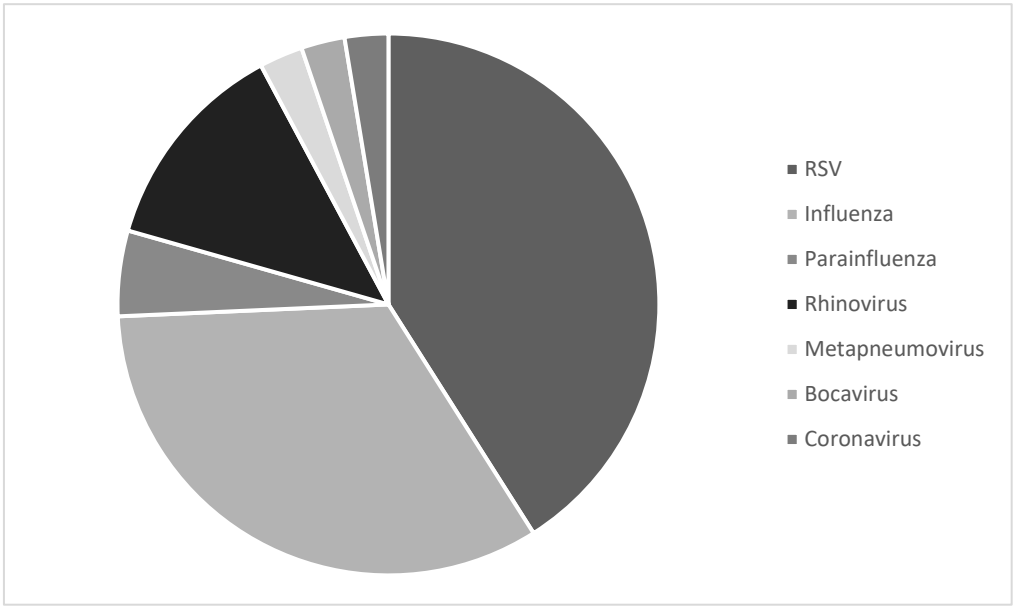


Figure 5-3-1: Microbiological etiology for definite LRTI hospitalizations with positive microbiological tests



Note: Percentages were omitted because some cell sizes were < 5

Figure 5-3-2: Proportion of definite LRTI hospitalizations caused by different viruses

We determined the clinical burden of both definite and possible LRTI hospitalizations. Table 5-3-2 shows the clinical burden of definite LRTI hospitalizations in the overall study cohort and different subgroups of immunocompromising conditions.

Table 5-3-2: Clinical burden of definite LRTI hospitalizations

Clinical Burden	**Overall** (n=101)	**Onc** (n=62)	**Immuno** (n=22)	**Rheum** (n=12)
Oxygen supplementation	31 (30.7%)	18 (29.0%)	10 (45.5%)	*
CPAP	9 (8.9%)	5 (8.1%)	*	-
ICU admission	8 (7.9%)	*	*	*
Mechanical ventilation	*	*	*	-
Mortality due to LRTIs	*	*	-	-
Duration of hospitalizations [a]	5 (3-11)	5 (3-11)	5 (3-11)	3 (2-8)
Duration of oxygen supplementation [a]	6 (3-11)	5.5 (3-11)	6 (5-20)	5 (2-8)
Duration of ICU admission [a]	8.5 (3.5-12.5)	11 (5.5-16)	7 (3-13)	4 (2-7)
Duration of mechanic ventilation [a]	9 (2-12)	10.5 (9-12)	2 (1-5)	-

* denotes cell size < 5
[a] days (median)
Note: Hematology and GI groups were omitted because cell sizes were < 5
CPAP = Continuous positive airway pressure, ICU = Intensive care unit, LRTI = Lower respiratory infection

For definite LRTIs, the median duration of hospitalization in the overall study cohort was 5 days. Among all study patients who were hospitalized with definite LRTIs, 30.7% required oxygen supplementation, 8.9% required CPAP and 7.9% required ICU admission. Less than 5 study patients required mechanical ventilation. The median duration of oxygen supplementation, ICU admission and mechanical ventilation were 6 days, 8 days and 9 days respectively. There were less than 5 deaths in total, which was attributable to definite LRTI.

Additionally, the clinical burden of definite LRTI hospitalizations was determined among different subgroups of immunocompromised children with oncological, immunological and rheumatological disorders. However, the clinical burden was not reported for the hematology and gastroenterology subgroups due to small sample sizes (cell sizes < 5). Similarly, the median duration of hospitalization for definite LRTIs was

5 days for both oncological and immunological disorders and 3 days for rheumatological disorders. We found that greater proportions of children with immunological disorders required oxygen supplementation (45.5%), CPAP (13.6%) and ICU admission (13.6%) than those with oncological and rheumatological disorders. On the other hand, while most clinical burden measures were generally higher in children with immunological disorders, the duration of ICU admission was relatively longer in the oncology group, with the median of 11 days compared to 7 days in the immunology group. The oncology group was the only subgroup with mortality in the study.

Table 5-3-3: Clinical burden of possible LRTI hospitalizations

Clinical Burden	**Overall** (n=21)	**Onc** (n=13)
Oxygen supplementation	*	*
CPAP	*	*
ICU admission	*	*
Mechanical ventilation	*	*
Mortality due to LRTIs	-	-
Duration of hospitalization [a]	6 (4-10)	6 (6-10)
Duration of oxygen supplementation [a]	8.5 (3-14)	8.5 (3-14)
Duration of ICU admission [a]	1.5 (1-2)	1
Duration of mechanical ventilation [a]	1	1

* denotes cell size < 5
[a] days (median)
- denotes nil value
Note: Hematology, immunology, rheumatology and GI groups were omitted because cell sizes were < 5
CPAP = Continuous positive airway pressure, ICU = Intensive care unit, LRTI = Lower respiratory tract infection

In addition, we also determined the clinical burden of possible LRTI hospitalizations among immunocompromised children in the study. Table 5-3-3 shows the clinical burden of possible LRTI hospitalizations in the overall study cohort, together with the subgroup of children with oncological disorders. The remaining subgroups of immunocompromising disorders were not included due to small sample sizes < 5.

The median duration of hospitalization for possible LRTIs was 6 days, which was similar to that of definite LRTI hospitalizations (5 days). Among patients who were

hospitalized with possible LRTIs, 9.5% required oxygen supplementation, 4.8% required CPAP, 9.5% required ICU admission and 4.8% required mechanical ventilation. The median duration of oxygen supplementation and ICU admissions were 9 days and 2 days respectively.

Table 5-3-4: Clinical burden of definite RSV LRTI hospitalizations

Clinical Burden	Overall (n=16)	Onc (n=9)	Immuno (n=6)
Duration of hospitalization [a]	5 (3-9.5)	4 (3-5)	6 (3-17)
Duration of oxygen supplementation [a]	11 (5-20)	11	12.5 (5-20)

[a] days (median)
Note: Hematology, rheumatology and GI groups were omitted because cell sizes were < 5

Table 5-3-5: Clinical burden of definite influenza LRTI hospitalizations

Clinical Burden	Overall (n=13)	Onc (n=5)
Duration of hospitalization [a]	5 (2-10)	14 (10-26)
Duration of oxygen supplementation [a]	9 (5-16)	12.5 (9-16)

[a] days (median)
Note: Hematology, immunology, rheumatology and GI groups were omitted because cell sizes were < 5

Table 5-3-4 and 5-3-5 report the clinical burden of definite LRTI hospitalizations attributed by RSV and influenza viruses respectively. Approximately 18% and 23% of immunocompromised children who were hospitalized with definite RSV and influenza LRTIs required oxygen supplementation. Although the duration of hospitalization with RSV and influenza definite LRTIs (both 5 days) was similar to that of overall definite LRTIs, we found that the duration of oxygen supplementation was longer in hospitalization with RSV LRTIs (11 days) and influenza LRTIs (9 days), compared to that of all definite LRTI hospitalizations (6 days). We also noted that among children with oncological disorders who were hospitalized with influenza definite LRTIs, the duration of hospitalization (14 days) and oxygen supplementation (12.5 days) was lengthier compared to the immunology group (4 days and 5 days respectively).

5.4. Objective 3: To Determine the Association Between the Baseline Characteristics and LRTI Hospitalizations in Immunocompromised Children

Both univariate and multivariate analyses were performed to determine the association between the baseline characteristics and definite LRTI hospitalizations in immunocompromised children. The baseline characteristics include types of immunocompromising conditions, age at diagnosis with immunocompromising conditions, gender, ethnicity, status of household crowding and passive smoking. Two of the baseline characteristics namely ethnicity and passive smoking were not included in the multivariate analyses due to high numbers of missing values and were removed by the backward elimination method.

5.4.1. Univariate Analyses

5.4.1.1. *Logrank Tests*

Logrank tests were conducted on each baseline characteristics variable to determine if the difference in observed and expected outcome events in the independent categories within each variable were statistically significant. The results of univariate logrank tests and the summary of observed and expected outcome events for the baseline characteristics variables are shown in Table 5-4-1.

The following baseline characteristics variables have statistically significant differences between their independent categories for definite LRTI hospitalizations: types of immunocompromising conditions, age at diagnosis with immunocompromising conditions, gender, and status of household crowding. This suggested that the observed definite LRTI hospitalizations of the independent categories in these baseline characteristics variables were either higher or lower than the expected definite LRTI hospitalizations. On the other hand, we did not find any statistical significance between the independent categories for the remaining two baseline characteristics variables: ethnicity and passive smoking. This should be interpreted with caution as the non-significance could be contributed to large number of missing values in these variables.

Table 5-4-1: Univariate log-rank tests of various baseline sociodemographic variables associated with definite LRTI hospitalizations

Baseline sociodemographic variables	Events Observed	Events Expected	P-value
Type of immunocompromising conditions			
Rheumatology	12	27	**< 0.001**[a]
Hematology	*	*	
Oncology	62	38	
Immunology	22	12	
Gastroenterology	*	18	
Age			
5-15 years	33	58	**< 0.001**[a]
0-4 years	68	42	
Gender			
Male	61	49	**0.018**[a]
Female	40	51	
Status of household crowding			
No	72	62	**0.043**[a]
Yes	22	22	
Unknown	7	15	
Ethnicity			
White	*	*	0.756
Black	*	*	
Asian	*	*	
Indigenous	*	*	
Mixed	*	*	
Unknown	91	93	
Passive smoking			
No	14	11	0.453
Yes	11	8	
Unknown	76	80	

* denotes cell size < 5

[a] p-value < 0.05 (statistically significant)

5.4.1.2. Kaplan-Meier Curves

Figure 5-4-1 shows the Kaplan-Meier curves for the different types of immunocompromising conditions associated with definite LRTI hospitalizations. The p-value from the univariate log-rank test was lower than 0.05, which showed that there was statistically significant difference in developing the outcome event (i.e. definite LRTI hospitalizations) between the different types of immunocompromising conditions. The survival probability (i.e. probability of surviving and not developing definite LRTI hospitalizations) was lower in oncology and immunology groups compared to hematology, rheumatology and gastroenterology groups. In oncology and immunology groups, the survival probability was approximately 0.6 and most patients had definite LRTI hospitalizations within the first 6 months of diagnosis with immunocompromising disorders. The survival probability was higher in the hematology group (approximately 0.8). The survival probability among children in the rheumatology and gastroenterology groups remains relatively steady and unchanged over time, indicating that LRTI are not a frequent occurrence.

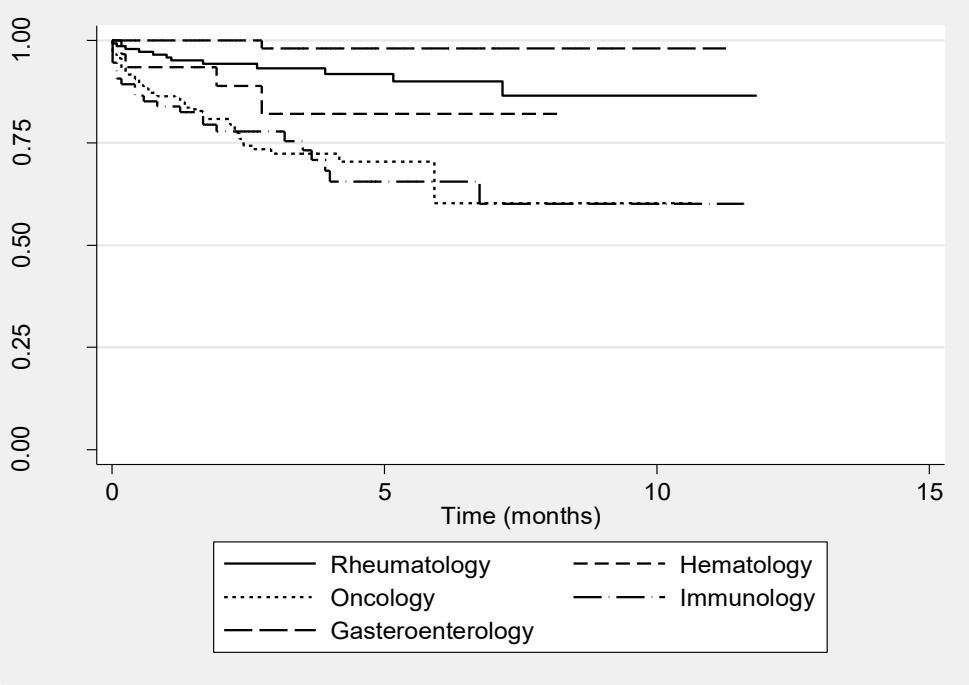


Figure 5-4-1: Kaplan-Meier curves of definite LRTI hospitalizations by type of immunocompromising conditions

Figure 5-4-2 shows the Kaplan-Meier curves of definite LRTI hospitalizations stratified by age at diagnosis with immunocompromising conditions. The p-value from the log-rank test was lower than 0.05, which showed that there was statistically significant difference in developing LRTI hospitalizations between the two age groups. We found that the survival probability (i.e. the probability of surviving and not developing definite LRTI hospitalizations) in children under the age of 5 years was approximately 0.6, which was lower compared to the older age group. Hence, children under the age of 5 years have higher risk of definite LRTI hospitalizations compared those above the age of 5 years.

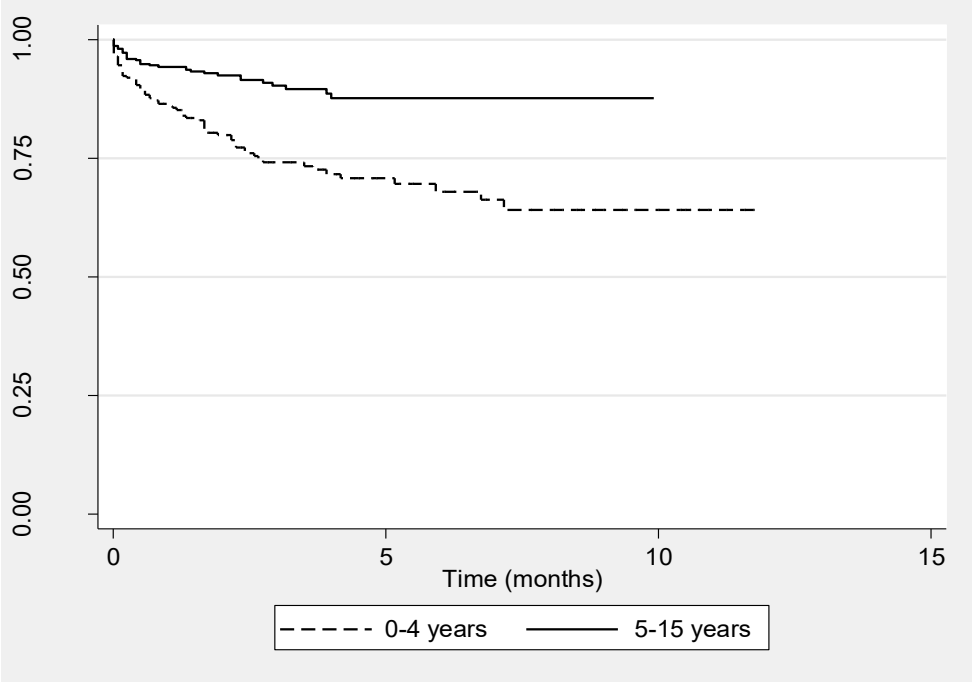


Figure 5-4-2: Kaplan-Meier curves of definite LRTI hospitalizations by age at diagnosis with immunocompromising conditions

Figure 5-4-3 shows the Kaplan-Meier curves of definite LRTI hospitalizations stratified by gender. The p-value from the log-rank test was lower than 0.05, which showed that there was statistically significant difference in developing definite LRTI hospitalizations between males and females. The survival probability (i.e. the probability of surviving and not developing definite LRTI hospitalizations) in males and female were approximately 0.7 and 0.8 respectively, which showed that males had higher risk of developing definite LRTI hospitalizations compared to females.

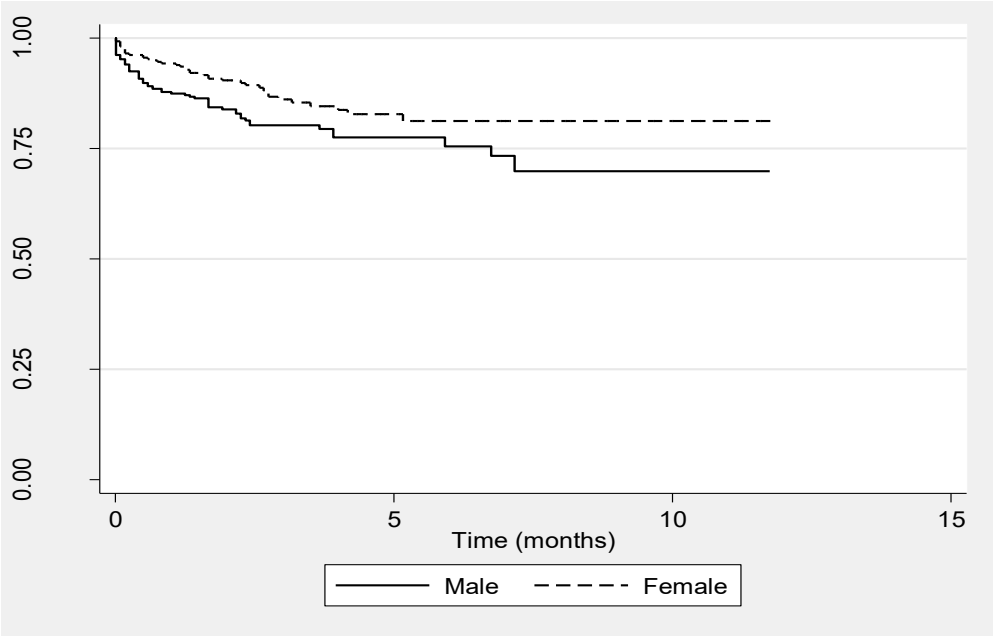


Figure 5-4-3: Kaplan-Meier curves of definite LRTI hospitalizations by gender

Figure 5-4-4 shows the Kaplan-Meier curves of definite LRTI hospitalizations stratified by the status of household crowding. According to the Kaplan-Meier curves, there seemed to be no obvious difference between the presence and absence of household crowding in the development of definite LRTI hospitalizations. However, the p-value of < 0.05 established by the log-rank test was possibly contributed to the statistically significant difference between the category of missing values (i.e. Unknown) and the other two categories (i.e. presence and absence of household crowding).

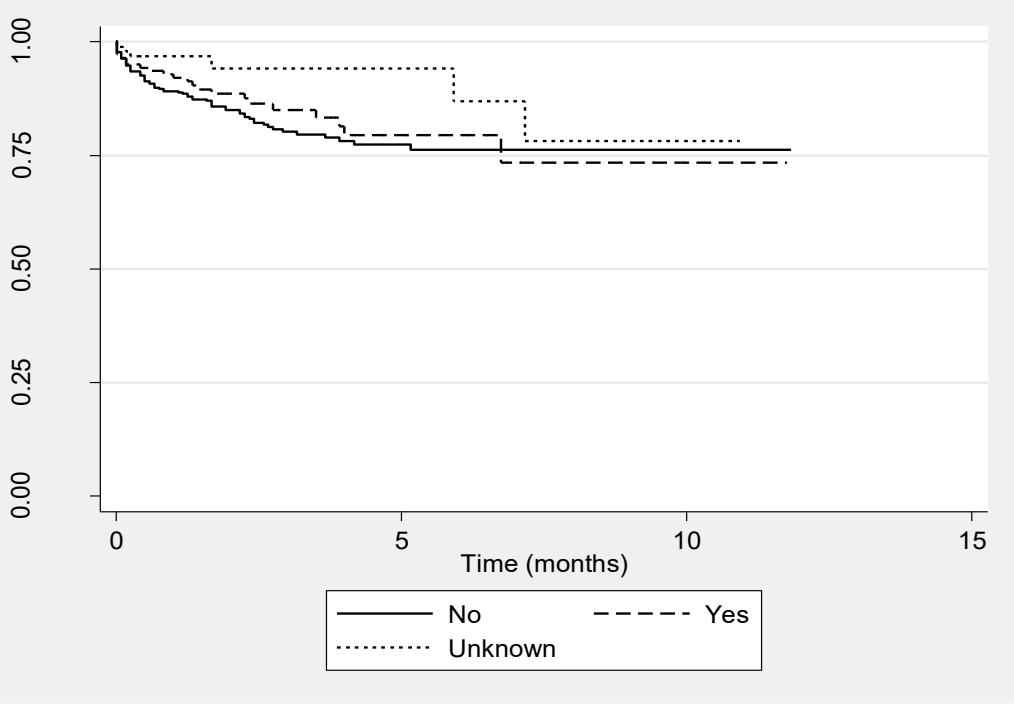


Figure 5-4-4: Kaplan-Meier curves of definite LRTI hospitalizations by status of household crowding

Figure 5-4-5 and Figure 5-4-6 show the Kaplan-Meier curves of definite LRTI hospitalizations stratified by ethnicity and the status of passive smoking respectively. The log-rank tests report p-values of greater than 0.05 for both abovementioned baseline characteristics variables and hence, there were no statistically significant differences in developing definite LRTI hospitalizations between the sub-categories in these variables. However, the Kaplan-Meier curves associated with them should be interpreted with caution as high numbers of missing values in variables could result in biased results and lead to inaccurate conclusions.

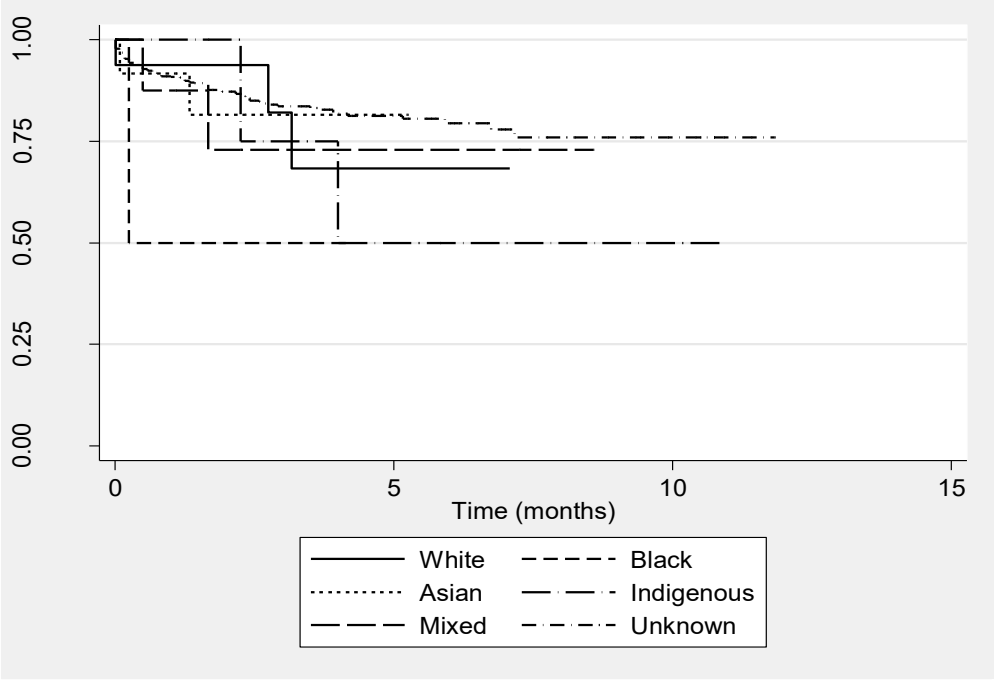


Figure 5-4-5: Kaplan-Meier curves of definite LRTI hospitalizations by ethnicity

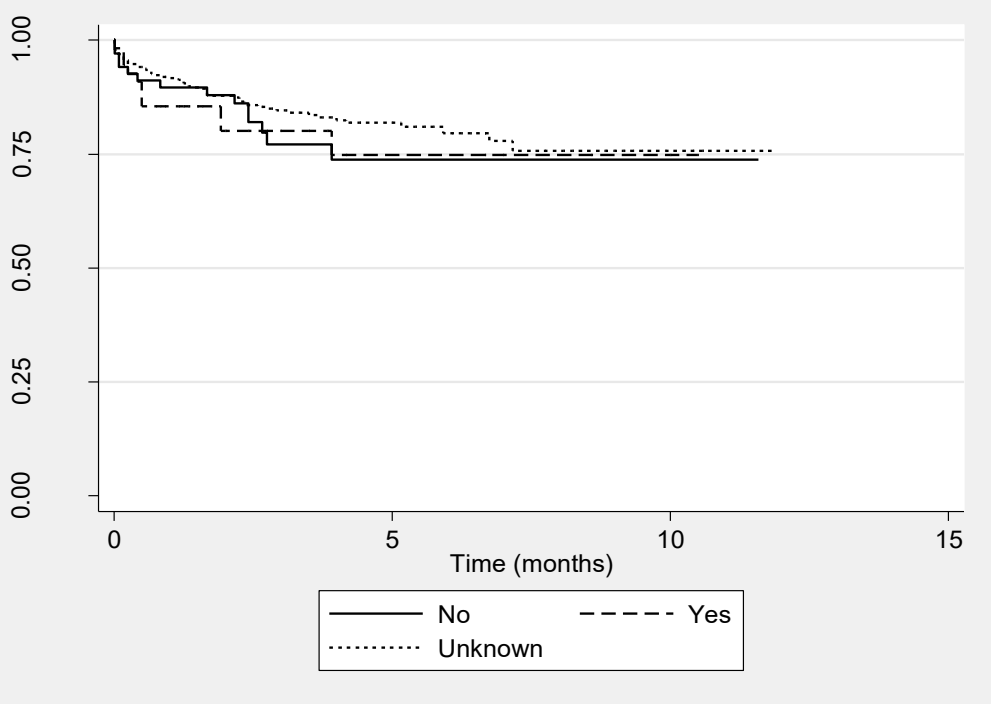


Figure 5-4-6: Kaplan-Meier curves of definite LRTI hospitalizations by status of passive smoking

5.4.2. Cox Proportional Hazard Regression Model

Using both univariate and multivariate Cox proportional hazard models, hazard ratios for definite LRTI hospitalizations for the baseline characteristics variables were attained. The following referent groups were used in all analyses: rheumatology patients, children above the age of 5 years, males and patients from smaller households with less than 5 members.

Table 5-4-2 and Figure 5-4-7 illustrate the hazard ratios of definite LRTI hospitalizations and 95% confidence intervals for each of the baseline characteristics variables using the univariate Cox proportional hazard model.

The oncology (HR 3.92) and immunology (HR 4.17) groups had statistically significant hazard ratios in comparison with the referent rheumatology group and as a result, they were more likely to develop definite LRTI hospitalizations compared to the rheumatology patients. Hematology patients had a hazard ratio above one (HR 1.95), but there was no statistical significance. On the other hand, children with gastrointestinal disorders had a statistically significant hazard ratio of 0.13 and hence, they were less likely to develop definite LRTI hospitalizations. Secondly, younger children had a statistically significant hazard ratio of 2.85 and hence they were more likely to develop the outcome event compared to their older counterparts. We also found that females had a statistically significant hazard ratio (0.63) and were less likely to develop definite LRTI hospitalizations than males. Lastly, there was no statistically significant difference between the groups in the status of household crowding.

Table 5-4-3 and Figure 5-4-8 illustrates the hazard ratios for definite LRTI hospitalizations, their p-values and 95% confidence intervals for each of the baseline characteristics variables using the multivariate Cox proportional model. With the multivariate model, we can explore the hazard ratio of individual predictor baseline characteristics variable while adjusting other potentially confounding independent variables.

The hazard ratios for definite LRTI hospitalizations were 0.16, 1.35, 3.32 and 3.50 in gastroenterology, hematology, immunology, and oncology groups, compared to the referent rheumatology group respectively. We only found statistical significance in

the oncology and immunology groups. Secondly, the hazard rate of children under the age of 5 years developing definite LRTI hospitalizations was approximately 2 times higher than that of older children, with a significant p-value. Moreover, females are less likely to develop definite LRTI hospitalizations than males, with a statistically significant multivariate Cox proportional hazard ratio of 0.65. We found no statistically significant difference (with a multivariate hazard ratio of 1.0) for developing definite LRTI hospitalizations between the different subgroups in the status of household crowding.

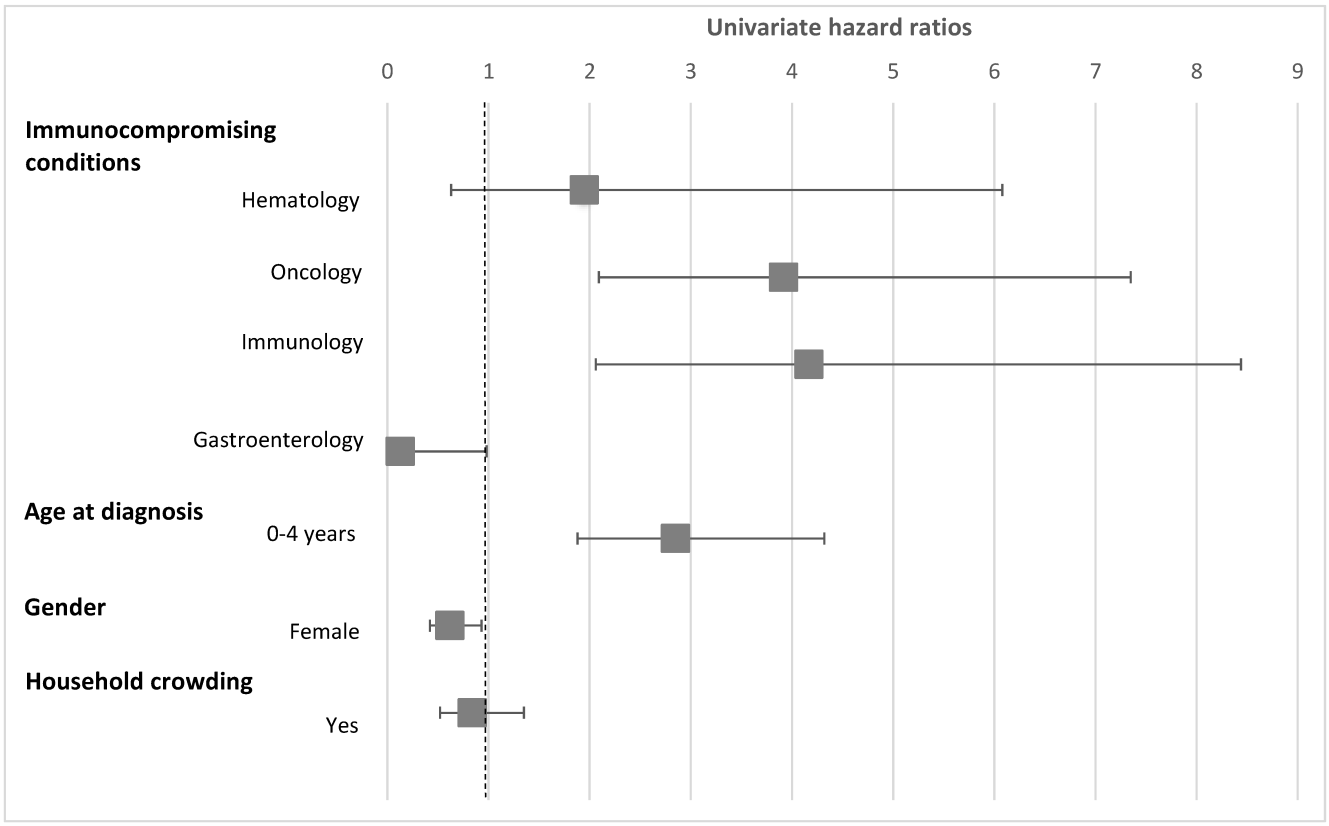
5.4.3. Testing of the Assumption of Cox Proportional Model

Using *stphplot* and *stcoxkm* graphical analytical methods, we evaluated the assumption of proportionality underlying the Cox hazard model used for our baseline characteristic variable, i.e. type of immunocompromising conditions. The *stphplot* graph (Figure 5-4-9) showed that there was near parallelism between the curves of each category for the variable. Additionally, *stcoxkm* graph (Figure 5-4-10) portrayed that the Kaplan-Meier observed survival curves were all similar with their respective Cox predicted curves for the variable. Hence, we could deduce that there were no major violations with the assumption of proportionality with the log rank test and Cox proportional hazard model.

Table 5-4-2: Univariate Cox proportional hazard ratios for definite LRTI hospitalizations by baseline characteristics variables

Baseline characteristics variables	Coefficient	95% CI	Hazard Ratio	95% CI
Type of immunocompromising conditions				
Rheumatology (referent)	-	--	1	--
Hematology	0.67	-0.46 - 1.81	1.95	0.63 - 6.08
Oncology	1.37	0.74 - 1.99	3.92	2.09 - 7.35
Immunology	1.43	0.72 - 2.13	4.17	2.06 - 8.44
Gastroenterology	-2.06	-4.1 - -0.02	0.13	0.02 - 0.98
Age at diagnosis				
5-15 years (referent)	-		1	--
0-4 years	1.05	0.63 - 1.46	2.85	1.88 - 4.32
Gender				
Male (referent)	-	--	1	--
Female	-0.48	-0.87 - - 0.08	0.62	0.42 - 0.93
Status of household crowding				
No (referent)	-	--	1	--
Yes	-0.18	-0.66 - 0.30	0.84	0.52 - 1.35
Unknown	-0.95	-1.72 - -0.17	0.39	0.18 - 0.84
Ethnicity				
White (referent)	-	--	1	--
Black	1.15	-1.11 - 3.42	3.17	0.33 - 30.53
Asian	0.13	-1.66 - 1.93	1.14	0.19 - 6.86
Indigenous	0.23	-1.56 - 2.02	1.25	0.21 - 7.5
Mixed	0.19	-1.6 - 1.98	1.21	0.2 - 7.22
Unknown	-0.16	-1.31 - 0.99	0.85	0.27 - 2.70
Passive smoking				
No (referent)	-	--	1	--
Yes	0.06	-0.73 - 0.85	1.06	0.48 - 2.34
Unknown	-0.26	-0.83 - 0.31	0.77	0.44 - 1.36

CI = Confidence interval



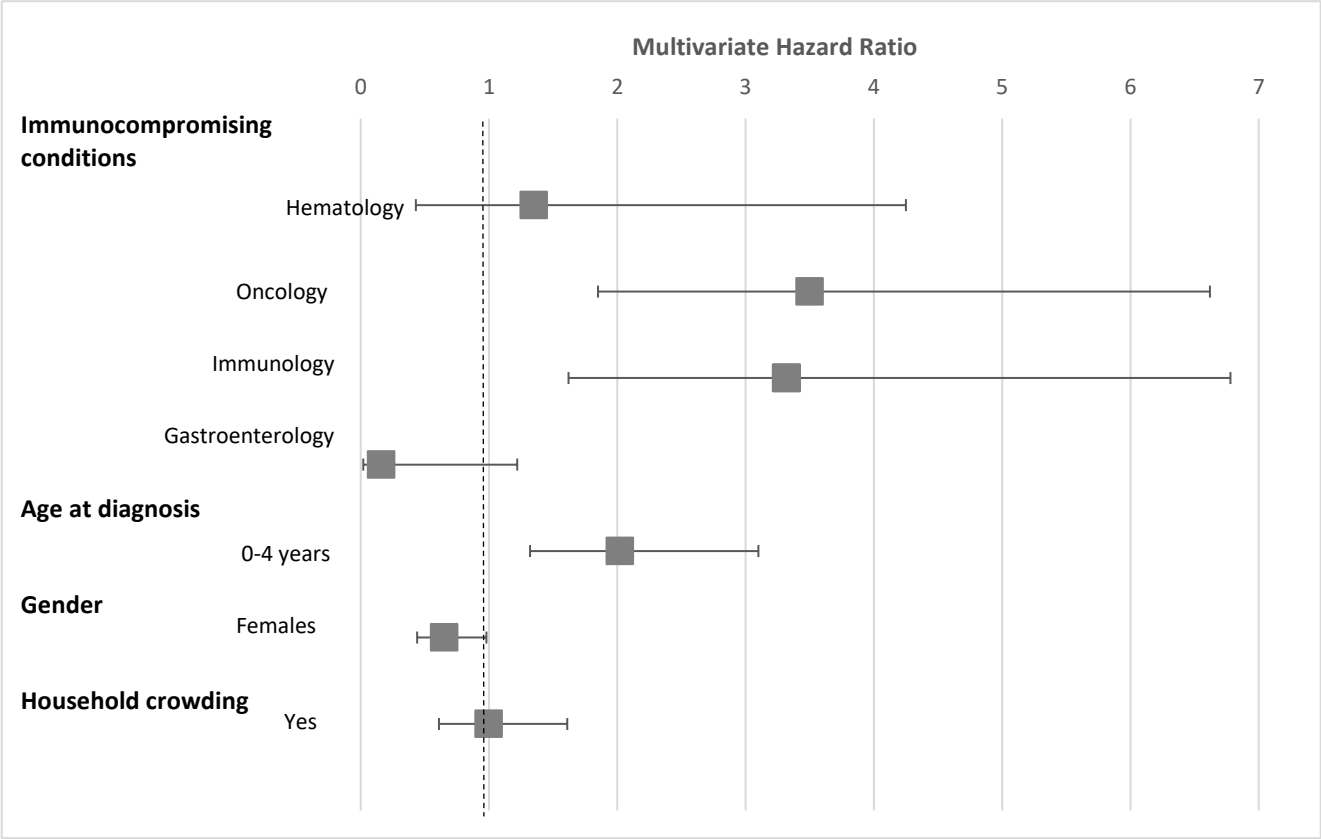
Note: Type of immunocompromising conditions: Rheumatology (referent group)
Age at diagnosis: 5-15 years (referent group)
Gender: Male (referent group)
Household crowding: No (referent group)
Small boxes indicate hazard ratios and horizontal lines indicate 95% confidence intervals.

Figure 5-4-7: Univariate Cox proportional hazard ratios for definite LRTI hospitalizations by baseline characteristics variables

Table 5-4-3: Multivariate Cox proportional hazard ratios for definite LRTI hospitalizations by baseline characteristics variables

Baseline characteristics variable	Coefficient	95% CI	Hazard Ratio	95% CI
Type of immunocompromising conditions				
Rheumatology (referent)	-	--	1	--
Hematology	0.3	-0.85 - 1.45	1.35	0.43 - 4.25
Oncology	1.25	0.62 - 1.89	3.50	1.85 - 6.62
Immunology	1.20	0.48 - 1.91	3.32	1.62 - 6.78
Gastroenterology	-1.85	-3.9 - 0.20	0.16	0.02 - 1.22
Age at diagnosis				
5-15 years (referent)	-	--	1	--
0-4 years	0.70	0.28 - 1.13	2.02	1.32 - 3.10
Gender				
Male (referent)	-	--	1	--
Female	-0.43	-0.83 - -0.02	0.65	0.44 - 0.98
Status of household crowding				
No (referent)	-	--	1	--
Yes	0.004	-0.48 - 0.49	0.996	0.61 - 1.61
Unknown	-0.86	-1.64 - -0.08	0.42	0.18 - 0.99

CI = Confidence interval



Note: Type of immunocompromising conditions: Rheumatology (referent group)
Age at diagnosis: 5-15 years (referent group)
Gender: Male (referent group)
Household crowding: No (referent group)
Small boxes indicate hazard ratios and horizontal lines indicate 95% confidence intervals.

Figure 5-4-8: Multivariate hazard ratios for definite LRTI hospitalizations by baseline characteristic variables

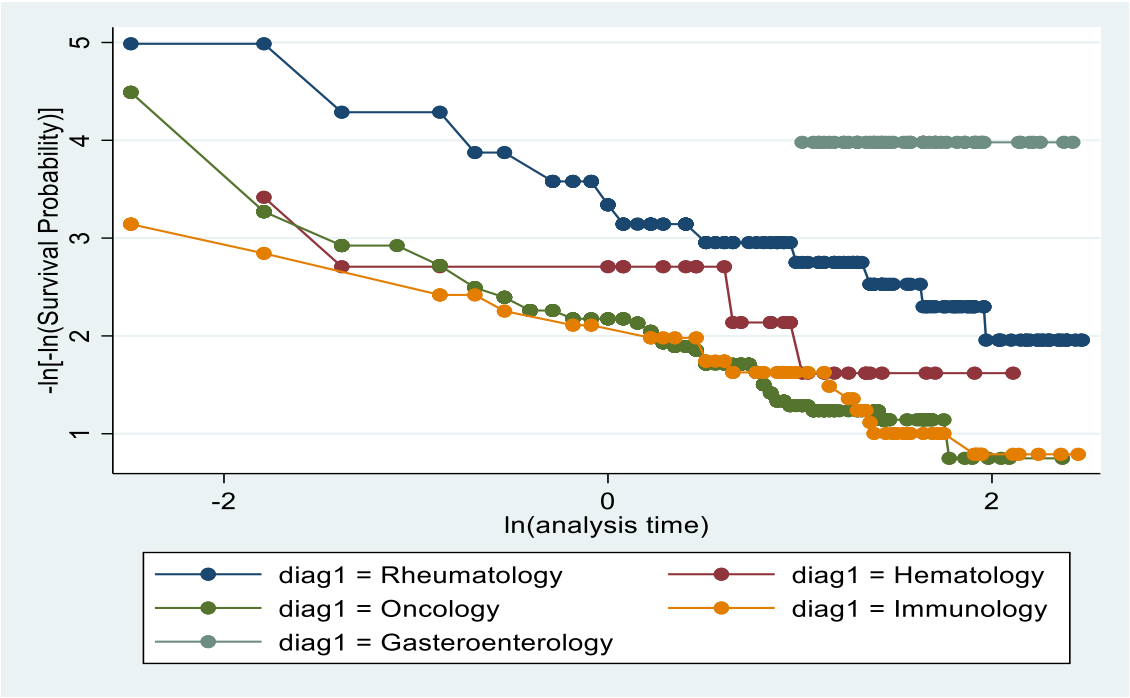


Figure 5-4-9: *Stphplot* of Kaplan-Meier survival function of definite LRTI hospitalizations by type of immunocompromising conditions

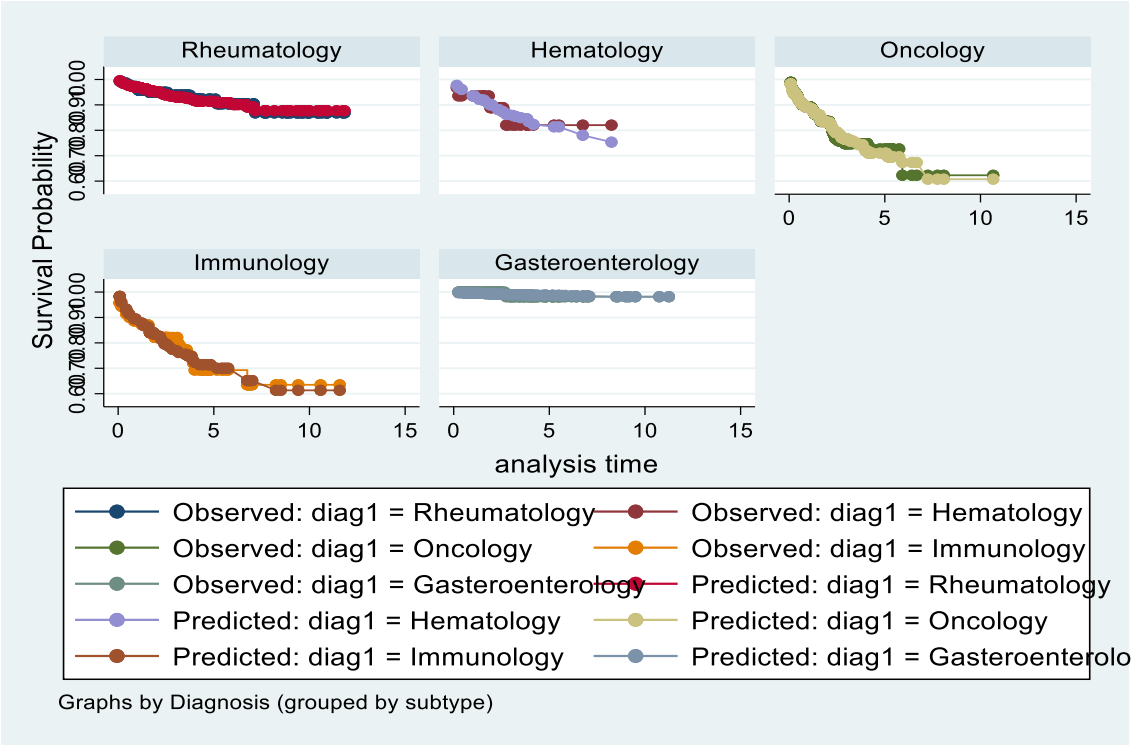


Figure 5-4-10: *Stcoxkm* of Kaplan Meier observed and Cox predicted curves of definite LRTI hospitalizations by type of immunocompromising conditions

CHAPTER 6: DISCUSSION

It has been hypothesized that LRTIs are common among immunocompromised children, however there are limited studies in the current literature on this topic. The principal objectives of our study were to determine the (1) incidence, (2) microbiological etiologies and clinical burden and (3) baseline characteristics associated with LRTI hospitalizations among immunocompromised children. In this chapter, our study results reported in the previous section are discussed and critically appraised in details. The study's strengths and limitations are reviewed at length. Moreover, we discuss the implications of our study results to clinical practice and how they could contribute to the management of LRTIs among immunocompromised children, and perhaps even lead to the development of new guidelines and protocols.

In our study, a total of 640 children diagnosed with different immunocompromising conditions in Nova Scotia were followed until the outcome event (definite LRTI hospitalizations), end of the immunocompromised status, or end of the study period, whichever comes first. The most common immunocompromising conditions in our study were oncological disorders, followed by rheumatological, gastrointestinal, immunological and hematological disorders. This was similar to the cross-sectional study conducted in Isfahan, Iran that reported immunological disorders, hematological malignancies (i.e. ALL, AML and Hodgkin's lymphoma) and solid cancers as the most common conditions. (81)

Our study reported ALL, CNS tumors and neuroblastoma as the top three oncological disorders, which was consistent with the findings reported by the Canadian national data (i.e. leukemia, CNS tumors and lymphoma). Additionally, the most common immunological disorders found in our study were antibody defects, followed by CVID and SCID. Similarly, Jeffrey Modell Centers Network (JMCN) survey reported that antibody defects were the most common, followed by CVID, autoinflammatory disorders, and SCID. (82) The most prevalent rheumatological conditions in our study were JIA, enthesitis and dermatomyositis and our findings were comparable to Huemer et al. study, where JIA was found to be the most common rheumatological condition among Austrian children, followed by spondyloarthropathy and SLE. (83) Neutropenia and

aplastic anemia were the most frequently diagnosed hematological disorders in our study. Anemia (both iron deficiency and non-iron deficiency) is typically found to be the most common types of hematological conditions in general population, but they were not included in our study because they do not cause immunosuppression.

Although gender proportion was comparable for the overall study cohort, there were more males in all subgroups of immunocompromising disorders except the rheumatology subgroup. This finding was supported by prior studies in the adult population, which reported that the majority of patients affected with autoimmune rheumatological diseases are women (approximately 78%). (84) The exact reason for this unequal gender distribution is unclear but it could be hypothesized that women respond to stress events and infections with higher levels of T helper 2-predominant immune response and antibody production. (84) It could also be explained by males having a higher likelihood of certain X-linked recessive congenital immunodeficiency disorders. The genetic favorability towards males for certain hematological and oncological disorders could be contributed by a myriad of differences in hormones, chromosomes, immunity, and genome surveillance mechanisms. (79)

A majority of study patients came from households with less than 5 members. This was consistent with the findings from 2011 Canadian Census, which reported that the average number in a household in Nova Scotia and Canada were 2.3 and 2.5 persons respectively. The data on ethnicity and passive smoking were absent from most charts and could not be collected or analyzed appropriately. However, it could be assumed that most study patients were Caucasians, comparable to the actual Nova Scotia racial demographics. The 2015 Canadian Tobacco, Alcohol and Drugs survey reported that the prevalence of smoking was about 18% in Nova Scotia, compared to the national rate of 13%. (85)

6.1. Objective 1 Findings

For objective 1, we aimed to estimate the incidence of LRTI hospitalizations among immunocompromised children in Nova Scotia by using both incidence proportion and crude incidence of LRTI hospitalizations.

There were previous studies on the incidence of LRTIs among the healthy pediatric population. Griffin et al. study reported that the incidence of ARIs was 18 per 1,000 children among the cohort of healthy children followed by the New Vaccine Surveillance Network. (86) The incidence of pneumonia and influenza among healthy children reported by Harris et al. and Munoz et al. were 3.3 and 0.3-3 per 1,000 children respectively. (23,27) However, our study is the first in the literature that reported the incidence of LRTI hospitalizations among immunocompromised children.

The incidence proportion of definite LRTI hospitalizations among immunocompromised children in Nova Scotia over the 12-year study period was 15.8%. This is very much higher than the incidence of ARIs (i.e. pneumonia and influenza) among healthy children reported by Griffin et al., Harris et al. and Munoz et al. studies. (23,27,86) This was expected given the immunocompromised status of the patients in our study with decreased humoral and cellular immune responses to microbial pathogens and stress events, compared to the cohort of healthy children in other studies.

Our study reported a crude incidence rate of 52.4 per 1,000 person-years in the overall cohort. Previous studies in the literature mostly used incidence proportion, in contrast to crude incidence rate. Crude incidence rate is considered to be more precise than incidence proportion to describe the incidence of definite LRTI hospitalizations among immunocompromised children due to the nature of the study in which subjects were enrolled and followed for different periods of time until development of LRTI hospitalizations (with some loss to follow up).

Among different subtypes of immunocompromising disorders included in our study, incidence proportions range from 0.9% to 29.3% and crude incidence rates range from 2.7 to 103.3 per 1,000 person-years. The immense disparities in the values of incidence proportion and crude incidence of definite LRTI hospitalizations between each subgroup could be contributory to the varying level of immunosuppression from different immunocompromising disorders, and also the intensity of the cytotoxic and immunosuppressive regimens that patients were receiving.

In our study, patients with oncological disorders were most likely to develop definite LRTI hospitalizations with incidence proportion and crude incidence rates of 22.2% and 103.3 per 1,000 person-years respectively. If patients with CNS tumors were

excluded from the overall oncology group, incidence proportion and crude incidence rates further increased to 26% and 129 per 1,000 person-time respectively. Multiple studies reported the prevalence of viral respiratory infections ranging from 50% to 86% among pediatric cancer patients. (110, 111, 112) The incidence rates reported in our study could be lower compared to other studies in the literature because only LRTI hospitalizations were included with our strict outcome definition criteria instead of all viral respiratory infections.

On the other hand, incidence proportion and crude incidence rates among children with only CNS tumors in our study were 4.2% and 14.8 per 1,000 person-years, which is similar to the values of immunocompetent children reported in Griffin et al. study. (86) This result could be explained by several reasons. Firstly, surgery and radiotherapy are the first lines of treatment for early stages of CNS tumors, which causes less systemic immunosuppression than chemotherapy. We could assume that the level of immunosuppression is reduced in these patients. However, a subset of very young children (i.e. < 3 years) with medulloblastoma or CNS tumors who require intensive chemotherapy protocols are expected to have severe immunosuppression. There were small numbers of this population in our study. The relatively low incidence in the subgroup of CNS tumors could therefore be contributed to the dilutional effect by the group that had surgery or radiotherapy.

The next highest incidence for definite LRTI hospitalizations was in the immunology group with the incidence proportion and crude incidence of 29.3% and 88.3 per 1,000 person-years respectively. The finding was supported by Jesenak et al. study where the occurrences of respiratory infections such as pneumonia were found to be relatively high among the pediatric population with immunological disorders, ranging between 37% and 90%. (88) This might be explained by the fact that patients with primary immunodeficiency disorders have defective innate and/or adaptive immune systems and hence, they are more at risk for infections, especially LRTIs.

We found that incidence proportion and crude incidence rates among children with hematological disorders were 12.9% and 47.1 per 1,000 person-years respectively. Renaud et al. study reported that the incidence of respiratory virus infections during post-HSCT period was found to be as high as 22% with significant morbidity and mortality.

(89) Hematological disorders such as aplastic anemia and bone marrow failure syndromes are associated with depletion of all cell lineages and eventually require HSCT during which patients are immunocompromised. Hence, they are more often at increased risk for infections especially acute respiratory infections, which ultimately progress to LRTIs.

Incidence proportion and crude incidence rates of definite LRTI hospitalizations in children with rheumatological conditions were 8.1% and 19.2 per 1,000 person-years respectively, which are relatively higher compared to healthy children. Similarly, Lee et al. reported that the crude incidence rate of hospitalizations associated with all serious infections for rheumatology patients on immunosuppressive medications was 27.2 per 1,000 person-years. (112) They also found that the median time to infection from the initial administration of immunosuppressive medications was approximately 90 days, with acute respiratory infections being the most common. (112) One of the possible reasons why these patients are more likely to develop LRTI hospitalizations is due to routine treatment with immunosuppressive biologic modifiers or steroids for their autoimmune conditions.

Children with gastrointestinal disorders had relatively lower absolute and crude incidence rates of definite LRTI hospitalizations (0.9% and 2.7 per 1,000 person-years respectively), which were comparable to that of healthy children. The reason contributing to the low incidence of definite LRTI hospitalizations among this population was unclear despite the fact that patients with gastrointestinal disorders were on biologic modifiers and corticosteroids and were possibly more immunocompromised than the general pediatric population. There is a lack of studies in the literature on the incidence of LRTI hospitalizations associated with gastroenterology patients on immunosuppressive regimens.

Additionally, the incidence of definite LRTI hospitalizations was categorized by the type of immunocompromising conditions and age at diagnosis with immunocompromising conditions. The incidence of definite LRTI hospitalizations was found to be higher in children diagnosed at less than the age of 5 years, compared to their old counterparts for most subgroups of immunocompromising conditions. Children diagnosed with oncological, immunological and rheumatological disorders under the age

of 5 years had incidence proportions that were 1.34, 2.83 and 4.46 times higher than their respective older groups. Our findings were supported by previous studies such as El Saleeby et al. study and Lee et al. study that reported that younger age was associated with LRTIs among cancer patients and hematopoietic stem cell transplant recipients. (48, 71) This could be explained by the immature immune systems, delayed antibody responses and lack of immunological memory in young children in these studies (< 2 years). Moreover, the adverse effects of cytotoxic and immunosuppressive therapies could be more prominent among younger children and result in greater degree of immunosuppression leading to increased susceptibility to infections. Moreover, none of the patients diagnosed with hematological conditions after the age of 5 years developed definite LRTI hospitalizations. There is a lack of studies in the literature to support this finding. One of the possible reasons could be because hematological disorders such as bone marrow failure syndromes, aplastic anemia and neutropenia were diagnosed at younger ages, with the mean age of diagnosis of 3.2 years in our study.

We also determined the incidence of definite LRTI hospitalizations categorized by type of immunocompromising conditions and gender. The incidence of definite LRTI hospitalizations between males and females were not substantially different among patients with hematological, immunological and rheumatological disorders in our study. Similarly, most studies in the literature did not report association between gender and LRTIs among immunocompromised children. (53, 113) However, our study found that male patients in the oncology group had both higher absolute and crude incidence rates for definite LRTI hospitalizations which were approximately 2 times higher than females. A retrospective study by Chemaly et al. also reported a higher trend of LRTIs in males compared to females among children with hematopoietic malignancies, although there was no statistical significance. (53) The variances in immune competencies between males and females could be multifactorial and possibly contributed by endocrine and genetic factors, as well as gender-related differences in lifestyle and behaviors. Regarding endocrine factors, the presence of testosterone in males has been shown to reduce interferon gamma and interleukin 4 secretion in T cells leading to overall immunosuppression whereas estrogen in females has a protective immune mechanism by enhancing Th1 and Th2 cellular immune responses and humoral immunity. (90)

In our study, we found that 15.8% of all definite LRTI hospitalizations were acquired nosocomially. Nosocomial LRTIs were the most frequent among oncology and immunology patients. High incidence of nosocomial LRTIs in these subgroups could possibly be due to the fact that they generally have longer and complicated stay in hospitals for intensive chemotherapy regimens and HSCT, which put them more at risk for nosocomial LRTIs. Similarly, French et al. study was a systematic review on the risk of transmission of nosocomial RSV infections during outbreaks and reported nosocomial transmission rates ranging between 6% and 56% (median: 28.5%) among pediatric immunocompromised population. (105) In contrast, Chow et al. study reported a much lower incidence of nosocomial viral ARIs (44 cases per 10,000 children) among non-immunocompromised pediatric patients. (106)

Regarding seasonality trends, the incidence rates for LRTI hospitalizations in our study were relatively higher during the fall and winter months especially between November and March. This is consistent with the epidemiological pattern of RSV, influenza and most other viral LRTIs in the general pediatric population established by prior studies in the literature. (91) Although the seasonality of respiratory infections is not completely understood, it could partially be influenced by certain climatological conditions and human behaviors associated with different seasons. The exposure of cold air induces lower core body temperature leading to pathophysiological responses such as vasoconstriction in the mucosa membranes of the respiratory tract and suppression of immune responses, which could be accountable for increased risk of infections. (109) On the other hand, the transmission of microbes tends to occur less during warmer months because of less indoor crowding during summer months and reduced numbers of children in daycare centers, which decreases the risk of droplet, airborne or contact transmission.

6.2. Objective 2 Findings

6.2.1. Microbiological Etiology of LRTI Hospitalizations

For objective 2, we aimed to describe the microbiological etiologies and clinical burden (i.e. morbidity and mortality) of LRTI hospitalizations among immunocompromised children in Nova Scotia. Routine microbiological tests such as

respiratory viral panels (RVPs) and blood cultures are typically conducted on immunocompromised children during LRTI hospitalizations. More invasive tests such as sputum and pleural fluid cultures, bronchoalveolar lavage (BAL), and lung aspiration/biopsy may be conducted in certain cases of severe LRTIs. Overall, there are limited studies in the literature on this topic especially among the immunocompromised pediatric population.

With a high percentage of the study patients (94.1%) having microbiological tests conducted for definite LRTI hospitalizations, we were able to comprehensively determine the microbiological etiologies associated with definite LRTI hospitalizations among immunocompromised children. They were positive in almost half of the patients with definite LRTI hospitalizations. Most studies in the literature reported the prevalence of respiratory viruses ranging from 50% to 75% among respiratory infections in children with cancer. (40, 41) However, this number could be underestimated for several reasons. Firstly, it has been shown in the literature that the sensitivity of RVPs by multiplex PCR ranges between 95% to 99%, which could fail to detect viruses resulting in false negative results. (98) Improper collection of specimens could also result in false negative tests. Additionally, laboratory tests might not be completed 100% of the time although they were performed on most patients during hospitalizations.

Respiratory viruses were the most common microbiological pathogens detected in 73.5% of positive samples among our study cohort and the most common viruses were RSV, followed by influenza, rhinovirus, and parainfluenza viruses. The result was consistent with the findings from previous studies, most of which stated that RSV was the most common in immunocompromised children (50, 52, 62). However, the variance in the distribution of viruses from studies to studies could be influenced by different geographical and sociodemographic factors of the study population.

Our study reported that influenza viruses were the second most prevalent viruses among immunocompromised children with LRTIs in Nova Scotia. Similarly, multiple studies in the literature reported influenza viruses as one of the three most common type respiratory viruses. (62, 63) Rhinoviruses and parainfluenza viruses were also diagnosed in a sizeable number of our study patients. There were two studies in the literature which reported that rhinoviruses were mostly frequently detected. (40, 56) Furthermore, our

study reported several patients who were detected with human metapneumovirus, bocavirus and coronavirus. Several studies showed that these viruses are common and usually self-limiting in healthy immunocompetent children but they tend to have severe morbidity and mortality among immunocompromised children. (114)

Our study found that fungal organisms (namely Candida albicans and Pneumocystic jiroveci) were only positive in a total of 5 patients (13.9% of positive tests). Bacterial pathogens were detected in approximately a quarter of patients with positive microbiological tests. *Mycoplasma pneumoniae* was the most common bacteria, followed by *Staphylococcus aureus, Haemophilus influenzae* and *Streptococcus pneumoniae.* The low prevalence of LRTIs associated with invasive bacteria in most developed nations like Canada nowadays could be contributable to the global implementation of vaccination programs that include PCV13 and Hib vaccines. In most developing countries, *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphalococcus aureus* are still commonly associated with LRTIs in children. (100, 101, 102) Currently, there is a gap in the literature on the prevalence of bacterial and fungal pathogens associated with LRTIs among immunocompromised children in Canada.

The prevalence of bacterial and fungal pathogens was possibly underestimated in our study for several reasons. Pleural fluid or sputum cultures are not routinely conducted in pediatric population due to their invasive nature. Non-invasive laboratory tests such as blood cultures might not be positive in most bacterial LRTIs unless infections become systemic by spreading into the blood stream. Tam et al. study reported only 5.14% positive blood cultures among patients with community acquired pneumonia. (100) Furthermore, the main factors that influence the growth of organisms on blood cultures include timing of collection and volume of blood collected (i.e. more than 2 milliliters collected at the time of fever spikes). (99) Fiorucci et al. study reported poor sensitivity (40%) and specificity (76%) of BAL cultures in predicting ventilator-associated pneumonia. (103) Several studies showed that the rate of ascertaining a specific microbiologic diagnosis with BAL cultures ranged 28 ± 86%, in immunology and oncology patients and the most frequently isolated organisms were Pneumocystis carinii and Cytomegalovirus. Other common microbes isolated by BAL include *Mycoplasma hominis, Legionella pneumophila* and other viruses. (104)

On subgroup analysis, there were higher numbers of positive microbiological tests in immunology group (15 out of 22 patients), compared to other subgroups. Respiratory viruses were present in about 70-80% of the positive laboratory tests in most subgroups. This is consistent with prior studies which reported respiratory viruses as the most common pathogens associated with approximately 50% to 75% of LRTIs. (40, 41) In some subgroups, we found that bacterial pathogens were present in about one quarter of patients with positive tests and most of them were detected among oncology and rheumatology patients. A majority of fungal pathogens were also diagnosed among oncology and immunology patients. This might be attributable to the extensive workups with invasive microbiological tests warranted in these subgroups due their severe immunocompromised states. They were also more likely to have coinfections with additional bacterial and fungal pathogens during complicated LRTI hospitalizations.

A majority of patients (86%) were infected with a single type of microbial pathogens in our study. However, there were 8 patients (approximately 8%), who had co-infection either with 2 or more viruses or with viruses and bacteria or with bacteria and fungi. Most patients who had coinfections were from the oncology and immunology groups. The coinfections rate among immunocompetent children reported by Asner et al. study was 17.2%, which was slightly higher than our study rate. (107) Additionally, there were studies which reported that respiratory virus coinfections were detected in up to 30% of children with LRTIs and co-infections were not significantly associated with morbidities such as length of hospitalization, oxygen supplementation, ICU admission and mechanical ventilation. (108) The number of coinfections in our study might be underestimated due to the abovementioned reasons – improper collection of specimens, non-routine testing of all study patients with invasive microbiological tests and also the retrospective nature of the study where missing data are abundant.

6.2.2. Clinical Burden of LRTI Hospitalizations

Approximately one third of study patients required oxygen supplementation during definite LRTI hospitalizations with the median duration of 6 days. Additionally, 8.9% and 7.9% of study patients required CPAP and ICU admission respectively. There was low mortality in the study contributable to definite LRTIs. The numbers in our study

were considerably lower than several studies in the literature. Wang et al. study reported that 16% had ICU admissions and 9.1% were mechanically ventilated, resulting in 6 deaths with a mortality rate of 0.87%. (93) In a Mendoza-Sanchez et al. study, 20% of children who were on antineoplastic treatment were admitted to ICU due to viral ARIs. (62) In pediatric HSCT and chemotherapy recipients, 28% to 40% of viral ARIs progress to LRTIs, with mortality rates as high as 10%. (40,55,56,62,63) This disparity could be due to significant differences in study populations where they included severely immunocompromised children with stem-cell transplantation, cardiac and pulmonary diseases.

The median duration of definite LRTI hospitalization was 5 days for our study patients, which was longer than the duration of LRTI hospitalizations among healthy children (2 days) as reported by prior studies (97). In our study, the length of ICU stay with the need for mechanical ventilation was supposedly more prolonged compared to patients hospitalized in the regular pediatric medical unit (8.5 days versus 5 days). Similar to our study findings, several studies reported that the duration of LRTI hospitalizations ranged from 3 days to 7 days among immunocompromised children. (92, 93) Longer duration of LRTI hospitalization among immunocompromised children was reported by Navas et al. and Tylka et al. study (39 days and 45 days respectively). (94, 95) However, only immunocompromised children with severe RSV and adenoviral infections were included in these studies, which might possibly explain the longer length of hospitalizations.

We also determined the clinical burden of possible LRTI hospitalizations among immunocompromised children in our study. Patients hospitalized with possible LRTIs have relatively lower rates of oxygen supplementation and CPAP than those with definite LRTIs (9.5% vs 30.7% and 4.8% vs 8.9%). Also, the duration of ICU admission among patients with possible LRTIs was of relatively shorter (1.5 days versus 8.5 days). There was no mortality among children with possible LRTI hospitalizations. The differences between the clinical burden of definite and possible LRTI hospitalizations could be due to less severe hospitalization courses of possible LRTIs as a result of the more inclusive outcome definition criteria. It could also be attributed to the data skewness and kurtosis resulting from the relatively small sample sizes of possible LRTIs.

On subgroup analysis, we also determined the clinical burden of definite LRTI hospitalizations contributable to RSV and influenza viruses. The length of hospitalization for RSV and influenza specific definite LRTIs was similar to that of overall definite LRTIs (5 days). However, patients with RSV and influenza positive definite LRTIs had more prolonged courses of oxygen supplementation (11 days and 9 days respectively versus 6 days for the overall definite LRTIs). None of the patients with RSV and influenza definite LRTIs required CPAP, mechanical ventilation or ICU admission. There was no mortality associated with RSV and influenza definite LRTIs. On literature review, we were not able to find any study that determined the clinical burden of RSV and influenza LRTIs. However, there were several limitations to the interpretation of the study's clinical data specific to RSV and influenza subgroups. Firstly, the sensitivity of respiratory viral panels (RVP) is not 100%. Also, laboratory tests were possibly not conducted in every immunocompromised child hospitalized with LRTIs, which might underestimate the actual numbers of RSV and influenza definite LRTIs. Additionally, the sample size of patients with RSV and influenza definite LRTIs was small. This could result in data skewness limiting proper analyses and description of the data associated with the clinical burden of LRTI hospitalizations.

The high morbidity and mortality associated with LRTI hospitalizations have negative impact on the health and wellbeing of immunocompromised patients, and also result in increased health care expenditure. Fendrick et al. study reported that the average cost of healthcare attributable to acute respiratory infections approaches $40 billion annually in the United States. (96) From our study, it is evident that the clinical burden is considerably high among the immunocompromised group of children having more prolonged courses of hospitalization, oxygen supplementation, mechanical ventilation and ICU admissions.

6.3. Objective 3 Findings

For objective 3, we aimed to describe the association between the baseline characteristics and definite LRTI hospitalizations among immunocompromised children in Nova Scotia using logrank tests, Kaplan-Meier curves and, univariate as well as multivariate Cox proportional hazard regression analyses.

According to the logrank test, we found statistically significant differences between the type of immunocompromising disorders in developing definite LRTI hospitalizations. As illustrated by Kaplan-Meier curves (Figure 5-4-1), oncology and immunology patients had comparable survival probabilities (i.e. probabilities of surviving and not developing definite LRTI hospitalizations), which were significantly lower than the remaining subgroups. Their hazard ratios in referent to rheumatology patients were also statistically significant. Hence, oncology and immunology patients were at increased risk for LRTI hospitalizations due to severe immunosuppression from intensive chemo/radiation therapy regimens adversely affecting their immune response. The survival probability and hazard risks of hematology patients did not differ significantly from the referent group in both univariate and multivariate models. Furthermore, we found that gastroenterology patients had the highest survival probabilities and hence, they were least likely to develop definite LRTI hospitalizations. The difference was statistically significant in the univariate model but not multivariate. We could assume that they had similar risks of developing LRTI hospitalizations as the general pediatric population, but further prospective studies are needed to portray the differences in the association of LRTI hospitalizations between immunocompromised and healthy children.

There was significant association between the age at diagnosis with immunocompromising conditions and definite LRTI hospitalizations as shown by the logrank test. Children diagnosed with immunocompromising conditions under the age of 5 years had lower survival probability (Figure 5-4-2) and significant hazard ratios (univariate HR: 2.85 and multivariate HR: 2.02), compared to the older group. This indicates that they were more likely to ha e definite LRTI hospitalizations than their older counterparts. The above finding was consistent with El Saleeby et al. and Lee et al. studies, which reported significant association between young age and development of LRTIs. (48, 71) This could be explained by the biological plausibility that younger children are more prone to infections due to their immature and underdeveloped immune system, delayed antibody responses and lack of immunological memory as mentioned above. It was, however, contradicted by several smaller studies that failed to show any significant association between the two variables. (50, 53, 54)

As per the logrank test, there was statistically significant association between gender and definite LRTI hospitalizations in our study. We found that females had significant hazard ratios (univariate HR: 0.62 and multivariate HR: 0.65), compared to their male counterparts. This reflects that immunocompromised males in our study were more likely to develop definite LRTI hospitalization than females. This difference could be contributed by the distinctive endocrine and genetic factors, as well as the gender-related differences in behaviors between males and females. It was reported by Chemaly et al. study that males tend to develop more LRTIs, although there was no statistical significance. (53) Other smaller studies in the literature showed no significant association between gender and LRTIs. (48, 54, 55)

There was statistical significance on the logrank test between the categories in the status of household crowding variable. However, after adjusting for variable factors including large numbers of missing values, hazard ratios of the status of household crowding variable were not statistically significant. It is, however, biologically plausible that immunocompromised children from overcrowded households with multiple young children are at increased risk for LRTI hospitalizations due to overcrowding, increased contact and higher level of exposure to community-acquired microbial pathogens. There are limited studies that determined the association between the status of household crowding and LRTI hospitalizations in the current literature.

There was no statistical significance in the logrank tests, Kaplan-Meier curves and univariate hazard ratios of ethnicity and passive smoking variables. However, this could not be interpreted accurately due to extremely high numbers of missing values in our study and hence no appropriate conclusion could be made from this result. Moreover, these variables were not included in the multivariate Cox proportional model due to statistical non-significance in the univariate models.

6.4. Study Implications for Health Care

Overall, our study provides relevant clinical information on the incidence, microbiological etiologies and clinical burden associated with LRTI hospitalizations in immunocompromised children categorized by types of immunocompromising disorders, gender and age at diagnosis with immunocompromised disorders.

It is evident from our findings that the incidence of LRTI hospitalizations was high in most immunocompromised children especially among oncology and immunology patients. Hence, preventative measures such as routine immunizations and education about infection control interventions should occur during health care maintenance visits for these patients especially during fall and winter months. Moreover, strict isolation measures (such as contact and droplet precautions) should be reinforced during their LRTI hospitalizations because the incidence of nosocomially transmitted LRTIs are found to be common among oncology and immunology patients. In addition to the incidence of LRTI hospitalizations, we found that the morbidity was relatively higher among the oncology and immunology groups, with a large proportion of children requiring oxygen supplementation, CPAP, mechanical ventilation and ICU admission. Hence, these patients should be closely monitored, routinely investigated with laboratory tests and aggressively managed during LRTI hospitalizations. Moreover, our study reported that patients diagnosed with immunocompromising conditions under 5 years and male patients were more likely to have LRTI hospitalizations compared to the older age group and female patients. Hence, extra caution should be taken with the aforementioned aggressive preventative, diagnostic and treatment regimens among these demographics groups.

We found a wide range of microbiological pathogens namely viruses, bacteria and fungi that could lead to LRTI hospitalizations. With a wide spectrum of clinical burden among different microbes, some were associated with higher morbidity and mortality than others. Hence, we should consider to routinely conduct non-invasive laboratory tests such as respiratory viral panels and blood cultures in every immunocompromised patient to anticipate the clinical burden associated with specific microbes. Invasive tests such as sputum cultures, lung and pleural fluid aspirates could be considered in highly immunocompromised patients on a case by case basis.

Viruses were the most dominant type of microbes associated with LRTI hospitalizations among immunocompromised children. In the child with an ANC over 500 who is well, with a clear respiratory presentation, consideration can be given to discontinuing broad-spectrum antibiotics after 48 hours if the investigation for other pathogens is negative. Continuous cardiopulmonary monitoring with ventilatory support

should be opted instead. Our study reported that RSV and influenza viruses were the most prevalent microbes leading to LRTI hospitalizations. We hope that our study would act as a stepping stone for RCTs on the effectiveness of palivizumab immunoprophylaxis among immunocompromised children. This could result in practice guidelines for routine administration of palivizumab immunoprophylaxis and influenza vaccination in immunocompromised children.

6.5. Strengths

One of the main strengths of our study is the inclusion of a wide range of patients including children < 16 years diagnosed with a variety of immunocompromising disorders in Nova Scotia. A comprehensive comparison and summary of the incidence, microbiological etiology, clinical burden and sociodemographic characteristics associated with LRTI hospitalizations among children with different subgroups of immunocompromising conditions is currently lacking in the literature as previous studies most often include only one specific group of immunocompromised children. Additionally, our study also provided relevant data on the overall prevalence and epidemiological pattern of different immunocompromising conditions in Nova Scotia.

Our study explored various sociodemographic risk factors such as age, gender, ethnicity, the status of household crowding and passive smoking among children with distinctive types of immunocompromising conditions. Provided there are limited studies on this topic in the current literature, our study contributes to the understanding of different risk factors associated with LRTI hospitalizations in this vulnerable group of immunocompromised population. With the latest comprehensive knowledge provided by our study, appropriate prevention and management strategies could be used for patients in the future.

An extensive search strategy was used to identify several subgroups of immunocompromised children in Nova Scotia via IWK Decision Support Services (using relevant ICD codes) and also IWK hematology/oncology and rheumatology databases. We included a considerably large sample of 640 immunocompromised children in the study. This gives us an advantage of greater statistical power leading to lower chance of having a Type II error or concluding there is no effect when, in fact, there is one (non-

rejection of the false null hypothesis). As a population-based retrospective cohort study with an extensive follow-up period of 12 years during which different groups of immunocompromised children were followed up for LRTI hospitalizations, the level of evidence of our study is stronger compared to other smaller retrospective and cross-sectional studies. All study patients were followed until the development of the outcome event or end of study period (if they failed to develop LRTI hospitalizations) with very low overall drop-out rates. Hence, there was minimal right-censoring in the survival analysis of study data. A study design with large sample size, extensive follow-up and low drop-out rates ensures negligible systematic errors and high accuracy of study results.

With the abovementioned comprehensive search strategy, the total number of patients included in our study most likely represent the actual numbers of immunocompromised children in Nova Scotia. Hence, the study results and conclusions are most likely generalizable to the immunocompromised pediatric population in Canada and other countries with similar population demographics and health care systems.

6.6. Limitations

One of the major limitations of our study is attributed to the retrospective nature where we jumped back in time to identify the inception cohort before the development of the outcome of interest. We established data collection, analyses and results via review of previous charts. As a result, retrospective studies could only establish association between sociodemographic characteristics and LRTI hospitalizations, but not necessarily causation. Retrospective studies are at risk for different types of biases (sampling and misclassification bias) and hence, the level of evidence is relatively weaker in comparison to prospective studies and randomized controlled trials. The study design that would ideally address our research objectives would be a prospective cohort study, which would not be entirely feasible for our study due to its complexity and cost associated with long follow-up period.

Regarding sampling of the inception cohort, we assumed that all immunocompromised children in Nova Scotia during the sampling phase were captured. Due to absence of pediatric subspecialists outside of Halifax, it is likely all children with

immunocompromised conditions were initially referred and followed at the IWK Health Center. However, even with a comprehensive search strategy using the IWK patient databases and ICD-10 codes, it is possible that we did not include all children with immunocompromising conditions in Nova Scotia resulting in sampling bias.

Also, we assumed that all immunocompromised children (especially from the remote areas in Nova Scotia) were routinely transferred to the IWK Health Center in Halifax when they developed LRTI hospitalizations. For less severe cases of LRTIs, patients might not get transferred to the IWK Health Center from their respective local community hospitals. We reviewed all clinic follow-up notes to determine off-site LRTI hospitalizations but detailed information could not be obtained for all patients. Hence, the incidence and clinical burden associated with LRTI hospitalizations could be underestimated.

As per our study protocol, we only considered the first LRTI hospitalization as an outcome event for each patient and subsequent LRTI hospitalizations were not captured to avoid confounding effects on the analyses of the clinical burden and baseline characteristics variables. Hence the specific microbes associated with subsequent LRTI hospitalizations and the burden of those illnesses were not included in our study; this study would therefore underestimate the incidence of microbiological etiology of viruses, bacteria and fungi in the study population.

Our study could also be affected by misclassification bias, which is a type of measurement error where prejudice or bias influence the determination of exposure or outcome variables. There could be misclassification bias with certain subgroups such as oncology and immunology patients, who were widely assumed to be more immunosuppressed. Hence, data collector could have the temptation to assess their charts more strictly and identify them with the development of the outcome event of LRTI hospitalizations. This could lead to overestimation of the incidence and clinical burden of LRTI hospitalizations in these subgroups.

In our study, information on several key exposure variables such as ethnicity and passive smoking were absent from most charts and could not be acquired, which resulted in large numbers of missing values. Consequently, extra caution should be taken with interpretation of the results associated with these baseline characteristic variables with a

large number of missing values. For missing data on secondary outcome variables (oxygen supplementation, CPAP and mechanical ventilation), it was assumed as negative for these variables. This could underestimate the results and adversely affect accuracy of the clinical burden, microbiological etiology and baseline characteristics associated with LRTI hospitalizations.

6.7. Future Research

At large, we found trends of higher incidence and clinical burden associated with LRTI hospitalizations among children with oncological and immunological disorders out of all immunocompromising disorders. Due to the retrospective nature of our study, we were not able to accurately investigate several important sociodemographic characteristics such as ethnicity, passive smoking and household crowding. Moreover, we were not able to examine relevant clinical risk factors such as lymphopenia and neutropenia, which were previously shown to be associated with LRTI hospitalizations in other retrospecitve studies. Hence, there is a need for future prospective cohort studies with a control group of healthy children to explore the incidence, clinical burden and risk factors of LRTI hospitalizations between different groups of immunocompromised children and the control group of general pediatric population.

Additionally, our study reported significant numbers of RSV and influenza viruses that cause LRTI hospitalizations among immunocompromised children with high clinical burden. There are no specific guidelines regarding the use of RSV immunoprophylaxis or influenza vaccination in the prevention of LRTI hospitalizations among immunocompromised children. With lack of studies in the current literature, it is practical to conduct further randomized controlled trials assessing the effectiveness of preventative and management strategies for LRTI hospitalizations caused by RSV, influenza and other viruses among immunocompromised children.

CHAPTER 7: CONCLUSION

In general, immunocompromised children are vulnerable to different types of infections throughout their lifetime due to their weak and defective immune systems. Our study reported high incidence associated with definite LRTI hospitalizations among most subgroups of immunocompromised children especially oncology and immunology patients. The hazard ratios of definite LRTI hospitalizations in the oncology and immunology group were significantly higher than the remaining subgroups of immunocompromised children. These groups of immunocompromised children were also reported to have prolonged duration of hospitalizations, oxygen supplementation and ICU admission. We also found viruses (especially RSV and influenza viruses) were most commonly associated with definite LRTI hospitalizations among immunocompromised children. Moreover, we found substantial numbers of nosocomially transmitted LRTI hospitalizations among our study patients. Some of the statistically significant sociodemographic characteristics were gender and age at diagnosis with immunocompromising conditions, with males and younger children found more at risk for LRTI hospitalizations. Our study provided understanding on the incidence, clinical burden and risk factors associated with LRTI hospitalizations that could be vital for clinicians in outlining the preventative and treatment strategies among immunocompromised children. Moreover, we found that immunocompromised groups of oncology and immunology patients were largely affected with RSV and influenza related LRTI hospitalizations and consequently, clinicians should consider the administration of routine palivizumab immunoprophylaxis and influenza vaccinations in these groups of vulnerable patients.

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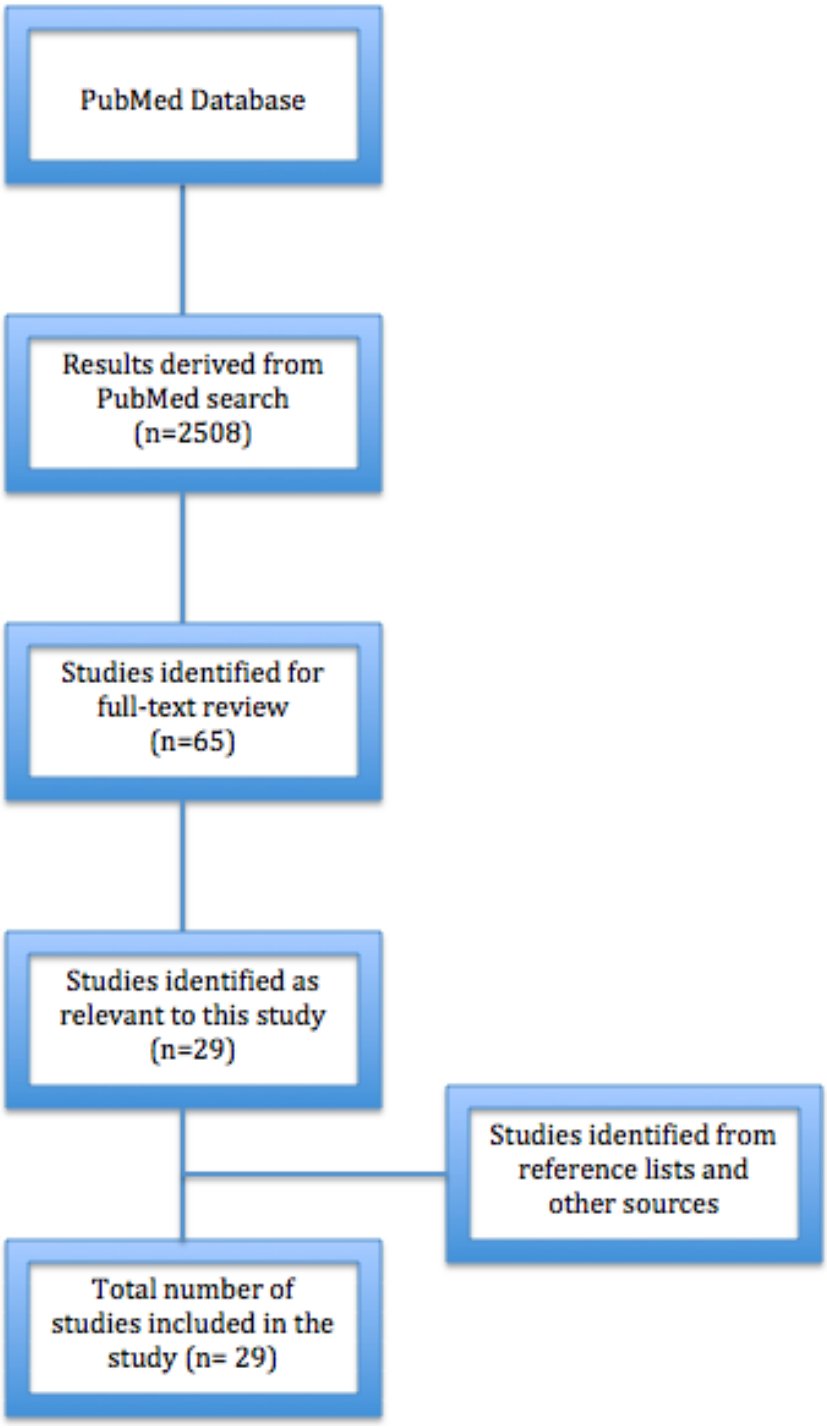
APPENDIX 1 – LITERATURE SEARCH STRATEGY

1. Respiratory tract infections [MeSH]
2. Cough [MeSH]
3. Dyspnea [MeSH]
4. Hyperventilation [MeSH]
5. Respiratory tract infection* [tw]
6. Respiratory infection* [tw]
7. RSV [All Fields]
8. Respiratory syncytial virus* [tw]
9. Influenza [tw]
10. Pneumonia [tw]
11. Bronchiolitis [tw]
12. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
13. Immunoproliferative disorders [MeSH]
14. Immunologic deficiency syndrome [MeSH]
15. Neoplasms [MeSH]
16. Stem cell transplantation [MeSH]
17. Immunosuppressed [tw]
18. Immunodeficien* [tw]
19. Immunocompromised [tw]
20. Cancer [tw]
21. Oncology [tw]
22. #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
23. Child [MeSH]
24. Infant [MeSH]
25. Pediatrics [MeSH]
26. Infant* [tw]
27. Neonat* [tw]
28. Child* [tw]
29. Pediatr* [tw]
30. Paediatr* [tw]
31. #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30
32. #12 AND #22 AND #31

Search restricted to cohort and case-control studies only
(((cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR retrospective studies[mesh:noexp] OR cohort[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB] OR “Case-Control Studies”[Mesh:noexp] OR "retrospective studies"[mesh:noexp] OR “Control Groups”[Mesh:noexp] OR (case[TIAB] AND control[TIAB]) OR (cases[TIAB] AND controls[TIAB]) OR (cases[TIAB] AND controlled[TIAB]) OR (case[TIAB] AND comparison*[TIAB]) OR (cases[TIAB] AND comparison*[TIAB]) OR “control group”[TIAB] OR “control groups”[TIAB])))))

APPENDIX 2 – LITERATURE SEARCH RESULTS



APPENDIX 3 – ICD-10-CM CODES

Hematological disorders

Immunocompromised conditions	ICD-10-CM
Acquired pure red cell aplasia [erythroblastopenia]	D60
Other aplastic anemias and other bone marrow failure syndromes	D61
Diseases of spleen	D73
Other and unspecified diseases of blood and blood-forming organs	D76
Other disorders of blood and blood-forming organs in diseases classified elsewhere	D77
Intraoperative and postprocedural complications of the spleen	D78

Immunological disorders

Immunocompromised conditions	ICD-10-CM
Neutropenia	D70
Functional disorders of polymorphonuclear neutrophils	D71
Other disorders of white blood cells	D72
Immunodeficiency with predominantly antibody defects	D80
Combined immunodeficiencies	D81
Immunodeficiency associated with other major defects	D82
Common variable immunodeficiency	D83
Other immunodeficiencies	D84
Other disorders involving the immune mechanism, not elsewhere classified	D89
Thymoma with immunodeficiency	D15
Ataxia-telangiectasia	G11

Oncological disorders

Immunocompromising conditions	ICD-10-CM
Hodgkin lymphoma	C81
Follicular lymphoma	C82
Non-follicular lymphoma	C83
Mature T/NK-cell lymphomas	C84

Other specified and unspecified types of non-Hodgkin lymphoma	C85
Other specified types of T/NK-cell lymphoma	C86
Malignant immunoproliferative diseases and certain other B-cell lymphomas	C88
Multiple myeloma and malignant plasma cell neoplasms	C90
Lymphoid leukemia	C91
Myeloid leukemia	C92
Monocytic leukemia	C93
Other leukemias of specified cell type	C94
Leukemia of unspecified cell type	C95
Other and unspecified malignant neoplasms of lymphoid, hematopoietic and related tissue	C96
Malignant neoplasm of thymus	C37
Malignant neoplasm of bone and articular cartilage of limbs	C40
Malignant neoplasm of bone and articular cartilage of other and unspecified sites	C41
Malignant neoplasm of other connective and soft tissue	C49
Malignant neoplasm of kidney, except renal pelvis	C64
Malignant neoplasm of renal pelvis	C65
Malignant neoplasm of eye and adnexa	C69
Malignant neoplasm of other and unspecified urinary organs	C68
Malignant neoplasm of meninges	C70
Malignant neoplasm of brain	C71
Malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system	C72
Malignant neoplasm of thyroid gland	C73
Malignant neoplasm of adrenal gland	C74
Malignant neoplasm of other endocrine glands and related structures	C75
Malignant neuroendocrine tumors	C7A
Secondary neuroendocrine tumors	C7B
Secondary and unspecified malignant neoplasm of lymph nodes	C77
Benign neuroendocrine tumors	D3A
Neoplasm of uncertain behavior of urinary organs	D41
Neoplasm of uncertain behavior of meninges	D42
Neoplasm of uncertain behavior of brain and central nervous system	D43
Neoplasm of uncertain behavior of endocrine glands	D44
Polycythemia vera	D45
Myelodysplastic syndromes	D46
Other neoplasms of uncertain behavior of lymphoid, hematopoietic and related tissue	D47

Rheumatological disorders

Immunocompromising conditions	**ICD-10-CM**
Rheumatoid arthritis with rheumatoid factor	M05
Other rheumatoid arthritis	M06
Enteropathic arthropathies	M07
Juvenile arthritis	M08
Other and unspecified arthropathy	M12
Other arthritis	M13
Polyarteritis nodosa and related conditions	M30
Other necrotizing vasculopathies	M31
Systemic lupus erythematosus (SLE)	M32
Dermatopolymyositis	M33
Systemic sclerosis [scleroderma]	M34
Other systemic involvement of connective tissue	M35
Systemic disorders of connective tissue in diseases classified elsewhere	M36
Ankylosing spondylitis	M45
Other inflammatory spondylopathies	M46
Spondylosis	M47
Other spondylopathies	M48
Spondylopathies in diseases classified elsewhere	M49

Gastrointestinal disorders

Immunocompromising conditions	**ICD-10-CM**
Crohn's disease	K50
Ulcerative colitis	K51

APPENDIX 4 – DATA COLLECTION FORM

Incidence and Clinical Burden of Lower Respiratory Tract Infections in Immunocompromised Children: A Retrospective Cohort Study

Study ID: ☐☐☐	**Date of Review (dd/mmm/yyyy):**

A. Inclusion/Exclusion criteria

1. Date of Birth (mmm/yyyy)	
2. Diagnosis of immunocompromising condition	**Hematologic disorders** ☐ Aplastic anemia (D60, D61) ☐ Other hematologic disorders (D76, D77) (specify:_____) **Oncologic disorders** ☐ Hodgkin's lymphoma (C81, C88) ☐ Non-Hodgkin's lymphoma (C82, C83, C84, C85, C86, C88) ☐ Multiple myeloma (C90) ☐ AML (C92, C93) ☐ ALL (C91) ☐ Other types of hematologic malignancies (C94, C95, C96, C77, D47) ☐ Central nervous system tumors (C70, C71, C72, D42, D43) ☐ Neuroblastoma (C74, C75, D44) ☐ Wilms tumors (C64, C65, C68, D41) ☐ Thyroid cancer (C73) ☐ Thymoma (C37, D15) ☐ Rhabdomyosarcoma (C49) ☐ Retinoblastoma (C69) ☐ Bone cancer (C40,C41) ☐ Myelodysplastic syndrome (D45, D46) ☐ Other types of malignancies (specify:_____) **Immunologic disorders** ☐ White blood cell disorders (D70, D71, D72) ☐ Severe combined immunodeficiency (D81)

	☐ Common variable immunodeficiency (D83) ☐ Immunodeficiency with antibody defects (D80) ☐ Complement deficiencies (D84) ☐ Other immunodeficiency syndromes (D82, D89) ☐ Ataxia-telangiectasia (G11) (specify:_____) **Rheumatologic disorders** ☐ Juvenile idiopathic arthritis (M05, M06, M07, M08, M12, M13, ☐ Systemic lupus erythematosus (M32) ☐ Spondyloarthropathies (M45, M46, M47, M48, M49) ☐ Other autoimmune rheumatologic disorders (M30, M31, M33, M34, , M35, M36) (specify:_____) **Gastrointestinal disorders** ☐ Crohn's disease (K50) ☐ Ulcerative colitis (K51)	
3. Date of diagnosis (mmm/yyyy)		
4. End of immunosuppression	**Yes** ☐ If Yes, specify date(mmm/yyyy): _____	**No** ☐
5. Prematurity	**Yes**☐(Exclude) **No**☐ **Unknown**☐	
6. Congenital heart diseases	**Yes**☐(Exclude) **No**☐ **Unknown**☐	
7. Chronic respiratory disorders	**Yes**☐(Exclude) **No**☐ **Unknown**☐	

B. Demographic Characteristics

1. Sex	**Male**☐ **Female**☐
2. Ethnicity	**White**☐ **Black**☐ **Asian**☐ **Indigenous**☐ **Mixed**☐ **Unknown**☐
3. Household crowding	**Yes**☐ **No**☐ **Unknown**☐ (# of household members: _____)

4. Passive smoking exposure	**Yes**☐ **No**☐ **Unknown**☐	
5. Other comorbidities	**Yes**☐ If Yes, specify diagnosis:	**No**☐

C. Outcome characteristics

1. LRTI hospitalization	**LRTI** ☐ **Possible LRTI** ☐ If Yes, specify the following: **LRT symptoms**: Yes☐ No ☐ ☐ Cough ☐ Tachypnea (Others:_____) **Positive radiological findings**: Yes ☐ No ☐ Date (dd/mmm/yyyy):_____ Findings: ☐ Opacity/consolidation/Infiltration ☐ Hyperinflation ☐ Bronchial thickening (Others:_____)	**No** ☐
2. Date of admission (dd/mmm/yyyy)		
3. Date of diagnosis (dd/mmm/yyyy)		
4. Microbiologic diagnostic tests	**Completed**☐ **Not completed**☐ Date (dd/mmm/yyyy):_____ If Completed, specify the following: **Specimen:** ☐ Nasopharyngeal aspirate ☐ Throat swab ☐ Bronchoalveolar lavage	

	☐ Lung biopsy ☐ Blood culture ☐ Others (specify:_____) ☐ Positive ☐ Negative **Microbiologic agents detected:** ☐ RSV ☐ Influenza viruses ☐ Parainfluenza viruses ☐ Adenovirus ☐ Rhinovirus ☐ Human metapneumovirus ☐ Bocavirus ☐ Other viruses (specify:_____) ☐ *Streptococcus pneumoniae* ☐ *Haemophilus influenzae* ☐ *Chlamydophila pneumoniae* ☐ *Mycoplasma pneumoniae* ☐ *Staphylococcus aureus* ☐ *Moraxella catarrhalis* ☐ Other bacteria (specify:_____) ☐ *Aspergillus fumigatus* ☐ *Candida albicans* ☐ Others (specify:_____)	
5. Intensive care unit admission	**Yes**☐ If yes, specify: Date of admission:_____ (dd/mmm/yyyy) Date of discharge:_____ (dd/mmm/yyyy)	**No** ☐
6. CPAP use in PICU	**Yes** ☐ **No**☐ **Unknown** ☐	
7. Mechanical ventilation	**Yes** ☐ **No**☐ **Unknown** ☐ If yes, specify: **Start date :** _____ (dd/mmm/yyyy)	

	End date : _____ (dd/mmm/yyyy)	
8. Oxygen supplementation	**Yes** ☐ **No**☐ **Unknown** ☐ If yes, specify: **Start date :** _____ (dd/mmm/yyyy) **End date :** _____ (dd/mmm/yyyy)	
9. Date of last recorded LRTI symptoms (dd/mmm/yyyy)		
10. Mortality attributable to LRTI	**Yes**☐ Date of death: _____ (mmm/yyyy)	**No** ☐