Fall 2010

Polymicrobial respiratory tract infections in a hospital-based pediatric population, with particular emphasis on the role of human rhinoviruses

Margaret Lynn Chorazy
University of Iowa

POLYMICROBIAL RESPIRATORY TRACT INFECTIONS IN A HOSPITAL-BASED PEDIATRIC POPULATION, WITH PARTICULAR EMPHASIS ON THE ROLE OF HUMAN RHINOVIRUSES

by

Margaret Lynn Chorazy

An Abstract

Of a thesis submitted in partial fulfillment
of the requirements for the Doctor of
Philosophy degree in Epidemiology
in the Graduate College of
The University of Iowa

July 2010

Thesis Supervisors: Professor James C. Torner
Adjunct Professor Gregory C. Gray

ABSTRACT

Pediatric acute respiratory tract infections (ARTIs) are a leading cause of morbidity and mortality. The objectives of this study were to describe the epidemiology of polymicrobial ARTI in a hospital-based pediatric population and to investigate the association of polymicrobial infection and severity of illness.

We conducted a retrospective study of 559 archived respiratory specimens from 421 children under the age of 10 years collected from March 28, 2008 through June 30, 2009 and stored by the University of Iowa Hospital and Clinics Clinical Microbiology Laboratory. Specimens were tested by direct immunofluorescent assay and/or viral culture at the time of collection (influenza A and B, parainfluenza [PIV] 1-3, respiratory syncytial virus [RSV], adenovirus [Ad]) and uniformly by RT-PCR (human metapneumovirus [hMPV], rhinovirus [HRV], human bocavirus [HBoV]) and PCR (Ad) for the current study. Demographic and clinical data were abstracted from electronic medical records.

Results from this study suggest that polymicrobial respiratory tract infections are common in this population. A virus was identified in 61.3% of 349 respiratory specimens from children with confirmed or suspected ARTI. HRV (27.5%), RSV (18.9%), HBoV (8.3%), hMPV (7.7%), and PIV (6.6%) were the most common viruses detected. A viral coinfection was identified in 21.5% of the 214 virus-positive specimens and was most often detected for Ad (53.3% of 15 Ad-positive specimens), HBoV (51.7% of 29 HBoV-positive specimens), PIV (43.5% of 23 PIV-positive specimens), HRV (35.4% of 96 HRV-positive specimens), and RSV (34.8% of 66 RSV-positive specimens). Among the 46 specimens with dual or triple viral coinfections detected, the most frequent virus-virus combination was HRV-RSV (n=12).

We hypothesized that certain host-specific risk factors were associated with the likelihood of viral coinfection. While none of the covariates in the final model were significant, the results were suggestive. Male gender (OR 1.70, 95% CI 0.83-3.46), age between 6 months to 1 year (as compared to children less than 6 months old, OR 2.15, 95% CI 0.75-6.19), and history of any chronic condition that may result in immunosuppression (OR 2.05, 95% CI 0.99-4.23) were each associated with increased odds of viral coinfection ($p > 0.05$).

We also hypothesized that children with coinfections would be more likely to have severe ARTI. Children with viral-bacterial coinfection, as compared to children with viral mono-infection, were more likely to be admitted to an intensive care unit (OR 5.58, 95% CI 1.95-15.96) even after controlling for age, history of prematurity, urban/rural residence, and leukocytosis.

This study will inform medical and public health professionals with regard to the epidemiology of mixed infections and their potential importance as a cause of severe acute respiratory tract infection in children. Furthermore, results of this study could contribute to the ongoing discussion of the importance of diagnostic ability to reliably detect multiple concurrent pathogens in a single patient.

Abstract Approved: _____
Thesis Supervisor

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Title and Department

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Date

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Thesis Supervisor

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Title and Department

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Graduate College
The University of Iowa
Iowa City, Iowa

CERTIFICATE OF APPROVAL

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PH.D. THESIS

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This is to certify that the Ph.D. thesis of

Margaret Lynn Chorazy

has been approved by the Examining Committee
for the thesis requirement for the Doctor of Philosophy
degree in Epidemiology at the July 2010 graduation.

Thesis Committee: _____
James C. Torner, Thesis Supervisor

_____
Gregory C. Gray, Thesis Supervisor

_____
Tara C. Smith

_____
James A. Merchant

_____
Sandra S. Richter

To the family and friends who supported me throughout this process, especially Chester Chorazy, Janina Chorazy, Philip Chorazy, and Greg Thomas – it was your love that kept me going

ACKNOWLEDGMENTS

This research study would not have been possible without the support I received from the many members of the Center for Emerging Infectious Diseases at the University of Iowa. I would like to particularly thank Mark Lebeck and Troy McCarthy who were both critical to my training in the molecular methods used here, and Dr. Gregory Gray who provided financial support for this study.

I am also especially grateful to Dr. Sandra Richter and the University of Iowa Hospital and Clinics Clinical Microbiology Laboratory for granting me permission to use their archived respiratory specimens for this study. I would also like to thank Dr. Alan Junkins and Dr. Sophie Arbefeville for the additional support they provided throughout the specimen retrieval process.

I also acknowledge Kirsten Kordick and her team of Health Care Information Systems specialists for abstracting patient demographic data from the electronic medical record system, and Dr. Dean D. Erdman from the Centers for Disease Control and Prevention (CDC), Atlanta, GA, for providing the human bocavirus plasmid which served as a positive control.

I thank my dissertation committee members for their support and guidance during this process. I especially thank Dr. Gregory Gray and Dr. James Torner for the support and mentorship they have offered me throughout my graduate education.

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Pediatric acute respiratory tract infections (ARTIs) are a leading cause of morbidity and mortality. The objectives of this study were to describe the epidemiology of polymicrobial ARTI in a hospital-based pediatric population and to investigate the association of polymicrobial infection and severity of illness.

We conducted a retrospective study of 559 archived respiratory specimens from 421 children under the age of 10 years collected from March 28, 2008 through June 30, 2009 and stored by the University of Iowa Hospital and Clinics Clinical Microbiology Laboratory. Specimens were tested by direct immunofluorescent assay and/or viral culture at the time of collection (influenza A and B, parainfluenza [PIV] 1-3, respiratory syncytial virus [RSV], adenovirus [Ad]) and uniformly by RT-PCR (human metapneumovirus [hMPV], rhinovirus [HRV], human bocavirus [HBoV]) and PCR (Ad) for the current study. Demographic and clinical data were abstracted from electronic medical records.

Results from this study suggest that polymicrobial respiratory tract infections are common in this population. A virus was identified in 61.3% of 349 respiratory specimens from children with confirmed or suspected ARTI. HRV (27.5%), RSV (18.9%), HBoV (8.3%), hMPV (7.7%), and PIV (6.6%) were the most common viruses detected. A viral coinfection was identified in 21.5% of the 214 virus-positive specimens and was most often detected for Ad (53.3% of 15 Ad-positive specimens), HBoV (51.7% of 29 HBoV-positive specimens), PIV (43.5% of 23 PIV-positive specimens), HRV (35.4% of 96 HRV-positive specimens), and RSV (34.8% of 66 RSV-positive specimens). Among the 46 specimens with dual or triple viral coinfections detected, the most frequent virus-virus combination was HRV-RSV (n=12).

We hypothesized that certain host-specific risk factors were associated with the likelihood of viral coinfection. While none of the covariates in the final model were significant, the results were suggestive. Male gender (OR 1.70, 95% CI 0.83-3.46), age between 6 months to 1 year (as compared to children less than 6 months old, OR 2.15, 95% CI 0.75-6.19), and history of any chronic condition that may result in immunosuppression (OR 2.05, 95% CI 0.99-4.23) were each associated with increased odds of viral coinfection ($p > 0.05$).

We also hypothesized that children with coinfections would be more likely to have severe ARTI. Children with viral-bacterial coinfection, as compared to children with viral mono-infection, were more likely to be admitted to an intensive care unit (OR 5.58, 95% CI 1.95-15.96) even after controlling for age, history of prematurity, urban/rural residence, and leukocytosis.

This study will inform medical and public health professionals with regard to the epidemiology of mixed infections and their potential importance as a cause of severe acute respiratory tract infection in children. Furthermore, results of this study could contribute to the ongoing discussion of the importance of diagnostic ability to reliably detect multiple concurrent pathogens in a single patient.

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CHAPTER 1 – INTRODUCTION

Acute respiratory tract infections (ARTIs) account for an estimated 75% of all acute morbidities and are the leading cause of hospitalization for infants and young children in developed countries [1]. Viral pathogens are the most common cause of ARTIs. A number of viruses have been identified as being causally associated with ARTIs, including influenza virus, parainfluenza virus (PIV), respiratory syncytial virus (RSV), adenovirus (Ad), and human rhinovirus (HRV). Additionally, the importance of newly recognized viruses such as human metapneumovirus (hMPV), human bocavirus (HBoV), coronaviruses (CoV), and human polyomaviruses (PyV) in the development of ARTIs is becoming increasingly evident. However, the relative importance of mixed infections, sometimes termed polymicrobial infections, has yet to be determined and constitutes an area of active research. The use of molecular detection techniques has more readily allowed for the simultaneous detection of pathogens in respiratory specimens though few studies have attempted to systematically address the clinical importance of polymicrobial infections [2-21]. Furthermore, the interpretation of the results from these studies is complicated by the numerous differences in study design including, but not limited to, the methods of pathogen detection, the composition of the respiratory pathogen panel included in analysis, and the specific population under review. However, results from recent studies suggest a role for mixed infections as a cause of severe viral ARTIs whereby multiple pathogens may act in synergy to increase the severity of illness (e.g., increased likelihood of hospitalization or more severe clinical manifestations) [3, 4, 7, 8, 11, 13, 17, 22-24].

The primary objectives of this study were to describe the epidemiology of polymicrobial ARTI in children and to investigate the association of polymicrobial infection and severity of illness, with an emphasis on mixed infections that include rhinoviruses, adenoviruses, or human bocavirus. Rhinovirus, adenovirus, and human bocavirus are pathogens for which it has been postulated that mixed infections may lead to increased severity of illness perhaps through an aggravation of symptoms caused by another virus or as helper viruses which enhance the virulence of other pathogens [18, 25-28]. Hence, the current study focused primarily on polymicrobial infections involving these three pathogens. The central hypothesis of the study was that among children with ARTI, those who were coinfected with rhinovirus, adenovirus, or human bocavirus and another pathogen were more likely to be hospitalized than those individuals with single pathogen infections. This hypothesis was addressed by the following specific aims:

Aim 1: To estimate the prevalence of polymicrobial infections associated with acute respiratory tract infection in children and to provide descriptive statistics regarding the epidemiologic and clinical significance of virus-specific mono-infection and coinfection.

Aim 2: To identify host risk factors associated with polymicrobial respiratory infections in children. We hypothesized that certain demographic and clinical covariates were associated with multiple pathogen infections.

Aim 3: To investigate the association of polymicrobial infections, particularly mixed infections involving rhinoviruses, adenoviruses, and/or human bocavirus, with severe acute respiratory tract infection in children. We hypothesized that children who were coinfected with rhinovirus, adenovirus, or human bocavirus and another pathogen were more likely to be hospitalized than those individuals with single pathogen infections.

In order to address these aims, we conducted a retrospective study of archived respiratory specimens from children under the age of 10 years collected between March 28, 2008 and June 30, 2009 and stored by the University of Iowa Hospitals and Clinics Clinical Microbiology Laboratory. The population included inpatients and outpatients. Biologic specimens were linked to the patient medical record in order to conduct in-depth analyses utilizing demographic and clinical covariates. Unlike many of its predecessors, this study was designed with an *a priori* hypothesis in mind concerning a role for coinfections in severe ARTI. A subset of the studies which detected no association between coinfection and illness severity likely were not sufficiently powered to detect an association if one truly existed. Furthermore, few studies controlled for potential confounders, and to our knowledge, none have explored the role of potential effect modifiers.

This study will inform medical and public health professionals with regard to the epidemiology of polymicrobial infections and their potential importance as a cause of severe acute respiratory tract infection in children, thus possibly contributing to the long-term goal of reduced mortality and morbidity associated with ARTI in children. Furthermore, the results of this study may contribute to the ongoing discussion of the importance of diagnostic ability to reliably detect multiple concurrent pathogens in a single patient.

CHAPTER 2 – BACKGROUND AND SIGNFICANCE

2.1 Pediatric acute respiratory tract infections

ARTIs account for an estimated 75% of all acute morbidities and are the leading cause of hospitalization for infants and young children in developed countries [1]. Furthermore, ARTIs are a major cause of death in developing nations [1]. Upper respiratory tract infections such as rhinitis and pharyngitis are among the most common childhood infections, with infants and young children becoming infected on average three to eight times per year [1]. The CDC estimates that between 12 and 32 million upper respiratory tract infections (URTIs) occur annually in children aged 1 to 2 years [29]. Furthermore, these infections can lead to complications such as acute asthma exacerbation, acute otitis media, and lower respiratory tract infections (LRTIs) like bronchitis and pneumonia [1].

Viral pathogens are the most common cause of ARTIs. A number of viruses have been identified as being causally related to ARTIs, including influenza virus, PIV, RSV, Ad, and HRV; newly identified viruses of the respiratory tract such as hMPV, CoV, PyV, and HBoV are being discovered with increasing frequency with the aid of molecular detection techniques [4]. However, the relative importance of mixed infections, sometimes termed polymicrobial infections, has been rarely studied. Results from recent studies emphasize the potential clinical importance of mixed infections as a cause of severe viral ARTIs suggesting that perhaps multiple pathogens may act in synergy to increase the severity of illness [8, 22, 23].

2.2 The importance of polymicrobial infections

The arrival of molecular methods in the biomedical sciences has given investigators the ability to detect polymicrobial infections with increasing ease. However, little is known about the clinical significance of these infections compared to single pathogen infections.

Polymicrobial infections (also known as complex infections, mixed infections, secondary infections, and coinfections) are defined as acute and chronic infections caused by various combinations of viruses, bacteria, fungi, and parasites [22]. Generally, these infections arise when one microorganism creates a niche for or predisposes the host to colonization by other pathogens [22]. More recently, an antagonistic association known as microbial interference, characterized by the generation of a niche in the host that suppresses colonization by other organisms, has been recognized as a potential mechanism of polymicrobial interaction [2].

In a review of prospective epidemiologic studies of community-acquired respiratory virus infections conducted between 1991 and 1995 at Baylor College of Medicine, Drews et al. examined charts for evidence of dual respiratory virus infection (DRVI) [8]. DRVIs were identified as the etiologic cause of 5% of acute respiratory virus infections in patients ranging from less than 1 year to 79 years of age. Of those patients with DRVIs, 42% percent were aged four years or less and 58% had underlying chronic lung disease. In this study, DRVIs were associated with upper and lower respiratory tract infections as well as exacerbations of asthma or chronic obstructive pulmonary disease (COPD). Influenza virus A and picornaviruses such as HRV were the most commonly detected pathogens in coinfections. Patients with DRVI were significantly more likely to be hospitalized than patients with a single virus infection (46.3% and

21.7%, respectively). The studies under review utilized various diagnostic tests including cell culture alone (n=2), cell culture with serology (n=4), and cell culture with serology and PCR (n=2). Not surprisingly, studies which used multiple diagnostic methods more frequently detected viral coinfections.

In a recent study, Bonzel et al. identified viral coinfection in 16.1% of children hospitalized with ARTI using real-time PCR to detect 12 respiratory viruses [4]. RSV was the most frequently detected virus (44.1%) followed by HBoV (19.3%) and HRV (6.7%). RSV-HBoV coinfection was the most frequent combination detected. Viral coinfection was found in 17% of children with bronchitis, 23% of children with bronchiolitis, and 33% of children with pneumonia. The investigators detected a weakly significant association between viral coinfection and more severe manifestation of disease.

The elucidation of the epidemiologic and clinical importance of mixed respiratory infections has become an area of active research in recent years. Coinfection rates vary widely among these studies and are estimated to account for 8.4% to 36.1% of ARTIs for which at least one virus was detected [3, 4, 6, 7, 9, 14-16, 19, 20]. Results from some studies suggest that children infected with 2 or more viruses do not have more severe clinical illness than children infected with only one virus [6, 9, 10, 12, 14]. However, results from other studies have suggested an association between respiratory coinfections and severe illness [3, 4, 7, 11, 13, 17, 20, 24]. In a study of community-acquired pneumonia in children less than 3 years of age, Cilla et al. detected at least one virus in 66.9% of specimens [7]. Of these virus-positive specimens, viral coinfections were detected in 27%. Furthermore, age and viral coinfection were shown to be independent risk factors for hospitalization. In a study of pediatric patients with LRTIs, Bharaj et al. detected at least one virus in 35.2% of specimens and mixed

infections in 18.8% of the virus-positive specimens [3]. A high proportion of children with mixed infections had severe or very severe acute LRTI. Few studies have included both viral and bacterial pathogens when assessing the presence of coinfections [11, 17, 30, 31]. Among these, studies by Jennings et al. and Templeton et al. have suggested increased severity in subjects with mixed virus-bacteria pneumonia [11, 17]. The remaining two studies detected no association.

As evidenced by the above studies, a wide range of coinfection rates have been reported in the literature. This may be due to multiple factors including differences in patient population (e.g., age range, hospital or community source, inclusion or exclusion of comorbidities), timing of the study (e.g., season), diagnostic methods used (e.g., cell culture versus PCR), and pathogens under review (e.g., viral and/or bacterial, inclusion or exclusion of newly recognized agents).

HRV, Ad, and HBoV are pathogens for which it has been postulated that mixed infections may lead to increased severity of illness perhaps through an aggravation of symptoms caused by another virus or as helper viruses which enhance the virulence of other pathogens [18, 25-28]. Each of these pathogens is frequently detected with co-pathogens in respiratory samples from children with ARTIs; however, little is known with regard to the impact of polymicrobial infections on the clinical course of disease.

2.3 Human rhinoviruses

2.3.1 Epidemiology and clinical characteristics

Discovered in the 1950s, human rhinoviruses (HRVs) have long been known for their association with mild upper respiratory disease [1]. To date, over

100 serotypes of HRV, distinguishable by serology or partial viral capsid sequencing, have been identified and grouped into two genetic clusters – HRV A and HRV B. Recently, a novel rhinovirus group (HRV C) has been identified and associated with a broader range of clinical disease than its predecessors, including lower respiratory tract infection [32-47]. Rhinoviruses are estimated to be the cause of 50% to 80% of common colds in the United States and are the most common cause of ARTIs worldwide [45, 48]. The incidence of HRV infection is higher in children than in adults, and almost all children will have experienced at least one HRV infection by the age of two years [49]. In a serological analysis of a prospective cohort of children during their first two years of life, Blomvquist et al. determined that by the age of two years, 91.3% of children in the cohort had rhinovirus-specific antibodies and 79% had confirmed rhinovirus infection as determined by virus detection (methods included observation of CPE in culture and RT-PCR) [50]. HRVs are also a leading cause of asthma and COPD exacerbations [48]. HRV infections are usually characterized by sore throat, nasal congestion, and rhinorrhea; malaise, coughing, and sneezing may also be present [51]. These symptoms are a result of the host's immune response to the virus rather than as a result of the cytopathic effects of the virus. HRVs are most prevalent in early spring and fall in temperate climates, though slight variations in seasonal peaks have been suggested for each of the HRV subgroups [33]. Little is known about the epidemiology of HRV C; however, recent studies suggest that these viruses are frequently detected in patients with other pathogens [47, 52-58], may account for up to half of all rhinovirus-associated hospitalizations [38, 43, 55, 59], and are frequently co-detected in patients with other pathogens.

2.3.2 Potential role in polymicrobial acute respiratory tract infections

Human rhinoviruses are often co-detected with other pathogens, and it has been recognized that HRV infection increases the risk of secondary bacterial infection [26]. Reported coinfection rates involving HRV and at least one additional pathogen vary widely. Recent studies report coinfection rates ranging from 17.7% to 47% [47, 52-58]. Furthermore, some studies suggest that coinfections with HRV lead to more severe disease manifestations [52, 57, 58].

HRV infects epithelial cells which leads to the release of inflammatory mediators by the host immune system such as pro-inflammatory cytokines, vasoactive peptides and chemokines resulting in the migration of leukocytes such as neutrophils, monocytes, and dendritic cells to the site of infection. HRVs have evolved mechanisms to evade the immune system's defenses. HRVs are believed to interfere with the Type I interferon (IFN) pathway, to modulate leukocyte interactions with the receptor ICAM-1, to modulate cytokine production by monocytes, and to target dendritic cells. Each of these mechanisms may result in decreased antiviral activity within the immune system, resulting in increased likelihood of secondary infection [26].

Paradoxically, a role for HRVs in microbial interference has also been postulated. A study by Greer et al. of pediatric inpatients and outpatients noted that although HRV was the most commonly detected pathogen, higher proportions of coinfections were detected for other respiratory viruses including HBoV, RSV, Ad, CoV, human enterovirus (HEV) and PyV [53]. Furthermore, detection of HRV was associated with a consistent pattern of reduced likelihood of coinfection with a number of other viruses. The authors suggest that HRV infection protects its host from infection by other viruses. Other studies have noted similar findings and suggest that the HRV-signaled production of IFNs and

other cytokines causes the cells to enter an antiviral state [60-62]. Further investigation regarding the role of HRV as facilitator and/or inhibitor of secondary infection is warranted.

2.4 Human adenoviruses

2.4.1 Epidemiology and clinical characteristics

Adenoviruses (Ads), first described in the 1950s and 1960s, are double-stranded, non-enveloped DNA viruses belonging to the family *Adenoviridae*. There are 51 recognized serotypes of human Ads which have been classified into six species (A-F) based on DNA homology among other characteristics [63]. Recently, a novel Ad serotype (Ad52, species G) has been described in a patient with gastroenteritis [64]. There is some clinical significance to the division of species as organ specificity and syndromic patterns seem to cluster within species, see Table 1 for associated respiratory syndromes [63]. Serotypes 1 through 5, 7, 14, and 21 most commonly infect the respiratory tract, resulting in a range of symptoms including but not limited to: fever, rhinitis, pharyngitis, cough, bronchiolitis, pneumonia, and acute respiratory distress syndrome. Ad serotypes 1, 2, 3, 5, and 6 are associated with endemic respiratory disease in children, including pharyngitis, bronchitis, croup, and pneumonia; Ad7 is sometimes a cause of fatal pneumonia in children [65]. By the age of two years, most children will have been infected by at least one Ad serotype [65]. The prevalence of adenoviral respiratory infection in children ranges from 2-14% [1]. It has been estimated that as much as 10% to 20% of childhood pneumonias in children under the age of 10 years can be attributed to Ads [65, 66]. The emergence of novel strains of Ad, most recently variants of Ad7, Ad3, and Ad14, have been

associated with outbreaks of respiratory disease in military and civilian populations [67-72].

2.4.2 Potential role in polymicrobial acute respiratory tract infections

As is the case with HRVs, several case reports and studies support the hypothesis that infection with Ad can facilitate secondary infection [18, 25, 27] with reported coinfection rates ranging from 0-77.8% [7, 14, 15, 53, 73-77]. However, the mechanisms by which this occurs require further elucidation. Singh et al. suggest that perhaps this is a result of direct virus-virus interactions, an effect of cohabitating viruses on host cell function, or a result of impaired host immune response [78]. Others suggest that perhaps the reports of severe pneumonia and bronchiolitis are a result of reactivation of latent adenoviral infection of the respiratory tract as a result of infection with another pathogen [79]. Replication-competent adenovirus and adenoviral DNA have been detected in human adenoidal and tonsillar tissue leading investigators to believe that the virus can remain latent in these tissues for years [80, 81]. More recently, Garnett et al. have shown that species C adenoviruses can persist in mucosal lymphocytes and can be reactivated upon stimulation resulting in RNA transcription, DNA replication, and infectious virus production [82, 83].

2.5 Human bocavirus

2.5.1 Epidemiology and clinical characteristics

Human bocavirus (HBoV) is a newly identified, single-stranded DNA virus in the family *Parvoviridae*. HBoV was first described in 2005 in nasopharyngeal aspirates of children with ARTIs and has subsequently been reported in respiratory samples from children worldwide with reported prevalence ranging

from 1.5-18.9% [28, 84]. A number of studies report that HBoV can be detected year-round with peaks in early winter [28, 85]. HBoV infection is most prevalent in children under the age of three years and is believed to be a likely cause of lower respiratory tract infections; however, causality has not been firmly established due to the few number of epidemiologic studies involving a control group without respiratory illness and inability to grow HBoV in cell culture until recently [28, 86]. However, evidence for HBoV virulence and a causal association with ARTI is increasing. Of the four case-control studies conducted to date, all but one detected HBoV more frequently in cases than asymptomatic controls [85, 87-89]. Additionally, a recent study by Don et al. concluded that HBoV is capable of inducing a specific immune response [90]. Furthermore, it was noted that an increasing antibody response was correlated with a decrease in detectable viral genomes. Clinical symptoms most frequently reported in individuals with HBoV infection include cough, rhinorrhea, and fever. The most common diagnoses associated with HBoV infection include upper respiratory tract infection, bronchitis, bronchiolitis, pneumonia, acute wheezing, and exacerbation of asthma [28]. Gastroenteric symptoms have been reported in up to 25% of HBoV-positive individuals, though the role of HBoV as an agent of gastrointestinal illness is heavily debated [91]. Two novel strains (HBoV-2 and HBoV-3) have recently been described in the literature; both strains were first isolated from stool samples and their epidemiologic and clinical importance in ARTI and gastroenteritis are unclear [92-95].

2.5.2 Potential role in polymicrobial acute respiratory tract infections

HBoV is frequently co-detected with other pathogens with co-detection rates ranging from 18% to 90% [28]. A number of hypotheses have been put

forward to explain this high rate of co-detection. One such hypothesis is that HBoV harmlessly persists and is shed for extended periods of time following symptomatic infection; some studies have noted prolonged periods of asymptomatic shedding (up to 4.5 months) following symptomatic illness in immunocompetent children [96-98]. Others believe that HBoV is more intimately associated with pathogenesis and the aggravation of respiratory symptoms caused by either an underlying condition such as asthma or infection by another respiratory pathogen. Some hypothesize that HBoV may act as a helper virus which increases the pathogenesis of other viruses or that HBoV itself requires another virus in order to infect epithelial cells. Manning et al. suggest that it is possible that HBoV increases the severity of RSV and other LRTI-associated viruses [99]. As Fry et al. note, parvoviruses such as HBoV are dependent on host cellular functions for replication and only multiply in cells that are in the process of their own DNA replication. They suggest that perhaps coviral-induced cellular damage results in increased levels of cellular division allowing for the replication of HBoV [87].

Several studies have found no significant clinical findings, such as increased severity of illness, in association with HBoV coinfection [100-103]. However, a few recent studies suggest that there may in fact be clinical significance to HBoV coinfection [13, 23, 87]. Fry et al. noted that more patients with pneumonia associated with HBoV-RSV or HBoV-PIV coinfections had wheezing than did patients with RSV and PIV alone [87]. Through a prospective study of HBoV in children with acute respiratory disease, Esposito et al. concluded that HBoV coinfections had a significantly greater clinical and socioeconomic impact on the children and their households as measured by increased association with LRTI, proportion of patients requiring laboratory tests

and radiographic examinations, and hospitalization rate as compared to children with HBoV infection alone [23].

Until recently, the direct study of HBoV coinfections has been limited by the lack of a permissive cell line [86]. Additional epidemiologic studies are necessary to further elucidate the clinical significance of HBoV coinfection.

2.6 Public health and clinical significance

ARTIs account for an estimated 75% of all acute morbidities and are the leading cause of hospitalization for infants and young children in developed countries [1]. Most ARTIs arise from a viral origin. This study will inform medical and public health professionals with regard to the epidemiology of mixed infections and their potential importance as a cause of severe acute respiratory tract infection in children, thus possibly contributing to the long-term goal of reduced mortality and morbidity associated with ARTI in children. Furthermore, results of this study could contribute to the ongoing discussion of the importance of diagnostic ability to reliably detect multiple concurrent pathogens in a single patient.

Table 1 Select respiratory clinical syndromes associated with adenovirus infections

Clinical Syndrome	Ad Species	Common Serotypes	Population at Risk
Endemic respiratory	B, C	1, 2, 3, 5, 6, 7	Infants, children
Epidemic respiratory	B, C	5, 7	Children (day care)
Acute respiratory disease	B, E	3, 4, 7, 14, 21	Military Recruits

CHAPTER 3 – RESEARCH DESIGN AND METHODS

3.1 Overview of study design

We conducted a retrospective, cross-sectional study of 559 frozen, archived respiratory specimens from 421 children under the age of 10 years collected from March 28, 2008 through June 30, 2009 and stored by the University of Iowa Hospital and Clinics (UIHC) Clinical Microbiology Laboratory. The population included outpatients and inpatients. In addition to routine testing for viral pathogens conducted by the UIHC laboratory, we (Center for Emerging Infectious Diseases, CEID) also tested these specimens for rhinoviruses, adenoviruses, human bocavirus, and human metapneumovirus by reverse transcription polymerase chain reaction (RT-PCR) or PCR methods followed by agarose gel electrophoresis. Specimens that were positive for HRV, Ad or HBoV were submitted for further analysis, specifically DNA/cDNA nucleotide sequencing to identify genotype and phylogenetic analysis to compare those strains circulating in our population to strains described in the published literature. A respiratory coinfection was defined as a sample with a positive test result for 2 or more pathogens from tests performed by UIHC and/or CEID.

All primary analyses were limited to either confirmed (physician diagnosis) or suspected (physician-documented signs and symptoms) ARTI. Secondary analyses also included a third group of children for whom a concern for ARTI existed but traditional signs and symptoms such as cough and runny nose were not present; for example, a neonate with episodes of oxygen desaturation and a child with episodes of febrile seizure unaccompanied by respiratory symptoms would be included in this latter category. Children for whom a specimen was

submitted but who were eventually diagnosed with a chronic respiratory condition (e.g., laryngomalacia) were excluded from all analyses.

We estimated the period prevalence of polymicrobial infections associated with acute respiratory tract infection in children under the age of 10 years whose samples were submitted to the UIHC Clinical Microbiology Laboratory during the study period (Aim 1). Furthermore, a review of the patient medical record was conducted to obtain relevant demographic and clinical covariates. These data were utilized in statistical analyses and modeling to identify host risk factors associated with polymicrobial respiratory tract infections in our study population (Aim 2). To investigate the association of polymicrobial infections, particularly mixed infections involving HRV, Ad, and HBoV with severe ARTI in children, we conducted additional case-control analyses of the cross-sectional data (Aim 3). Exposure was defined as a positive test result for rhinovirus, adenovirus, or human bocavirus (as performed by CEID) and at least one additional positive result from other tests performed on the specimen by UIHC and/or CEID. A case was defined as a child who was hospitalized at the UIHC between March 28, 2008 and June 30, 2009 as a result of ARTI for whom a respiratory specimen was submitted. Children for whom a respiratory specimen was submitted but who were not hospitalized during this time period as a result of ARTI served as controls. Once again, clinical and demographic data from the patient medical record were utilized in statistical analyses to identify host risk factors, control for potential confounders, and identify effect modifiers associated with severe ARTI and respiratory coinfections. Secondary analyses were conducted to identify associations between ARTI coinfection and other markers of severe infection. Among hospitalized patients, secondary outcomes of interest included intensive care unit admission, length of stay, and requirement for mechanical ventilation.

Among all patients, additional outcomes of interest included requirement for supplemental oxygen, oxygen saturation less than 90%, and use of a bronchodilator.

This study was approved by the University of Iowa Institutional Review Board and was granted a waiver of informed consent and a waiver of HIPAA authorization.

3.2 Clinical respiratory specimens

The Clinical Microbiology Laboratory at the University of Iowa Hospital and Clinics (UIHC) receives specimens for respiratory viral direct antigen assays and/or culture from various clinics, hospital wards, and intensive care units. Most often, respiratory virus specimens are obtained from nasopharyngeal washes, tracheal aspirates, and bronchoalveolar lavage procedures. Occasionally, nasal swabs and other respiratory specimens are submitted. In the year previous to the current study period, approximately 50% of all respiratory specimens submitted to the UIHC Clinical Microbiology Laboratory originated from outpatients. In order to be eligible for this study, the respiratory sample must have originated from a child under the age of 10 years at the time of specimen collection and must have been collected between November 1, 2007 and June 30, 2009. As the UIHC Clinical Microbiology Laboratory stores specimens for a period of 1 year, only specimens collected on or after March 28, 2008 were available for this study. Furthermore, specimens that were not archived were not available for the study. A complete description of eligible, included, and excluded respiratory specimens appears in Chapter 4 (Figure 1). Specimens were transported to the CEID laboratory in dry ice transport containers and stored at -80°C until thawed for nucleic acid extraction procedures.

Respiratory specimens received from the UIHC Clinical Microbiology Laboratory were labeled with patient name, patient medical record number, and laboratory accession number. Patient identifiers were removed and the specimen was blinded according to the following procedure: Upon arrival at the CEID laboratory, specimens were taken to a data coordinator. The data coordinator was not involved in the testing of the specimens. The data coordinator recorded the patient medical record number and the laboratory accession number into a password-protected database file maintained in Microsoft Access. Members of the research team who were charged with molecular testing of the specimens did not have access to this file until all laboratory testing was complete, and then only to link medical record information to the appropriate specimen. Within the database, the data coordinator assigned a 4-digit study ID number (beginning with 0001) to each specimen. The data coordinator removed the original label from the specimen, and the specimen was re-labeled using the 4-digit study ID number. Specimen labels with patient identifiers were destroyed.

3.3 Clinical data

3.3.1 Description

UIHC Clinical Microbiology Laboratory specimens were labeled with a laboratory accession number and patient medical record number. These identification numbers were retained by the investigator and were linked to patient medical record data via the Epic electronic medical record system. These data were used to generate descriptive statistics for virus-specific mono-infections and coinfections (Aim 1), for risk factor analyses (Aim 2), and for the

control of potential confounders and identification of effect modifiers in multivariate models (Aim 3).

A database containing the following demographic variables was requested from the university's Health Care Information Systems (HCIS) specialists: patient gender, date of birth, date of death if applicable, race/ethnicity, and zip code of primary residence.

Due to time constraints and a significant delay in receiving data from HCIS, the following clinical covariates were abstracted from the patient's medical record by the principal investigator: clinic source for specimen, date of specimen collection, clinical signs and symptoms, clinical diagnosis, hospital admission and discharge dates if applicable, ICU admission and discharge dates if applicable, date and cause of death if applicable, laboratory results regarding other pathogens detected in specimens collected during illness (viral, bacterial, and fungal), current or recent use of antimicrobials, vaccination history, exposure to second-hand tobacco smoke, history of chronic respiratory conditions, history of chronic medical conditions that may lead to immunosuppression, related hospital visits (inpatient or outpatient), requirement for mechanical ventilation, requirement for supplemental oxygen, bronchodilator use, vitals associated with infection of interest (e.g., oxygen saturation), white blood cell count at time of visit (if available), C-reactive protein level at time of visit (if available), and payor (insurance coverage).

The following laboratory covariates were provided by the UIHC Clinical Microbiology Laboratory: patient medical record number, specimen accession number, date specimen received, specimen source (e.g., nasopharyngeal wash), and results from viral antigen testing and/or culture.

3.3.2 Coding of clinical data

A complete list of clinical variables included in this study, the source of the variable, and a description of how variables were coded can be found in Table 2.

3.4 Specimen processing

3.4.1 UIHC Clinical Microbiology Laboratory procedures

The Clinical Microbiology Laboratory routine respiratory virus culture procedure involved inoculating supernatant fluid from processed specimens into two R-Mix Too shell vials (mixed cell line of A549/MDCK). These vials were then centrifuged for 1 hour and incubated for 48 hours at 37°C. The cover slip of one shell vial was fixed and stained by immunofluorescence (IF) using a pooled reagent for influenza A and B, parainfluenza 1, 2, and 3, adenovirus, and respiratory syncytial virus. A positive pooled result was followed by staining for individual respiratory viruses. Cells were stained independent of the presence of CPE. If CPE was observed, but the IF stain was negative, then the specimen was re-inoculated and evaluated for other viruses routinely cultured in the laboratory. A 1-2 ml aliquot of remaining processed specimen was diluted with an equal amount of 20% MEM and stored in cryovials at -80°C.

Direct IF antibody stains (DFAs) are performed directly on patient specimens and may be ordered for single viruses or the full respiratory virus panel. Because DFA is less sensitive than culture, specimens with negative DFA results were submitted for virus culture. If the DFA was positive, culture was not performed. Furthermore, if a specimen is submitted out of season for viral culture, DFA would not normally be completed.

3.4.2 CEID procedures

3.4.2.1 Overview of Molecular Methods. Ad PCR and HRV, HBoV and hMPV RT-PCRs were performed at the CEID laboratory. Even though a specific hypothesis regarding hMPV coinfection was not included in this study, the virus was included in molecular analyses for completeness of data regarding coinfections as hMPV is recognized as a common viral cause of ARTI in children. At the time of this study, the Clinical Microbiology Lab did not perform routine testing for hMPV.

3.4.2.2 Nucleic acid extraction. The MagMax-96 Total RNA Isolation Kit (Applied Biosystems/Ambion, Austin, TX) and Thermo KingFisher magnetic processor were used to extract viral nucleic acids (both RNA and DNA) from respiratory specimens. Briefly, a guanidinium thiocyanate-based solution rapidly releases viral RNA and DNA while simultaneously inactivating nucleases within the sample (50µl volume). Paramagnetic beads with a nucleic acid binding surface were added to bind nucleic acids. The beads and attached nucleic acids were captured on magnets while proteins, other contaminants, and residual binding solution were washed away. Nucleic acids were eluted in a small volume of elution buffer. Approximately 50µl of total nucleic acid (includes viral and cellular nucleic acid) was stored at -80°C until further processing by PCR.

3.4.2.3 Two-step reverse transcription polymerase chain reaction (RT-PCR). A two-step RT-PCR was utilized to generate cDNA for all virus-specific RT-PCR assays (includes HRV, HBoV, and hMPV). Random decamers (4.0µl, 50µM) were added to 22.0µl of each sample or control in 0.2ml thin-walled PCR tubes. Samples were then placed in the thermocycler at 80°C for 3 minutes.

14.0µl of RT reaction mix (containing 7.7µl Gibco UltraPure dH_2O, 4.0µl 10X RT buffer, 0.8µl 25mM dNTP, 0.5µl 40U/µl Ambion RNase inhibitor, and 1.0µl 100U/µl Ambion M-MLV-Reverse Transcriptase per sample) was added to each tube. RT was performed under the following conditions: 44°C for 1 hour, followed by 92°C for 10 minutes and a 4°C holding period.

3.4.2.4 Rhinovirus PCR. Procedures have been adapted from Kiang et al. [104] and Savolainen et al. [105, 106]. A gold standard molecular typing method for human rhinoviruses does not exist. Current classification of HRVs is based on capsid region (VP4/VP2) coding sequences. More recent interest in HRV genetic typing has focused on the 5' noncoding region (NCR) which possesses relatively conserved areas that allow for broad-spectrum primer design. Genotyping results from different regions do not always agree. Piralla et al. compared the methods of Kiang et al. (5' NCR) and Savolainen et al. (VP4/VP2) side-by-side and showed that (1) the 5' NCR method showed greater sensitivity allowing strains not typeable by the VP4/VP2 method to be typed, (2) the VP4/VP2 method classified all HRV C strains as belonging to a single homogenous group, and (3) the 5' NCR method classified new HRV C stains into four groups (including HRV A), all of which fell into the HRV C group when tested by the VP4/VP2 method. Given our interest in comparing results from this study to previous studies of HRV and HRV C and the frequency with which the methods of Savolainen et al. were used in these studies, we decided to test all clinical samples by the VP4/VP2 method first, followed by typing of all HRV-positive samples by the 5' NCR method.

The first strand cDNA generated by the RT step described above was used as the template for HRV PCR. A clinical isolate of HRV A was used as a positive control.

PCR was performed using primer pair 9895-forward (5'-GGG ACC AAC TAC TTT GGG TGT CCG TGT-3') and 9565-reverse (5'-GCA TCI GGY ARY TTC CAC CAC CAN CC-3') generating a product of 549 bp spanning the hypervariable region of the 5' NCR, the entire VP4 gene, and the 5' terminus of the VP2 gene [106]. Briefly, 5µl of the first strand cDNA produced during RT was added to 45.0µl PCR master mix (containing 37.2 µl Gibco UltraPure dH_2O, 5.0µl Invitrogen 10X PCR Buffer minus Mg, 0.4µl 25mM dNTP, 1.5µl 50mM $MgCl_2$, 0.2µl each of 50mM forward and reverse primers, and 0.5µl 5U/µl Invitrogen Platinum Taq DNA polymerase per sample). PCR was performed under the following conditions: 94°C for 5 minutes, followed by 40 cycles of 94°C for 15 seconds, 60°C for 15 seconds, and 72°C for 30 seconds. PCR products were visualized on an ethidium bromide-stained 1% agarose gel, and positive samples were submitted for cDNA nucleotide sequencing and phylogenetic analysis to determine genotype.

For all HRV-positive specimens, a second PCR was performed using forward primer DK001 (5'-CAA GCA CTT CTG TTT CCC-3') and reverse primer DK004 (5'-CAC GGA CAC CCA AAG TAG T-3') generating a product of 390 bp spanning approximately two-thirds of the 5' NCR [104]. Briefly, 5µl of the first strand cDNA produced during RT was added to 45.0µl PCR master mix (containing 37.2 µl Gibco UltraPure dH_2O, 5.0µl Invitrogen 10X PCR Buffer minus Mg, 0.4µl 25mM dNTP, 1.5µl 50mM $MgCl_2$, 0.2µl each of 50mM forward and reverse primers, and 0.5µl 5U/µl Invitrogen Platinum Taq DNA polymerase per sample). PCR was performed under the following conditions: 95°C for 5

minutes, followed by 40 cycles of 95°C for 15 seconds, 55°C for 15 seconds, and 72°C for 30 seconds. PCR products were visualized on an ethidium bromide-stained 1% agarose gel, and positive samples were submitted for cDNA nucleotide sequencing and phylogenetic analysis to determine genotype.

3.4.2.5 Human bocavirus PCR. Procedures have been adapted from Sloots et al. [107]. The first strand cDNA generated by the RT step described above was used as the template for the HBoV PCR. A plasmid containing partial NS1 and NP-1 genes corresponding to nucleotide numbers 1394 to 2691 of HBoV strain st1 was used as a positive control (kindly provided by Dr. Dean Erdman, CDC).

PCR was performed using primer pair HBoV01.2 (5'-TAT GGC CAA GGC AAT CGT CCA AG-3') and HBoV02.2 (5'- GCC GCG TGA ACA TGA GAA ACA GA-3') generating a product of 266 bp spanning the NS1 gene. Briefly, 5µl of the first strand cDNA produced during RT was added to 45.0µl PCR master mix (containing 37.2 µl Gibco UltraPure dH_2O, 5.0µl Invitrogen 10X PCR Buffer minus Mg, 0.4µl 25mM dNTP, 1.5µl 50mM $MgCl_2$, 0.2µl each of 50mM forward and reverse primers, and 0.5µl 5U/µl Invitrogen Platinum Taq DNA polymerase per sample). PCR was performed under the following conditions: 94°C for 1 minute, followed by 45 cycles of 94°C for 20 seconds, 56°C for 20 seconds, and 72°C for 30 seconds; and a single cycle at 72°C for 5 minutes. PCR products were visualized on an ethidium bromide-stained 1% agarose gel, and positive samples were submitted for cDNA nucleotide sequencing and phylogenetic analysis.

3.4.2.6 Human metapneumovirus PCR. Procedures have been adapted from Gray et al. [108]. The first strand cDNA generated by the RT step described above was used as the template for the HBoV PCR. A clinical isolate of hMPV was used as a positive control.

PCR was performed using primer pair F2 forward (5'-GAG CAA ATT GAA AAT CCC AGA CA-3') and F2 reverse (5'-GAA AAC TGC CGC ACA ACA TTT AG-3') generating a product of 347 bp spanning the F2 gene [109]. Briefly, 5µl of the first strand cDNA produced during RT was added to 45.0µl PCR master mix (containing 37.2 µl Gibco UltraPure dH_2O, 5.0µl Invitrogen 10X PCR Buffer minus Mg, 0.4µl 25mM dNTP, 1.5µl 50mM $MgCl_2$, 0.2µl each of 50mM forward and reverse primers, and 0.5µl 5U/µl Invitrogen Platinum Taq DNA polymerase per sample). PCR was performed under the following conditions: 95°C for 2 minutes, followed by 34 cycles of 94°C for 30 seconds, 52°C for 30 seconds, and 72°C for 1 minute; and a single cycle at 72°C for 10 minutes. PCR products were visualized on an ethidium bromide-stained 1% agarose gel. hMPV-positive samples were not submitted for sequencing.

3.4.2.7 Adenovirus PCR. Procedures have been adapted from Lu et al. [110]. A clinical isolate of human Ad5 was used as a positive control. As molecular methods are considered to be more sensitive than DFA procedures for the detection of adenoviruses [1, 6], the results of the adenovirus PCR assay superseded the results of the DFA assay and viral culture performed by the UIHC Clinical Microbiology Laboratory. A comparison of the results of these methods was included in our analysis.

PCR was performed on an initial sample of 5µl using primer pair AdhexF1 (5'-TIC TTT GAC ATI CGI GGI GTI CTI GA-3') and AdhexR1 (5'-CTG TCI ACI

GCC TGR TTC CAC A-3') generating a product of 764 to 896 bp spanning the hypervariable regions 1-6 of the hexon gene [110]. Briefly, 5µl of the eluted sample was added to 45.0µl PCR master mix (containing 37.2 µl Gibco UltraPure dH_2O, 5.0µl Invitrogen 10X PCR Buffer minus Mg, 0.4µl 25mM dNTP, 1.5µl 50mM $MgCl_2$, 0.2µl each of 50mM forward and reverse primers, and 0.5µl 5U/µl Invitrogen Platinum Taq DNA polymerase per sample). PCR was performed under the following conditions: 94°C for 2 minutes, followed by 34 cycles of 94°C for 30 seconds, 50°C for 30 seconds, and 72°C for 1 minute, followed by one cycle 72°C for 5 minutes. M13 universal priming tails (forward, 5'-TGT AAA ACG ACG GCC AGT-3'; and reverse, 5'-CAG GAA ACA GCT ATG ACC-3') have been added to the previously described primers to facilitate sequencing. PCR products were visualized on an ethidium bromide-stained 1% agarose gel, and positive samples were submitted for DNA nucleotide sequencing to determine genotype.

3.4.2.8 DNA/cDNA sequencing. The University of Iowa's DNA Core Facility houses an Applied Biosystems Model 3730xl (96-capillary) DNA sequencer and offers DNA sequencing on a fee-for-service basis to investigators. The forward and reverse sequences were combined using BioEdit software (Ibis Therapeutics) and were compared with nucleotide sequences submitted to NCBI GenBank. Specimens that yielded identity scores of ≥ 90% were considered good genotypic matches.

3.4.2.9 Phylogenetic analyses. Amplified nucleotide sequences were aligned and neighbor-joining phylogenetic trees were generated using a maximum composite likelihood method. Bootstrap analysis was completed using

1000 repetitions. Alignment and phylogenetic analyses were performed using Mega 4.0 software [111].

3.5 Power calculations

Power calculations were based upon Specific Aim 3: To investigate the association of mixed infections, particularly mixed infections involving rhinoviruses, adenoviruses, or human bocavirus, with severe acute respiratory tract infection in children.

Severity of acute respiratory tract infection was defined as a categorical variable (outpatient/control or inpatient/case). Note that the probability of coinfection was based upon virus-specific prevalence and coinfection estimates (rhinovirus – 50% prevalence, 25% coinfection rate; adenovirus – 10% prevalence, 25% coinfection rate; human bocavirus - 10% prevalence, 75% coinfection rate) and the assumption that 30% of patients with single pathogen infections were inpatients.

Although we adjusted for several covariates in many of our analyses, here we considered the theoretical power of a simple comparison of two groups. The sample size needed to have 80% power to detect an unadjusted 4.0 odds ratio of hospitalization (among subjects with mixed pathogen acute respiratory tract infection when compared to subjects with single pathogen acute respiratory tract infection) was determined to be 300-1000 subjects (varied by virus).

Under Aim 3, due to time constraints for specimen collection and processing, we were only able to achieve a sufficient sample size to address HRV coinfections.

3.6 Statistical analyses

3.6.1 Specific aim 1

To estimate the prevalence of polymicrobial infections associated with acute respiratory tract infection in children and to provide descriptive statistics regarding the epidemiologic and clinical significance of virus-specific mono-infection and coinfection.

Period prevalence and 95% binomial confidence intervals were calculated for the following: infection with HRV, HBoV, Ad, hMPV, influenza A, influenza B, PIV 1-3, and RSV and coinfection. Coinfection was defined as a sample with a positive test result for 2 or more respiratory viruses from tests performed by UIHC and/or CEID. Though other viral, bacterial, and fungal microbiology results may have been available for an included episode of ARTI, since these tests were not performed on the same specimen as was viral culture, viral antigen detection, or viral PCR, they were not included in the primary analysis for this aim. However, information regarding the frequency of these other infections was included in secondary descriptive analyses.

The prevalence of selected demographic, clinical, and laboratory variables was also determined for all samples (virus-positive or -negative), virus-specific mono-infections, and all coinfections. Similar descriptive statistics were alslo generated for HRV-positive mono-infections and coinfections stratified by HRV group.

3.6.2 Specific aim 2

To identify host risk factors associated with polymicrobial respiratory infections in children. We hypothesized that certain demographic and clinical covariates were associated with multiple pathogen infections.

This analysis was conducted for (1) all coinfections and (2) HRV-positive coinfections. Analyses were limited to either confirmed (physician diagnosis) or suspected (physician-documented signs and symptoms) ARTI and were further limited to the first specimen collected from the first ARTI episode per individual (excludes duplicates). Secondary analyses also included a third group of children for whom a concern for ARTI existed but traditional signs and symptoms such as cough and runny nose were not present. Children for whom a specimen was submitted but who were eventually diagnosed with a chronic respiratory condition (e.g., laryngomalacia) were excluded from all analyses. Furthermore, to be included in analysis, a specimen must have been positive for at least one virus. We excluded specimens from individuals for whom medical record abstraction was not possible.

Univariate descriptive statistics were calculated for categorical (frequency, percent) and continuous (mean, standard deviation, maximum and minimum values) variables. Continuous variables (i.e., age) were re-classified as categorical variables where a linear effect was not considered biologically plausible. Bivariate analyses such as Pearson's chi-square test, Fisher's exact test, and bivariate logistic regression were used to examine potential risk factor associations with the respiratory coinfection.

The following variables were included in the analysis: patient gender, age, race/ethnicity, rural or urban residence as determined by zip code, exposure to second-hand tobacco smoke (when available), history of chronic respiratory conditions, history of chronic medical conditions that may lead to immunosuppression, and payor (insurance coverage).

Beginning with a saturated model, manual backwards elimination and multivariate logistic regression modeling were used to identify the model that best

predicted the occurrence of polymicrobial infections in this population. Variables were kept in the model if the corresponding parameter estimate was significant at $p<0.2$. Nested models were compared using the likelihood ratio test. If the difference in the maximum likelihood estimate was significant ($p<0.05$) then we concluded that the full model provided a better fit to the data than the reduced model. Otherwise, if the difference in the maximum likelihood estimate was not significant, we continued with the reduced model.

3.6.3 Specific aim 3

To investigate the association of polymicrobial infections with severe acute respiratory tract infection in children. We hypothesized that children who were coinfected with more than one pathogen were more likely to be hospitalized than those individuals with single pathogen infections. Analyses were conducted separately for all coinfections and for rhinovirus-positive coinfections.

Analyses were limited to either confirmed (physician diagnosis) or suspected (physician-documented signs and symptoms) ARTI and were further limited to the first specimen collected from the first ARTI episode per individual (excludes duplicates). Secondary analyses also included a third group of children for whom a concern for ARTI existed but traditional signs and symptoms such as cough and runny nose were not present. Children for whom a specimen was submitted but who were eventually diagnosed with a chronic respiratory condition (e.g., laryngomalacia) were excluded from all analyses. Furthermore, to be included in analysis, a specimen must have been positive for at least one virus. We excluded specimens from individuals for whom medical record abstraction was not possible.

Severity of acute respiratory tract infection was the outcome of interest and was included as a categorical variable (defined as outpatient or hospitalized). Secondary analyses were conducted to identify associations between ARTI coinfection and other potential indicators of severe infection. Among hospitalized patients, secondary outcomes of interest included intensive care unit admission, number of days hospitalized (required linear regression), and requirement for mechanical ventilation. Among all patients, additional outcomes of interest included requirement for supplemental oxygen, oxygen saturation less than 90%, and use of a bronchodilator.

The exposures of interest were presence of any respiratory coinfection or presence of an HRV-positive coinfection. Subjects with an acute respiratory tract infection caused by a single pathogen were considered unexposed for the purpose of analysis. Secondary analyses of virus-bacteria coinfections were limited to children with confirmed or suspected ARTI for whom (1) any bacterial test was ordered or (2) any respiratory bacterial test was ordered (not limited to respiratory culture).

Univariate descriptive statistics were calculated for categorical (frequency, percent) and continuous (mean, standard deviation, maximum and minimum values) variables. Continuous variables (i.e., age) were re-classified as categorical variables where a linear effect was not considered biologically plausible. Bivariate analyses were performed to identify covariates of interest, potential confounders associated either with exposure and outcome, and potential effect modifiers. Identified confounders remained in the final model even if the confounder itself was not statistically significant. Bivariate logistic regression was used to determine crude unadjusted odds ratios (and 95% confidence intervals) for hospitalization among exposed as compared to

unexposed. Odds ratios and 95% confidence intervals were adjusted for the effect of potential confounders (identified in the literature or in bivariate analyses) using multivariate logistic regression. The potential for effect modification by history of chronic respiratory disease and history of immunosuppressive condition was also of interest to the investigator; hence, interaction terms including these variables with the exposure variable (coinfection) were included in analyses and remained in the final model if significant. Beginning with a saturated model, manual backwards elimination and multivariate logistic regression modeling was used to decide which of the remaining covariates of interest identified in bivariate analyses, if any, were to be included in the model.

The following variables were included in the analysis: patient gender, age, race/ethnicity, rural or urban residence as determined by zip code, current or recent use of antimicrobials, exposure to second-hand tobacco smoke (when available), history of chronic respiratory conditions, history of chronic medical conditions that may lead to immunosuppression, payor (insurance coverage), white blood cell count, and C-reactive protein levels.

3.7 Quality assurance/quality control

3.7.1 Laboratory analysis

All laboratory tests were performed by trained CEID laboratory personnel with approximately 95% of all laboratory testing completed by the principal investigator. Appropriate positive and negative method (i.e., nucleic acid extraction and PCR) controls were analyzed alongside clinical respiratory specimens. Additionally, nucleic acid extraction and amplification procedures were physically separated into different laboratory suites in order to avoid contamination of clinical specimens by amplicons.

3.7.2 Data analysis

Clinical and demographic data from the patient medical record were checked for completeness and accuracy by the principal investigator using SAS v9.2. Incomplete, missing, or erroneous data were corrected following further review of the patient medical record by the principal investigator.

Table 2 Clinical covariates abstracted from the medical record

Covariate	Source	Comments
Gender	HCIS database, MR	Male (yes/no)
Date of birth	HCIS database, MR	Used to calculate age (continuous) and age categories 4 level – <6 months, 6 months – 1 year, 1-5 years, >5 years 3 level – <1 year, 1-5 years, >5 years
Date of death	HCIS database, MR	
Race/ethnicity	HCIS database, MR	Categorical 4 level – Caucasian, African-American, Hispanic, other 2 level – Caucasian, other (combines all non-Caucasian categories)
Zip code	HCIS database, MR	Applied RUCA 2 codes to categorize as urban or rural 4 level – urban, large rural, small rural, isolate rural 2 level – urban, rural (combines 3 rural categories)
Payor/Insurance coverage	MR – H&P notes, discharge notes, physician notes	Categorized primary payor as Medicaid or other (yes/no)
Clinic	MR – Patient encounter summary	
Date of specimen collection	MR – Microbiology results	
Clinical signs and symptoms	MR – H&P notes, discharge notes, physician notes	Abstracted information about presence of symptoms (yes/no) such as fever, cough, wheezing, nasal symptoms, breathing difficulty, apnea
Clinical diagnosis	MR – H&P notes, discharge notes, physician notes	
Hospital admission and discharge dates	MR – discharge notes	Used to calculate length of stay (continuous)
ICU admission and discharge dates	MR – discharge notes	Used to calculate length of stay (continuous)
Cause of death	MR – discharge notes, medical examiner's notes	Used to determine if ARTI was cause of death
Other microbiology lab results	MR – Microbiology Results	Used to identify additional coinfections (particularly bacterial)
Antimicrobial use	MR – H&P notes, discharge notes, physician notes	Categorized as recent use/prior to UIHC visit (yes/no), UIHC administered (yes/no), and UIHC prescription to take home (yes/no)
Vaccination history	MR – Immunization history	
History of chronic respiratory condition	MR – H&P notes, patient summary	Categorized as any (yes/no) and further defined as structural defect (yes/no) and asthma (yes/no); structural defects include conditions such as bronchopulmonary dysplasia, laryngomalacia, bronchomalacia, tracheomalacia, restrictive lung disease, etc.
History of chronic medical condition that may lead to increased risk of ARTI	MR – H&P notes, patient summary	Categorized as history of cancer (yes/no), history of transplant (yes/no), history of any immunosuppressive condition other than prematurity (includes cancer, transplant, primary or secondary immunodeficiency such as genetic disorders, congenital cardiac defects, malnutrition, etc.), and history of premature birth (yes/no)
Related hospital visits (inpatient or outpatient)	MR – H&P notes, discharge notes, physician notes	
Requirement for mechanical ventilation	MR – H&P notes, discharge notes, physician notes	Yes/no
Requirement for supplemental oxygen	MR – H&P notes, discharge notes, physician notes	Yes/no

Table 2 Continued

Covariate	Source	Comments
Bronchodilator administered	MR – H&P notes, discharge notes, physician notes	Yes/no
Oxygen saturation less than 90%	MR – H&P notes, discharge notes, physician notes	Yes/no
White blood cell (WBC) count	MR – Lab results	Categorized as leukopenia (yes/no) and/or leukocytosis (yes/no) based on age appropriate normal WBC count ranges
C-reactive protein (CRP) > 0.5 mg/L	MR – Lab results	Yes/no
Second-hand tobacco smoke exposure	MR – H&P notes	None, direct (adult smokes with child in same room), indirect (adult smokes away from the child, but does not change clothes before contacting child)

Note: HCIS (Health Care Information Systems), MR (Medical Record), H&P (History and Physical)

CHAPTER 4 – RESULTS

4.1 Overview of specimen population

We conducted a retrospective study of 559 archived respiratory specimens from children under the age of 10 years collected from March 28, 2008 through June 30, 2009 and stored by the University of Iowa Hospital and Clinics Clinical Microbiology Laboratory. Primary analysis was limited to the first specimen collected from the first ARTI episode per child during the study period thereby excluding duplicates (n=421), specimens from children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI (n=349), and to children with accessible medical records (n=346). Details regarding the number of eligible, included, and excluded respiratory specimens appear in Figure 1.

Not all respiratory specimens collected from children less than 10 years of age from the study period were archived and available for study. A total of 116 specimens were unavailable for the following reasons – 39 virus-negative specimens had no remaining volume to archive following routine UIHC testing, 75 virus-positive specimens were not archived at the discretion of the laboratory technician, and 2 virus-positive specimens were set aside for validation of in-house diagnostic assays. These 116 specimens represented 105 unique individuals and 100 children with accessible medical records.

Additional data from all 559 included specimens (with duplicates) and all 116 unavailable specimens (with duplicates) appears in the Appendix.

4.2 Specific aim 1

4.2.1 Virus-specific mono-infection and co-infection prevalence estimates

A virus was identified in 56.3% of the 421 respiratory specimens arising from unique individuals (no duplicates) (Table 3). The most prevalent respiratory viruses were HRV (24.5%), RSV (18.5%), HBoV (7.6%), hMPV (6.7%), and all PIV (6.2%), which include PIV 1-3 and PIV not otherwise specified. Of the 103 HRV-positive specimens, HRV A was the most common group detected (45.6%) followed by HRV C (41.8%), and HRV B (0.9%). Non-typeable HRVs represented 11.7% of the HRV-positive specimens. A coinfection was identified in 21.1% of the 237 virus-positive specimens. Coinfections were detected more often for Ad (53.3% of 15 Ad-positive specimens), HBoV (50.0% of 32 HBoV-positive specimens), all PIV (42.3% of 26 PIV-positive specimens), HRV (34.9% of 103 HRV-positive specimens), and RSV (34.6% of 78 RSV-positive specimens). Among the 50 specimens with detected coinfections, the most frequent virus-virus combinations (Table 4) were HRV-RSV (n=14), HRV-HBoV (n=6), and HRV-PIV 3 (n=4). Among the 103 HRV-positive specimens, 58.3% of the non-typeable HRV specimens, 36.2% of the HRV A specimens, 27.9% of the HRV C specimens, and the single HRV B specimen were involved in coinfections.

When limiting the analysis to the 349 respiratory specimens from children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI, a virus was identified in 61.3% of the specimens (Table 5). HRV (27.5%), RSV (18.9%), HBoV (8.3%), hMPV (7.7%) and all PIV (6.6%) remained the most prevalent viruses detected. Of the 96 HRV-positive specimens, HRV A was the most common group detected (46.3%) followed by HRV C (41.1%), and non-typeable HRVs (12.6%). A coinfection was identified in

21.5% of the 214 virus-positive specimens. Coinfections were again detected more often for Ad (53.3% of 15 Ad-positive specimens), HBoV (51.7% of 29 HBoV-positive specimens), all PIV (43.5% of 23 PIV-positive specimens), HRV (35.4% of 96 HRV-positive specimens), and RSV (34.8% of 66 RSV-positive specimens). Among the 46 specimens with detected coinfections, the most frequent virus-virus combinations (Table 6) were HRV-RSV (n=12), HRV-HBoV (n=6), and HRV-PIV 3 (n=4). Among the 96 HRV-positive specimens, 58.3% of the non-typeable HRV specimens, 36.4% of the HRV A specimens, and 30.8% of the HRV C specimens were involved in coinfections.

When including specimens from children for whom physicians had a concern for ARTI in the absence of traditional symptoms (n=56) in the analysis alongside confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI, a virus was identified in 56.5% of the 405 specimens (Table 7). Of the 103 HRV-positive specimens, HRV A was the most common group detected (46.5%) followed by HRV C (41.6%), and non-typeable HRVs (11.9%). A coinfection was identified in 21.0% of the 229 virus-positive specimens. Coinfections were detected more often for Ad (53.3% of 15 Ad-positive specimens), HBoV (50.0% of 30 HBoV-positive specimens), all PIV (44.0% of 25 PIV-positive specimens), HRV (34.6% of 101 HRV-positive specimens), and RSV (34.2% of 73 RSV-positive specimens). Among the 48 specimens with detected coinfections, the most frequent virus-virus combinations (Table 8) were HRV-RSV (n=13), HRV-HBoV (n=6), and HRV-PIV 3 (n=4). Among the 101 HRV-positive specimens, 58.3% of the non-typeable HRV specimens, 36.2% of the HRV A specimens, and 28.6% of the HRV C specimens were involved in coinfections.

When examining the 105 specimens from eligible children excluded from study due to an unavailable specimen, a virus was identified in 70.5% of the

specimens (Table 9). The most prevalent respiratory viruses were RSV (53.3%), all PIV (8.6%), and influenza B (4.8%). A coinfection was identified in 2.7% of the 74 virus-positive specimens. The 2 coinfections detected included RSV-Ad and RSV-PIV 2 (Table 10). The latter part of this study coincided with the emergence of the novel H1N1 (nH1N1) influenza virus; 1 of the excluded specimens was identified as influenza A virus-positive during this time period and was subsequently characterized as nH1N1.

4.2.2 Summary of demographic and clinical characteristics of the study population with accessible medical records

Results presented here are limited to unique individuals (no duplicates) with accessible medical records. Of the 421 unique individuals included in this study, 407 had accessible medical records. Of the 105 eligible individuals excluded due to an unavailable specimen, 100 had accessible medical records. Additional data from (1) all 559 included specimens (with duplicates), (2) children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI, (3) children for whom physicians had a concern for ARTI in the absence of traditional symptoms in addition to those with confirmed or suspected ARTI, and (4) all 116 unavailable specimens (with duplicates) appears in the Appendix. Results are comparable to those presented here.

Among the 407 children included in the study, 54.0% were male, 86.2% were under the age of 5 years, 72.9% were Caucasian, 47.8% used Medicaid as the primary payor for medical services, and 60.1% resided in an urban area (Table 11). Among those residing in rural areas, 54.0% used Medicaid as the primary payor; whereas among those residing in urban areas, 44.5% used Medicaid as the primary payor ($p=0.061$, data not shown). The mean age was 2.07 years (Table 12).

A large proportion of the children were hospitalized (76.9%), and of those that were hospitalized, 36.1% were patients in an intensive care unit at the time of specimen collection (Table 13). Hypoxemia (oxygen saturation less than 90%) was common (33.7% of children). Additionally, 44.5% required supplemental oxygen and 17.0% were mechanically ventilated. A bronchodilator was administered to 28.0% of the children. The median total length of hospitalization was 5.00 days (Table 14). Antimicrobials were frequently administered prior to the UIHC visit (29.7%), any time during the UIHC visit (59.7%), and as take-home prescriptions (26.0%) (Table 15). Data with regard to white blood cell count and C-reactive protein (CRP) levels were missing in a large proportion of individuals (23.3% and 37.1%, respectively); among those with complete information, elevated white blood cell count/leukocytosis (26.0%) and elevated CRP levels (67.2%) were common.

In 46.7% of the children, an ARTI-specific physician diagnosis was identified; respiratory tract infection, pneumonia, and bronchiolitis were common diagnoses (Table 16). Additionally, for 38.3% of the children a physician documented ARTI symptoms, though no ARTI diagnosis code was recorded in the medical record. It is interesting to note that of the 232 virus-positive specimens, 3.5% of the children did not have an acute respiratory tract infection. Common symptoms included fever (54.6%), cough (54.1%), and nasal congestion/runny nose (40.3%) (Table 17). Chronic respiratory conditions were common in this group (35.4%), as were chronic medical conditions that could lead to increased frequency of respiratory infection (29.7%) and history of prematurity (22.4%) (Table 18).

Specimens most often originated from nasal washes (85.8%), and overall, respiratory viruses were most commonly detected in the winter and spring months (January through June) (Table 19).

Among the 100 children excluded from the study due to unavailable specimens, 60.0% were male, 90.0% were under the age of 5 years, 75.0% were white, and 78.0% resided in an urban area (Table 20). The mean age was 1.64 years (Table 21). Less than half of the children (44.0%) were hospitalized, and of those that were hospitalized, 27.3% were ever patients in an intensive care unit (Table 22). The median total length of stay was 2.00 days (Table 23). Specimens most often originated from nasal washes (84.0%), and overall, respiratory viruses were most commonly detected in the winter and early spring months (January through March) (Table 24).

Compared to those children for whom specimens were included in the study, children for whom specimens were unavailable were significantly younger ($p=0.035$), were more likely to reside in an urban area ($p=0.009$), and were less likely to be admitted to the hospital ($p<0.001$).

4.2.3 Summary of demographic and clinical characteristics of the HRV-positive study population with accessible medical records

Figure 2 demonstrates the phylogeny of all HRV-positive specimens according to PCR assays utilizing the VP4/VP2 protocol. Figure A1 in the appendix demonstrates the phylogeny according to PCR assays utilizing the 5'NCR protocol. The HRV group data presented here are based upon the VP4/VP2 typing strategy.

Of the 407 unique specimens with accessible medical records, 102 (25.1%) tested positive for HRV; of these 30.4% were characterized as HRV C, 28.2% as HRV A, 0.1% as HRV B, and 3.9% as non-typeable HRVs. Of the 102 HRV-positive specimens, 56.9% were male, 85.3% were under the age of 5 years, 75.0% were white, 46.1% used Medicaid as the primary payor for medical

services, and 62.8% resided in an urban area (Table 25). The mean age was 2.07 years (Table 26).

A large proportion of the children were hospitalized (75.5%), and of those that were hospitalized, 24.7% were patients in an intensive care unit at the time of specimen collection (Table 27). Additionally, 35.3% required supplemental oxygen and 33.0% were administered a bronchodilator. Few required mechanical ventilation (7.8%). The median total length of stay was 3.00 days (Table 28). Antimicrobials were frequently administered prior to the UIHC visit (32.4%), any time during the UIHC visit (54.9%), and as take-home prescriptions (30.4%) (Table 29). Data with regard to white blood cell count and C-reactive protein (CRP) levels were missing in a large proportion of individuals (23.3% and 37.1%, respectively); among those with complete information, elevated white blood cell count/leukocytosis (25.7%) and elevated CRP levels (61.8%) were common.

In 52.9% of the children, an ARTI-specific physician diagnosis was identified (Table 30). Additionally, for 40.2% of the children a physician documented ARTI symptoms, though no ARTI diagnosis code was recorded in the medical record. Of the 102 HRV-positive specimens, 2.0% of the children did not have an acute respiratory tract infection. Common symptoms included cough (63.7%), nasal congestion/runny nose (50.0%), fever (46.1%) and wheeze (30.4%) (Table 31). Chronic respiratory conditions were common in this group (46.1%) (Table 32).

Specimens most often originated from nasal washes (88.0%), and overall, HRVs were commonly detected in all seasons, though HRV A was more commonly detected in the spring and summer months whereas HRV C was more commonly detected in the late winter and early spring (Table 33).

Compared to HRV A-positive specimens, HRV C-positive specimens were less likely to be male (p=0.028), to be Caucasian (p=0.037), to be given antibiotics prior to their first UIHC appointment (p=0.007), and to be admitted to the hospital (0.054). HRV C-positive specimens were more likely to be associated with cough (p=0.053) and wheeze (p=0.007).

4.3 Specific aim 2

4.3.1 Bivariate and multivariate analysis of selected host-specific factors and coinfection among virus-positive specimens with accessible medical records

Results presented here are limited to analyses using virus-positive specimens with accessible medical record information from unique children (no duplicates) with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI (n=212). Results were similar when including a third group of children, those with physician concern for ARTI in the absence of traditional symptoms (data not shown).

Table 34 details results from bivariate logistic regression models of selected host-specific factors and virus-virus coinfection (versus viral mono-infection). Table 35 provides the final model selected following a backwards elimination strategy beginning with a saturated model. While none of the covariates in the final model are significant at $p < 0.05$, the results are suggestive. Males were at increased odds of coinfection compared to females (OR 1.70, 95% CI 0.83-3.46). Children aged 6 months to 1 year had increased odds of coinfection as compared to children aged less than 6 months (OR 2.15, 95% CI 0.75-6.19) and the odds of coinfection decreased with increasing age after 1 year though this trend was not statistically significant (p for trend 0.5881). Children with a history of any chronic condition that may result in immunosuppression, and specifically increased risk of ARTI, had increased odds

of coinfection as compared to children with no history of such conditions (OR 2.05, 95%CI 0.99-4.23).

4.3.2 Bivariate and multivariate analysis of selected host-specific factors and coinfection among virus-positive specimens with accessible medical records and complete tobacco smoke exposure data

Results presented here are limited to analyses using virus-positive specimens with accessible medical record information from unique children (no duplicates) with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI with complete tobacco smoke exposure (n=96).

Table 36 details results from bivariate logistic regression models of selected host-specific factors and virus-virus coinfection (versus viral mono-infection). Table 37 provides the final model selected following a backwards elimination strategy beginning with a saturated model. While none of the covariates in the final model are significant at $p < 0.05$, the results are suggestive. Children aged 6 months to 1 year had increased odds of coinfection as compared to children aged less than 6 months (OR 3.27, 95% CI 0.72-14.94) and the odds of coinfection decreased with increasing age after 1 year thought this trend was not statistically significant (p for trend 0.5265). Children with a history of any chronic condition that may result in immunosuppression, and specifically increased risk of ARTI, had increased odds of coinfection as compared to children with no history of such conditions (OR 2.26, 95%CI 0.63-8.15). Children with direct exposure to tobacco smoke (adults smoke with child present in same room) had increased odds of coinfection as compared to children with no tobacco exposure (OR 4.26, 95% 0.88-20.67).

4.3.3 Bivariate and multivariate analysis of selected host-specific factors and coinfection among HRV-positive specimens with accessible medical records

Results presented here are limited to analyses using HRV-positive specimens with accessible medical record information from unique children (no duplicates) with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI (n=95). Results were similar when including a third group of children, those with physician concern for ARTI in the absence of traditional symptoms (data not shown).

Table 38 details results from bivariate logistic regression models of selected host-specific factors and HRV-specific coinfection (versus HRV mono-infection). Table 39 provides the final model selected following a backwards elimination strategy beginning with a saturated model. While none of the covariates in the final model are significant at $p < 0.05$, the results are suggestive. Males were at increased odds of HRV coinfection compared to females (OR 1.89, 95% CI 0.71-5.03). Children aged 6 months to 1 year had increased odds of HRV coinfection as compared to children aged less than 6 months (OR 3.70, 95% CI 0.87-15.67), and the odds of HRV coinfection decreased with increasing age after 1 year thought this trend was not statistically significant (p for trend 0.7025). Children residing in large rural areas had increased odds of HRV coinfection as compared to children living in urban areas (OR 3.17, 95% 0.77-13.1), and the odds of HRV coinfection decreased as the rural characterization increased though this trend was not statistically significant (p for trend 0.3864). Children with a history of any chronic condition that may result in immunosuppression, and specifically increased risk of ARTI, had increased odds of HRV coinfection as compared to children with no history of such conditions (OR 2.24, 95%CI 0.81-6.22).

4.4 Specific aim 3

Crude odds ratios for all indicators of severity other than ICU admission (for all coinfections and HRV-specific coinfection) and bronchodilator administration (for HRV-specific coinfection only) were not significant or marginally significant, and multivariate logistic regression models were not generated.

4.4.1 Modeling odds of ICU admission associated with virus-virus coinfection

Results presented here are limited to analyses using virus-positive specimens with accessible medical record information from unique children (no duplicates) with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI who were hospitalized (n=160). Results were similar when including a third group of children, those with physician concern for ARTI in the absence of traditional symptoms (data not shown).

Table 40 details the results from bivariate logistic regression models of selected factors (potential confounders as identified in the literature or stratified analyses) and odds of virus-virus coinfection (versus viral mono-infection). No significant effect modifiers were identified. Table 41 details the results from bivariate logistic regression models of selected factors (potential confounders as identified in the literature or stratified analyses) and odds of ICU admission. A significant trend was observed for the association between urban/rural residence and ICU admission (p for trend 0.032); as characterization of residence became more rural, the odds of ICU admission decreased. A significant trend was also observed for the association between tobacco smoke exposure and ICU admission (p for trend 0.030); as the degree of tobacco smoke exposure increased so did the risk of ICU admission. History of chronic respiratory

condition and history of immunosuppression did not significantly modify the association between coinfection and ICU admission.

The unadjusted odds ratio for ICU admission associated with virus-virus coinfection was 0.30 (95% CI 0.09-1.04). After controlling for potential confounders, the adjusted odds ratio was 0.32 (0.08-1.27) (Table 42). Male gender (OR 3.11, 95% CI 1.20-8.06), history of any immunosuppressive condition (OR 3.20, 95% CI 1.12-9.17), history of prematurity (OR 5.06, 95% CI 1.61-15.93), and leukocytosis (OR 4.44, 95% CI 1.68-11.74) were significantly associated with increased odds of ICU admission in this population.

4.4.2 Modeling odds of ICU admission associated with HRV coinfection

Results presented here are limited to analyses using HRV-positive specimens with accessible medical record information from unique children (no duplicates) with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI who were hospitalized (n=73). Results were similar when including a third group of children, those with physician concern for ARTI in the absence of traditional symptoms (data not shown).

Table 43 details the results from bivariate logistic regression models of selected factors (potential confounders as identified in the literature or stratified analyses) and odds of HRV coinfection (versus HRV mono-infection). No significant effect modifiers were identified. Table 44 details the results from bivariate logistic regression models of selected factors (potential confounders as identified in the literature or stratified analyses) and odds of ICU admission. No significant effect modifiers were identified.

The unadjusted odds ratio for ICU admission associated with HRV coinfection was 0.34 (95% CI 0.09-1.33). After controlling for potential confounders, the adjusted odds ratio was 0.51 (0.09-2.80) (Table 45). Rural

residence was significantly associated with decreased odds of ICU admission in this population (OR 0.15, 95% CI 0.03-0.83). History of any immunosuppressive condition (OR 5.48, 95% CI 0.79-38.05), history of prematurity (OR 11.72, 95% CI 0.81-169.35), and leukocytosis (OR 4.84, 95% CI 0.82-28.66) were associated with marginally increased odds of ICU admission ($p < 0.10$).

4.4.3 Modeling odds of bronchodilator administration associated with HRV coinfection

Results presented here are limited to analyses using HRV-positive specimens with accessible medical record information from unique children (no duplicates) with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI and includes inpatients and outpatients (n=95). Results were similar when including a third group of children, those with physician concern for ARTI in the absence of traditional symptoms (data not shown).

Table 46 details the results from bivariate logistic regression models of selected factors (potential confounders as identified in the literature or stratified analyses) and odds of HRV coinfection (versus HRV mono-infection). No significant effect modifiers were identified. Table 47 details the results from bivariate logistic regression models of selected factors (potential confounders as identified in the literature or stratified analyses) and odds of bronchodilator administration. Age 6 months to 5 years and history of asthma were significantly associated with increased odds of bronchodilator administration ($p <0.05$). History of any immunosuppressive condition was significantly associated with decreased odds of bronchodilator administration ($p < 0.05$). No significant effect modifiers were identified.

The unadjusted odds ratio for bronchodilator administration associated with HRV coinfection was 2.60 (95% CI 1.08-6.23). After controlling for potential

confounders, the adjusted odds ratio was 3.02 (1.06-8.65) (Table 48). Age 6 months to 1 year (OR 5.70, 95% CI 1.26-25.73, as compared to age less than 6 months) and history of asthma (OR 6.62, 95% CI 1.60-27.52) were significantly associated with increased odds of bronchodilator administration.

4.5 Secondary analysis – viral-bacterial coinfection

Table 49 details the prevalence estimates for virus-specific mono-infection and virus-bacteria coinfections for specimens from hospitalized children (no duplicates) with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI for whom any bacterial test was ordered (not limited to respiratory sources) (n=217). Compared to children who did not have a bacterial test ordered, those who did were more likely to be older (age 1-5 years p=0.035, age greater than 5 years p=0.025), to have a history of cancer (p=0.022), to have an elevated white blood cell count (p=0.048), to have a fever (p=0.005), and to be hospitalized (p <0.001). They were also less likely to have nasal congestion/runny nose (p=0.002) and wheeze (p < 0.001).

Crude odds ratios for all indicators of severity other than ICU admission (for all coinfections) were not significant or marginally significant, and multivariate logistic regression models were not generated.

Results presented here are limited to analyses using virus-positive specimens with accessible medical record information from hospitalized children (no duplicates) with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI for whom any bacterial test was ordered (not limited to respiratory sites) (n=124). Coinfection is defined as infection with at least one virus and one bacterium. The comparison group is defined as infection with a single virus.

Table 50 details the results from bivariate logistic regression models of selected factors (potential confounders as identified in the literature or stratified analyses) and odds of virus-bacteria coinfection (versus viral mono-infection). No significant effect modifiers were identified. Age 1 to 5 years was associated with significantly decreased odds of virus-bacteria coinfection (OR 0.37, 95% CI 0.16-0.83). Rural residence (OR 2.14, 95% CI 1.03-4.43) and history of prematurity (OR 3.14, 95% CI 1.37-7.18) were associated with significantly increased odds of virus-bacteria coinfection. Table 51 details the results from bivariate logistic regression models of selected factors (potential confounders as identified in the literature or stratified analyses) and odds of ICU admission. Age 1 to 5 years, history of a chronic respiratory condition (structural defect or asthma), and history of prematurity were associated with significantly increased odds of ICU admission ($p < 0.05$). A significant trend was observed for the association between age and ICU admission (p for trend 0.048); as age increased, the odds of ICU admission decreased. A significant trend was also observed for the association between urban/rural residence and ICU admission (p for trend 0.037); as characterization of residence became more rural, the odds of ICU admission decreased.

The unadjusted odds ratio for ICU admission associated with virus-bacteria coinfection was 6.00 (95% CI 2.51-14.33). After controlling for potential confounders, the adjusted odds ratio was 5.58 (1.95-15.96) (Table 52). History of prematurity (OR 3.17, 95% CI 1.03-9.77) was also significantly associated with increased odds of ICU admission.

Table 53 details the prevalence estimates for virus-specific mono-infection and virus-bacteria coinfections for specimens from hospitalized children (no duplicates) with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI for whom any respiratory bacterial test was

ordered (n=93). Compared to children who did not have a respiratory bacterial test ordered, those who did were more likely to have a history of a structural respiratory condition (p=0.014) and an elevated white blood cell count (p=0.005). They were also less likely to have a history of cancer (p=0.026).

Crude odds ratios for all indicators of severity other than ICU admission (for all coinfections) were not significant or marginally significant, and multivariate logistic regression models were not generated.

Results presented here are limited to analyses using virus-positive specimens with accessible medical record information from hospitalized children (no duplicates) with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI for whom any respiratory bacterial test was ordered (n=60). Coinfection is defined as infection with at least one virus and one bacterium present. The comparison group is defined as infection with a single virus.

Table 54 details the results from bivariate logistic regression models of selected factors (potential confounders as identified in the literature or stratified analyses) and odds of virus-bacteria coinfection (versus viral mono-infection). No significant effect modifiers were identified. History of asthma was associated with increased likelihood of coinfection; however, this result was only marginally significant (p=0.056). Table 55 details the results from bivariate logistic regression models of selected factors (potential confounders as identified in the literature or stratified analyses) and odds of ICU admission.

The unadjusted odds ratio for ICU admission associated with virus-bacteria coinfection in this group is 9.75 (95% CI 2.54-37.40). The sample size was insufficient to allow for multivariate logistic regression modeling to control for potential confounders.

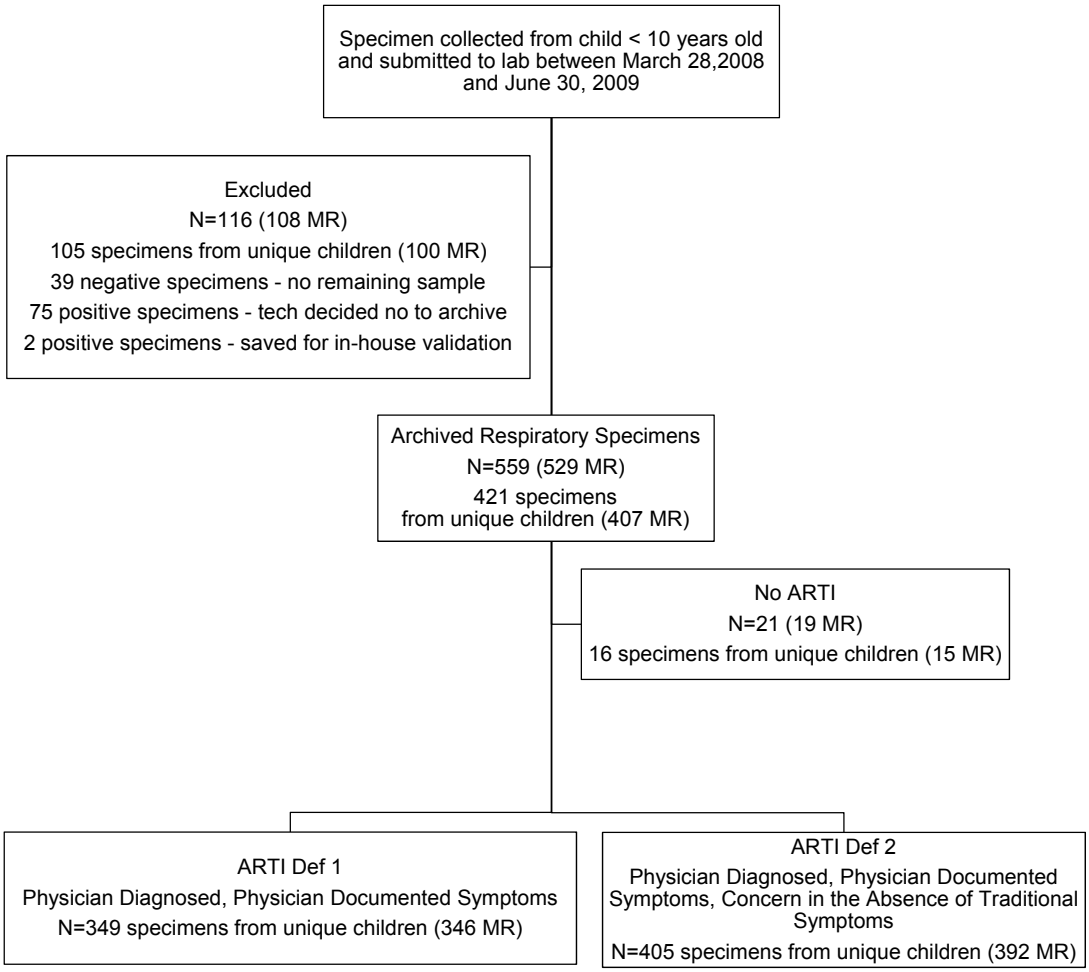

Figure 1. Description of eligible, included, and excluded respiratory specimens
MR=Medical record, unique refers to first specimen of first ARTI (no duplicates)

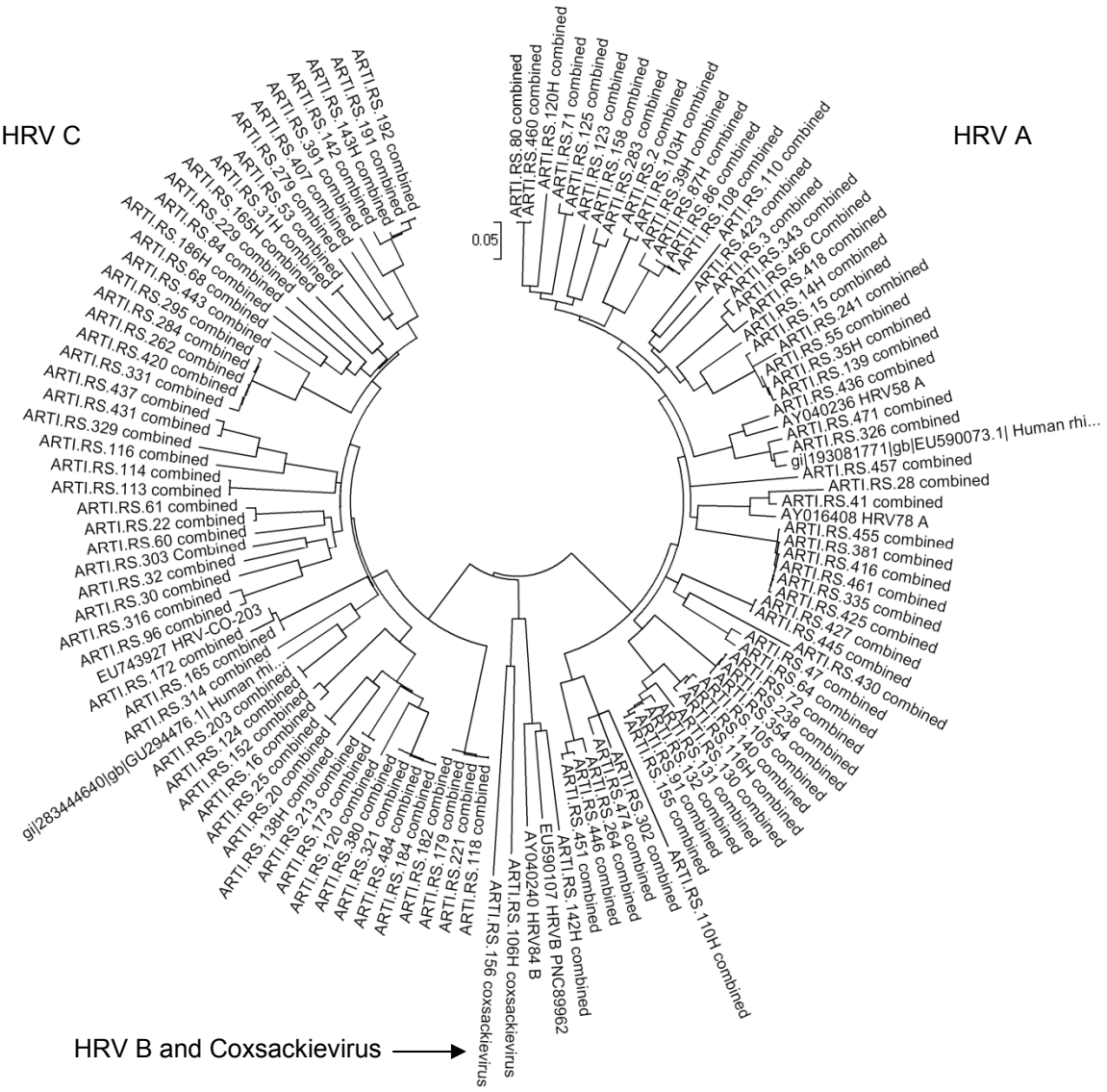

Figure 2. Evolutionary relationships of 125 HRV taxa (VP4/VP2 protocol). The evolutionary history was inferred using the Neighbor-Joining method [1]. The bootstrap consensus tree inferred from 1000 replicates [4] is taken to represent the evolutionary history of the taxa analyzed [4]. Branches corresponding to partitions reproduced in less than 50% bootstrap replicates are collapsed. The tree is drawn to scale, with branch lengths in the same units as those of the evolutionary distances used to infer the phylogenetic tree. The evolutionary distances were computed using the Maximum Composite Likelihood method [2] and are in the units of the number of base substitutions per site. All positions containing gaps and missing data were eliminated from the dataset (Complete deletion option). There were a total of 348 positions in the final dataset. Phylogenetic analyses were conducted in MEGA4 [3]. Prefix ARTI.RS denotes study specimens.

Source: 1. Saitou N & Nei M (**1987**) The neighbor-joining method: A new method for reconstructing phylogenetic trees. *Molecular Biology and Evolution* **4**:406-425.

2. Tamura K, Nei M & Kumar S (**2004**) Prospects for inferring very large phylogenies by using the neighbor-joining method. *Proceedings of the National Academy of Sciences* (*USA*) **101**:11030-11035.

3. Tamura K, Dudley J, Nei M & Kumar S (**2007**) MEGA4: Molecular Evolutionary Genetics Analysis (MEGA) software version 4.0. *Molecular Biology and Evolution* **24**:1596-1599.

4. Felsenstein J (**1985**) Confidence limits on phylogenies: An approach using the bootstrap. *Evolution* **39**:783-791.

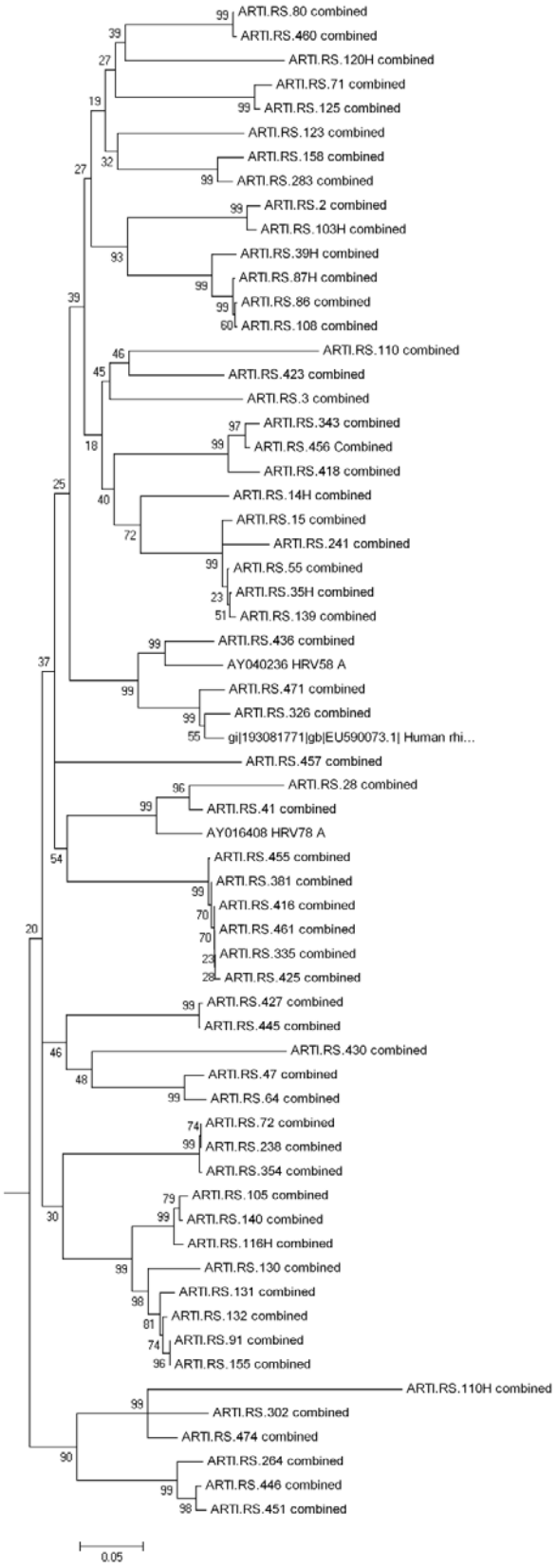

Figure 3. Detail of Figure 2, HRV A phylogeny.

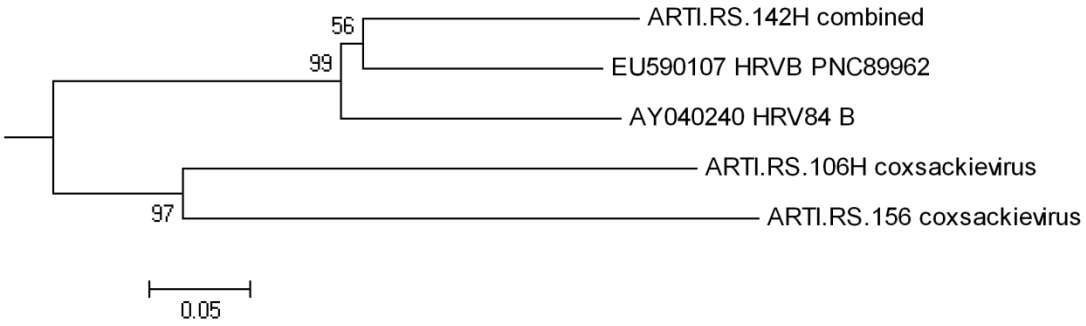

Figure 4. Detail of Figure 2, HRV B and Coxsackievirus phylogeny.

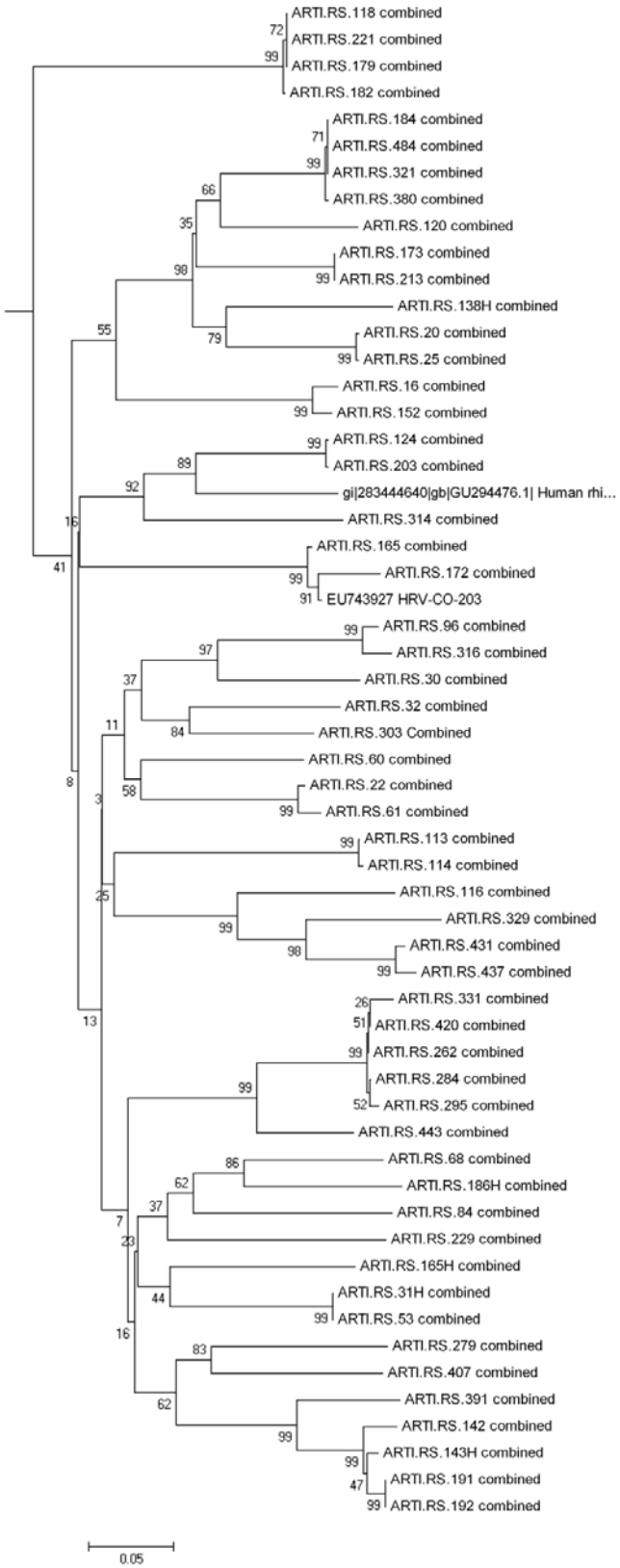

Figure 5. Detail of Figure 2, HRV C phylogeny.

Table 3 Virus-specific mono-infection and coinfection prevalence estimates for all specimens, without duplicates (n=421)

Virus	Mono-infection, n (% Total Positive[a])	Co-infection, n (% Total Positive[a])	Total Positive, n (% Total Specimens[b])	95% CI[c]
Ad[d]	7 (46.7)	8 (53.3)	15 (3.6)	2.0-5.8
HRV	67 (65.1)	36 (34.9)	103 (24.5)	20.4-28.9
HBoV	16 (50.0)	16 (50.0)	32 (7.6)	5.3-10.6
hMPV	20 (71.4)	8 (28.6)	28 (6.7)	4.5-9.5
CoxS	0 (0)	1 (100)	1 (0.2)	0.0-1.3
Flu A	5 (100)	0 (0)	5 (1.2)	0.4-2.8
Flu B	6 (100)	0 (0)	6 (1.4)	0.5-3.1
RSV	51 (65.4)	27 (34.6)	78 (18.5)	14.9-22.6
PIV 1	1 (100)	0 (0)	1 (0.2)	0.0-11.3
PIV 2	1 (100)	0 (0)	1 (0.2)	0.0-11.3
PIV 3	13 (61.9)	8 (38.1)	21 (5.0)	3.1-7.5
PIV NOS	0 (0)	3 (100)	3 (0.7)	0.2-2.1
Total	187 (78.9)	50 (21.1)	237 (56.3)	51.4-61.1

Note: CoxS (coxsackievirus), Flu A (influenza A virus), Flu B (influenza B virus), PIV NOS (parainfluenza virus not otherwise specified).

[a] Denominator is virus-specific total number of positive specimens.

[b] Denominator is total number of specimens, n=421.

[c] 95% binomial confidence interval associated with prevalence percent estimate for total number of positive specimens.

[d] Ad genotypes include Ad1 (n=1, 0% coinfected), Ad2 (n=4, 75.0% coinfected), Ad3 (n=7, 57.1% coinfected), Ad5 (n=1, 0% coinfected), Ad41 (n=1, 100% coinfected), and non-typeable (n=1, 0% coinfected).

Table 4 Frequency of viral coinfections for all specimens, without duplicates (n=421)

Co-detected Viruses	**N**
2 Viruses	
HRV + RSV	14
HRV + HBoV	6
HRV + PIV3	4
HRV + hMPV	3
HBoV + RSV	2
Ad + RSV	2
Ad + HRV	2
PIV 3 + HBoV	2
PIV 3 + RSV	2
hMPV + RSV	2
PIV 3 + hMPV	1
PIV NOS + RSV	1
hMPV + CoxS	1
HBoV + Ad	1
3 Viruses	
Ad + HRV + HBoV	2
HRV + HBoV + hMPV	1
HRV + HBoV + RSV	1
HRV + hMPV + RSV	1
HRV + PIV NOS + RSV	1
hMPV + PIV NOS + RSV	1
Ad + HRV + RSV	1
Total	50

Note: CoxS (coxsackievirus), PIV NOS (parainfluenza virus not otherwise specified).

Table 5 Virus-specific mono-infection and coinfection prevalence estimates for specimens from children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI, without duplicates (n=349)

Virus	Mono-infection, n (% Total Positive[a])	Co-infection, n (% Total Positive[a])	Total Positive, n (% Total Specimens[b])	95% CI[c]
Ad[d]	7 (46.7)	8 (53.3)	15 (4.3)	2.4-7.0
HRV	62 (64.6)	34 (35.4)	96 (27.5)	22.9-32.5
HBoV	14 (48.3)	15 (51.7)	29 (8.3)	5.6-11.7
hMPV	19 (70.4)	8 (29.6)	27 (7.7)	5.2-11.1
CoxS	0 (0)	1 (100)	1 (0.3)	0.0-1.6
Flu A	5 (100)	0 (0)	5 (1.4)	0.5-3.3
Flu B	5 (100)	0 (0)	5 (1.4)	0.5-3.3
RSV	43 (65.2)	23 (34.8)	66 (18.9)	14.9-23.4
PIV 1	1 (100)	0 (0)	1 (0.3)	0.0-1.6
PIV 2	1 (100)	0 (0)	1 (0.3)	0.0-1.6
PIV 3	11 (61.1)	7 (38.9)	18 (5.2)	3.1-8.0
PIV NOS	0 (0)	3 (100)	3 (0.9)	0.2-2.5
Total	168 (78.5)	46 (21.5)	214 (61.3)	56.0-66.5

Note: CoxS (coxsackievirus), Flu A (influenza A virus), Flu B (influenza B virus), PIV NOS (parainfluenza virus not otherwise specified).

[a] Denominator is virus-specific total number of positive specimens.

[b] Denominator is total number of specimens, n=349.

[c] 95% binomial confidence interval associated with prevalence percent estimate for total number of positive specimens.

[d] Ad genotypes include Ad1 (n=1, 0% coinfected), Ad2 (n=4, 75.0% coinfected), Ad3 (n=7, 57.1% coinfected), Ad5 (n=1, 0% coinfected), Ad41 (n=1, 100% coinfected), and non-typeable (n=1, 0% coinfected).

Table 6 Frequency of viral coinfections for specimens from children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI, without duplicates (n=349)

Co-detected Viruses	**N**
2 Viruses	
HRV + RSV	12
HRV + HBoV	6
HRV + PIV3	4
HRV + hMPV	3
HBoV + RSV	2
Ad + RSV	2
Ad + HRV	2
PIV NOS + RSV	2
PIV 3 + HBoV	2
PIV 3 + hMPV	1
hMPV + RSV	1
hMPV + CoxS	1
HBoV + Ad	1
3 Viruses	
Ad + HRV + HBoV	2
HRV + HBoV + hMPV	1
HRV + HBoV + RSV	1
HRV + hMPV + RSV	1
HRV + PIV NOS + RSV	1
Ad + HRV + RSV	1
Total	46

Note: CoxS (coxsackievirus), PIV NOS (parainfluenza virus not otherwise specified).

Table 7 Virus-specific mono-infection and coinfection prevalence estimates for specimens from children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI or concern for ARTI in the absence of traditional symptoms, without duplicates (n=405)

Virus	Mono-infection, n (% Total Positive[a])	Co-infection, n (% Total Positive[a])	Total Positive, n (% Total Specimens[b])	95% CI[c]
Ad[d]	7 (46.7)	8 (53.3)	15 (3.7)	2.1-6.0
HRV	66 (65.4)	35 (34.6)	101 (24.9)	20.8-29.5
HBoV	15 (50.0)	15 (50.0)	30 (7.4)	5.1-10.4
hMPV	20 (71.4)	8 (28.6)	28 (6.9)	4.6-9.8
CoxS	0 (0)	1 (100)	1 (0.3)	0.0-1.4
Flu A	5 (100)	0 (0)	5 (1.2)	0.4-2.9
Flu B	6 (100)	0 (0)	6 (1.5)	0.6-3.2
RSV	48 (65.8)	25 (34.2)	73 (18.0)	14.4-22.1
PIV 1	1 (100)	0 (0)	1 (0.3)	0.0-1.4
PIV 2	1 (100)	0 (0)	1 (0.3)	0.0-1.4
PIV 3	12 (60.0)	8 (40.0)	20 (4.9)	3.0-7.5
PIV NOS	0 (0)	3 (100)	3 (0.7)	0.2-2.2
Total	181 (79.0)	48 (21.0)	229 (56.5)	51.6-61.4

Note: CoxS (coxsackievirus), Flu A (influenza A virus), Flu B (influenza B virus), PIV NOS (parainfluenza virus not otherwise specified).

[a] Denominator is virus-specific total number of positive specimens.

[b] Denominator is total number of specimens, n=405.

[c] 95% binomial confidence interval associated with prevalence percent estimate for total number of positive specimens.

[d] Ad genotypes include Ad1 (n=1, 0% coinfected), Ad2 (n=4, 75.0% coinfected), Ad3 (n=7, 57.1% coinfected), Ad5 (n=1, 0% coinfected), Ad41 (n=1, 100% coinfected), and non-typeable (n=1, 0% coinfected).

Table 8 Frequency of viral coinfections for specimens from children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI or concern for ARTI in the absence of traditional symptoms, without duplicates (n=405)

Co-detected Viruses	**N**
2 Viruses	
HRV + RSV	13
HRV + HBoV	6
HRV + PIV3	4
HRV + hMPV	3
HBoV + RSV	2
Ad + RSV	2
Ad + HRV	2
PIV NOS + RSV	2
PIV 3 + HBoV	2
PIV 3 + RSV	1
PIV 3 + hMPV	1
hMPV + RSV	1
hMPV + CoxS	1
HBoV + Ad	1
3 Viruses	
Ad + HRV + HBoV	2
HRV + HBoV + hMPV	1
HRV + HBoV + RSV	1
HRV + hMPV + RSV	1
HRV + PIV NOS + RSV	1
Ad + HRV + RSV	1
Total	48

Note: CoxS (coxsackievirus), PIV NOS (parainfluenza virus not otherwise specified).

Table 9 Virus-specific mono-infection and coinfection prevalence estimates for specimens from eligible children excluded from study due to unavailable specimen, without duplicates (n=105)

Virus[a]	Mono-infection, n (% Total Positive[b])	Co-infection, n (% Total Positive[b])	Total Positive, n (% Total Specimens[c])	95% CI[d]
Ad[e]	2 (66.7)	1 (33.3)	3 (2.9)	0.6-8.1
Flu A	3 (100)	0 (0)	3 (2.9)	0.6-8.1
Flu B	5 (100)	0 (0)	5 (4.8)	1.6-10.8
RSV	54 (96.4)	2 (3.6)	56 (53.3)	43.3-63.1
PIV 1	0 (0)	0 (0)	0 (0)	NA
PIV 2	2 (66.7)	1 (33.3)	3 (2.9)	0.6-8.1
PIV 3	6 (100)	0 (0)	6 (5.7)	2.1-12.0
PIV NOS	0 (0)	0 (0)	0 (0)	NA
Total	72 (97.3)	2 (2.7)	74 (70.5)	60.8-79.0

Note: CoxS (coxsackievirus), Flu A (influenza A virus), Flu B (influenza B virus), PIV NOS (parainfluenza virus not otherwise specified).

[a] Limited to UIHC Clinical Microbiology Laboratory virological assays.

[b] Denominator is virus-specific total number of positive specimens.

[c] Denominator is total number of specimens, n=105.

[d] 95% binomial confidence interval associated with prevalence percent estimate for total number of positive specimens.

[e] Ad genotypes not determined.

Table 10 Frequency of viral coinfections for specimens from eligible children excluded from study due to unavailable specimen, without duplicates (n=105)

Co-detected Viruses	**N**
RSV + Ad	1
RSV + PIV 2	1
Total	2

Table 11 Demographic characteristics of children for all specimens with accessible medical record information, without duplicates (n=407)

	Number of Specimens (%)											
	Total (n=407)	**Positive (n=232)**	**Negative (n=175)**	**Ad (n=7)**	**HRV (n=65)**	**HBoV (n=15)**	**hMPV (n=19)**	**Flu A (n=5)**	**Flu B (n=6)**	**RSV (n=50)**	**All PIV[a] (n=15)**	**Coinfection (n=50)**
Gender												
Female	187 (46.0)	104 (44.8)	83 (47.4)	3 (42.9)	31 (47.7)	7 (46.7)	11 (57.9)	2 (40.0)	1 (16.7)	23 (46.0)	7 (46.7)	19 (38.0)
Male	220 (54.0)	128 (55.2)	92 (52.6)	4 (57.1)	34 (52.3)	8 (53.3)	8 (42.1)	3 (60.0)	5 (83.3)	27 (54.0)	8 (53.3)	31 (62.0)
Age (years)												
0 to < 0.5	153 (37.6)	76 (32.8)	77 (44.0)	1 (14.3)	24 (36.9)	2 (13.3)	6 (31.6)	0 (0)	1 (16.7)	24 (48.0)	5 (33.3)	13 (26.0)
0.5 to < 1	49 (12.0)	41 (17.7)	8 (4.6)	3 (42.9)	11 (16.9)	4 (26.7)	5 (26.3)	0 (0)	0 (0)	6 (12.0)	1 (6.7)	11 (22.0)
1 to < 5	149 (36.6)	86 (37.1)	63 (36.0)	2 (28.6)	19 (29.2)	7 (46.7)	6 (31.6)	4 (80.0)	2 (33.3)	18 (36.0)	8 (53.3)	20 (40.0)
≥ 5	56 (13.8)	29 (12.5)	27 (15.4)	1 (14.3)	11 (16.9)	2 (13.3)	2 (10.5)	1 (20.0)	3 (50.0)	2 (4.0)	1 (6.7)	6 (12.0)
Race												
Caucasian	272 (72.9)	158 (73.8)	114 (71.1)	4 (66.7)	43 (72.8)	11 (73.3)	15 (88.2)	4 (80.0)	6 (100)	30 (63.8)	11 (78.6)	34 (75.6)
African-American	42 (11.3)	23 (10.8)	19 (12.0)	2 (33.3)	7 (11.9)	2 (13.3)	1 (5.9)	0 (0)	0 (0)	8 (17.0)	0 (0)	3 (6.7)
Hispanic	34 (9.1)	20 (9.4)	14 (8.8)	0 (0)	6 (10.2)	1 (6.7)	1 (5.9)	1 (20.0)	0 (0)	6 (12.8)	2 (14.3)	3 (6.7)
Other	25 (6.7)	13 (6.1)	12 (7.6)	0 (0)	3 (5.1)	1 (6.7)	0 (0)	0 (0)	0 (0)	3 (6.4)	1 (7.1)	5 (11.1)
Missing	34	18	16	1	6	0	2	0	0	3	1	5
Medicaid												
Yes	193 (47.8)	109 (47.4)	84 (48.3)	1 (16.7)	31 (47.7)	5 (33.3)	10 (52.6)	0 (0)	2 (33.3)	29 (59.2)	8 (53.3)	23 (46.0)
No	211 (52.2)	121 (52.6)	90 (51.7)	5 (83.3)	34 (52.3)	10 (66.7)	9 (47.4)	5 (100)	4 (66.7)	20 (40.8)	7 (46.7)	27 (54.0)
Missing	3	2	1	1	0	0	0	0	0	1	0	0
Urban/Rural												
Urban	244 (60.1)	142 (61.2)	102 (58.6)	4 (57.1)	43 (66.2)	9 (60.0)	7 (36.8)	5 (100)	2 (33.3)	36 (72.0)	8 (53.3)	28 (56.0)
Large rural	63 (15.5)	33 (14.2)	30 (17.2)	1 (14.3)	6 (9.2)	1 (6.7)	7 (36.8)	0 (0)	2 (33.3)	5 (10.0)	2 (13.3)	9 (18.0)
Small rural	49 (12.1)	30 (12.9)	19 (10.9)	1 (14.3)	8 (12.3)	3 (20.0)	3 (15.8)	0 (0)	0 (0)	7 (14.0)	3 (20.0)	5 (10.0)
Isolated rural	50 (12.3)	27 (11.6)	23 (13.2)	1 (14.3)	8 (12.3)	2 (13.3)	2 (10.5)	0 (0)	2 (33.3)	2 (4.0)	2 (13.3)	8 (16.0)
Missing	1	0	1	0	0	0	0	0	0	0	0	0

Table 11 Continued

	Number of Specimens (%)											
	Total (n=407)	**Positive (n=232)**	**Negative (n=175)**	**Ad (n=7)**	**HRV (n=65)**	**HBoV (n=15)**	**hMPV (n=19)**	**Flu A (n=5)**	**Flu B (n=6)**	**RSV (n=50)**	**All PIV [a] (n=15)**	**Coinfection (n=50)**
Smoke exposure												
None	110 (65.9)	64 (62.1)	46 (71.9)	3 (75.0)	16 (69.6)	4 (57.1)	3 (37.5)	2 (66.7)	1 (50.0)	14 (63.6)	7 (87.5)	14 (53.9)
Direct	18 (10.8)	10 (9.7)	8 (12.5)	0 (0)	1 (4.4)	0 (0)	2 (25.0)	0 (0)	1 (50.0)	1 (4.6)	0 (0)	5 (19.2)
Indirect	39 (23.4)	29 (28.2)	10 (15.6)	1 (25.0)	6 (26.1)	3 (42.9)	3 (37.5)	1 (33.3)	0 (0)	7 (31.8)	1 (12.5)	7 (26.9)
Missing	240	129	111	3	42	8	11	2	4	28	7	24

Note: Excludes 14 specimens for which medical record information was inaccessible. Percentages may not add to 100.0 due to rounding. Virus-specific estimates exclude coinfections.

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

Table 12 Mean age of children for all specimens with accessible medical record information, without duplicates (n=407)

	Total (n=407)	Positive (n=232)	Negative (n=175)	Ad (n=7)	HRV (n=65)	HBoV (n=15)	hMPV (n=19)	Flu A (n=5)	Flu B (n=6)	RSV (n=50)	All PIV [a] (n=15)	Coinfection (n=50)
Age (years)												
Mean	2.07	1.99	2.18	2.04	2.17	1.95	1.87	4.44	4.35	1.23	2.04	2.04
Std deviation	2.51	2.34	2.73	2.99	2.63	1.98	1.97	2.60	2.85	1.59	1.96	2.53
Minimum	0.00	0.01	0.00	0.01	0.03	0.20	0.13	1.51	0.31	0.02	0.06	0.10
Maximum	9.79	9.73	9.80	8.64	9.73	6.94	6.13	8.59	7.31	7.44	6.71	9.62

Note: Excludes 14 specimens for which medical record information was inaccessible. Percentages may not add to 100.0 due to rounding. Virus-specific estimates exclude coinfections.

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

Table 13 Clinical characteristics (indicators of severity) associated with specimens for all children with accessible medical record information, without duplicates (n=407)

	Number of Specimens (%)											
	Total (n=407)	**Positive (n=232)**	**Negative (n=175)**	**Ad (n=7)**	**HRV (n=65)**	**HBoV (n=15)**	**hMPV (n=19)**	**Flu A (n=5)**	**Flu B (n=6)**	**RSV (n=50)**	**All PIV [a] (n=15)**	**Coinfection (n=50)**
Inpatient												
Yes	313 (76.9)	174 (75.0)	139 (79.4)	6 (85.7)	50 (76.9)	15 (100)	19 (100)	1 (20.0)	1 (16.7)	36 (72.0)	11 (73.3)	35 (70.0)
No	94 (23.1)	58 (25.0)	36 (20.6)	1 (14.3)	15 (23.1)	0 (0)	0 (0)	4 (80.0)	5 (83.3)	14 (28.0)	4 (26.7)	15 (30.0)
ICU admission, if hospitalized												
Ever	122 (39.0)	46 (26.4)	76 (54.7)	1 (16.7)	15 (30.0)	8 (53.3)	4 (21.1)	0 (0)	1 (100)	13 (36.1)	0 (0)	4 (11.4)
Never	191 (61.0)	128 (73.6)	63 (45.3)	5 (83.3)	35 (70.0)	7 (46.7)	15 (79.0)	1 (100)	0 (0)	23 (63.9)	11 (100)	31 (88.6)
ICU at collection												
Yes	113 (36.1)	44 (25.3)	69 (49.6)	1 (16.7)	15 (30.0)	7 (46.7)	3 (15.8)	0 (0)	1 (100)	13 (36.1)	0 (0)	4 (11.4)
No	200 (63.9)	130 (74.7)	70 (50.4)	5 (83.3)	35 (70.0)	8 (53.3)	16 (84.2)	1 (100)	0 (0)	23 (63.9)	11 (100)	31 (88.6)
Mechanically ventilated												
Yes	69 (17.0)	23 (9.9)	46 (26.3)	1 (14.3)	7 (10.8)	4 (26.7)	2 (10.5)	0 (0)	0 (0)	8 (16.0)	0 (0)	1 (2.0)
No	338 (83.1)	209 (90.1)	129 (73.7)	6 (85.7)	58 (89.2)	11 (73.3)	17 (89.5)	5 (100)	6 (100)	42 (84.0)	15 (100)	49 (98.0)
Oxygen requirement												
Yes	181 (44.5)	91 (39.2)	90 (51.4)	2 (28.6)	21 (32.3)	12 (80.0)	10 (52.6)	0 (0)	1 (16.7)	24 (48.0)	3 (20.0)	18 (36.0)
No	226 (55.5)	141 (60.8)	85 (48.6)	5 (71.4)	44 (67.7)	3 (20.0)	9 (47.4)	5 (100)	5 (83.3)	26 (52.0)	12 (80.0)	32 (64.0)
Bronchodilator administered												
Yes	114 (28.0)	86 (37.1)	28 (16.0)	1 (14.3)	17 (26.2)	9 (60.0)	8 (42.1)	2 (40.0)	0 (0)	27 (54.0)	2 (13.3)	20 (40.0)
No	293 (72.0)	146 (62.9)	147 (84.0)	6 (85.7)	48 (73.9)	6 (40.0)	11 (57.9)	3 (60.0)	6 (100)	23 (46.0)	13 (86.7)	30 (60.0)
Oxygen saturation < 90%												
Yes	137 (33.7)	70 (30.2)	67 (38.3)	1 (14.3)	17 (26.2)	8 (53.3)	6 (31.6)	0 (0)	1 (16.7)	20 (40.0)	2 (13.3)	15 (30.0)
No	270 (66.3)	162 (69.8)	108 (61.7)	6 (85.7)	48 (73.9)	7 (46.7)	13 (68.4)	5 (100)	5 (83.3)	30 (60.0)	13 (86.7)	35 (70.0)

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

Table 14 Clinical characteristics (length of hospitalization) associated with specimens for all children with accessible medical record information, without duplicates (n=407)

	Total (n=407)	Positive (n=232)	Negative (n=175)	Ad (n=7)	HRV (n=65)	HBoV (n=15)	hMPV (n=19)	Flu A (n=5)	Flu B (n=6)	RSV (n=50)	All PIV [a] (n=15)	Coinfection (n=50)
UIHC hospitalization Length of stay, days												
N	313	174	139	6	50	15	19	1	1	36	11	35
Median	5.00	3.00	8.00	3.50	3.00	6.00	6.00	5.00	153.00	3.00	2.00	2.00
Mean	22.01	15.43	30.24	3.17	12.36	23.40	34.58	5.00	153.00	14.75	2.73	9.17
Std deviation	46.51	41.65	50.93	1.83	31.48	41.00	88.99	NA	NA	27.22	1.68	28.70
Minimum	<1.00	<1.00	1.00	1.00	<1.00	<1.00	1.00	5.00	153.00	1.00	1.00	1.00
Maximum	377.00	369.00	377.00	5.00	204.00	140.00	369.00	5.00	153.00	112.00	6.00	172.00
Non-ICU days												
N	253	161	92	5	46	12	18	1	0	33	11	35
Median	3.00	2.00	3.00	3.00	2.00	2.50	5.00	5.00	NA	2.00	2.00	2.00
Mean	6.86	7.34	6.01	2.80	5.20	3.42	28.78	5.00	NA	3.82	2.73	5.97
Std deviation	24.49	30.15	7.78	1.79	11.45	3.55	85.69	NA	NA	4.40	1.68	11.48
Minimum	<1.00	<1.00	1.00	1.00	<1.00	<1.00	1.00	5.00	NA	1.00	1.00	1.00
Maximum	369.00	369.00	55.00	5.00	77.00	12.00	369.00	5.00	NA	19.00	6.00	67.00
ICU days												
N	122	46	76	1	15	8	4	0	1	13	0	4
Median	15.50	10.00	25.50	5.00	5.00	9.00	10.00	NA	153.00	16.00	NA	2.50
Mean	42.27	32.67	48.08	5.00	25.27	38.75	34.75	NA	153.00	31.15	NA	28.00
Std deviation	57.40	48.68	61.52	NA	51.89	52.51	54.97	NA	NA	38.24	NA	51.34
Minimum	<1.00	<1.00	1.00	5.00	<1.00	1.00	2.00	NA	153.00	2.00	NA	2.00
Maximum	377.00	204.00	377.00	5.00	204.00	140.00	117.00	NA	153.00	112.00	NA	105.00

Table 14 Continued

	Total (n=407)	Positive (n=232)	Negative (n=175)	Ad (n=7)	HRV (n=65)	HBoV (n=15)	hMPV (n=19)	Flu A (n=5)	Flu B (n=6)	RSV (n=50)	All PIV [a] (n=15)	Coinfection (n=50)
Total hospitalization, days[b]												
N	313	174	139	6	50	15	19	1	1	36	11	35
Median	5.00	3.00	8.00	4.00	3.00	6.00	6.00	5.00	153.00	3.00	2.00	3.00
Mean	22.80	16.64	30.51	3.50	15.70	24.07	34.68	5.00	153.00	15.06	4.09	9.29
Std deviation	47.46	43.68	50.92	2.17	40.20	41.00	88.95	NA	NA	27.15	5.49	28.85
Minimum	<1.00	<1.00	1.00	1.00	<1.00	<1.00	1.00	5.00	153.00	1.00	1.00	1.00
Maximum	377.00	369.00	377.00	6.00	204.00	140.00	369.00	5.00	153.00	112.00	20.00	173.00

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

[b] Includes non-UIHC hospitalizations when applicable.

Table 15 Clinical characteristics (antimicrobial use and inflammation markers) associated with specimens for all children with accessible medical record information, without duplicates (n=407)

	Number of Specimens (%)											
	Total (n=407)	**Positive (n=232)**	**Negative (n=175)**	**Ad (n=7)**	**HRV (n=65)**	**HBoV (n=15)**	**hMPV (n=19)**	**Flu A (n=5)**	**Flu B (n=6)**	**RSV (n=50)**	**All PIV [a] (n=15)**	**Coinfection (n=50)**
Antimicrobial use												
Prior use[b]												
Yes	121 (29.7)	71 (30.6)	50 (28.6)	3 (42.9)	22 (33.9)	4 (26.7)	5 (26.3)	1 (20.0)	0 (0)	17 (34.0)	2 (13.3)	17 (34.0)
No	286 (70.3)	161 (69.4)	125 (71.4)	4 (57.1)	43 (66.2)	11 (73.3)	14 (73.7)	4 (80.0)	6 (100)	33 (66.0)	13 (86.7)	33 (66.0)
UIHC administered												
Yes	243 (59.7)	130 (56.0)	113 (64.6)	4 (57.1)	35 (53.9)	11 (73.3)	13 (68.4)	2 (40.0)	3 (50.0)	25 (50.0)	8 (53.3)	29 (58.0)
No	164 (40.3)	102 (44.0)	62 (35.4)	3 (42.9)	30 (46.2)	4 (26.7)	6 (31.6)	3 (60.0)	3 (50.0)	25 (50.0)	7 (46.7)	21 (42.0)
Take-home prescription												
Yes	106 (26.0)	70 (30.2)	36 (20.6)	2 (28.6)	17 (26.2)	5 (33.3)	8 (42.1)	2 (40.0)	1 (16.7)	10 (20.0)	6 (40.0)	19 (38.0)
No	301 (74.0)	162 (69.8)	139 (79.4)	5 (71.4)	48 (73.9)	10 (66.7)	11 (57.9)	3 (60.0)	5 (83.3)	40 (80.0)	9 (60.0)	31 (62.0)
Leukopenia												
Yes	73 (23.4)	40 (23.4)	33 (23.4)	1 (16.7)	8 (16.7)	1 (7.1)	5 (27.8)	1 (33.3)	3 (100)	11 (32.4)	3 (30.0)	7 (20.0)
No	239 (76.6)	131 (76.6)	108 (76.6)	5 (83.3)	40 (83.3)	13 (92.9)	13 (72.2)	2 (66.7)	0 (0)	23 (67.6)	7 (70.0)	28 (80.0)
Missing	95	61	34	1	17	1	1	2	3	16	5	15
Leukocytosis												
Yes	81 (26.0)	42 (24.6)	39 (27.7)	2 (33.3)	13 (27.1)	9 (64.3)	5 (27.8)	0 (0)	0 (0)	5 (14.7)	1 (1.0)	7 (20.0)
No	231 (74.0)	129 (75.4)	102 (72.3)	4 (66.7)	35 (72.9)	5 (35.7)	13 (72.2)	3 (100)	3 (100)	29 (85.3)	9 (90.0)	28 (80.0)
Missing	95	61	34	1	17	1	1	2	3	16	5	15
CRP > 0.5 mg/dl												
Yes	172 (67.2)	92 (69.2)	80 (65.0)	5 (100)	24 (61.5)	11 (84.6)	11 (73.3)	1 (100)	2 (100)	15 (55.6)	8 (88.9)	15 (68.2)
No	84 (32.8)	41 (30.8)	43 (35.0)	0 (0)	15 (38.5)	2 (15.4)	4 (26.7)	0 (0)	0 (0)	12 (44.4)	1 (11.1)	7 (31.8)
Missing	151	99	52	2	26	2	4	4	4	23	6	28

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

[b] Denotes antibiotics used prior to UIHC episode during which specimen was collected.

Table 16 Clinical characteristics (diagnoses) associated with specimens for all children with accessible medical record information, without duplicates (n=407)

	Number of Specimens (%)											
	Total (n=407)	**Positive (n=232)**	**Negative (n=175)**	**Ad (n=7)**	**HRV (n=65)**	**HBoV (n=15)**	**hMPV (n=19)**	**Flu A (n=5)**	**Flu B (n=6)**	**RSV (n=50)**	**All PIV [a] (n=15)**	**Coinfection (n=50)**
ARTI												
None	15 (3.7)	8 (3.5)	7 (4.0)	0 (0)	1 (1.5)	1 (6.7)	0 (0)	0 (0)	0 (0)	3 (6.0)	1 (6.7)	2 (4.0)
Physician diagnosed	190 (46.7)	134 (57.8)	56 (32.0)	5 (71.4)	33 (50.8)	7 (46.7)	15 (79.0)	3 (60.0)	1 (16.7)	35 (70.0)	5 (33.3)	30 (60.0)
Physician documented symptoms	156 (38.3)	78 (33.6)	78 (44.6)	2 (28.6)	27 (41.5)	6 (40.0)	4 (21.1)	2 (40.0)	4 (66.7)	8 (16.0)	8 (53.3)	17 (34.0)
Concern for ARTI without traditional symptoms	46 (11.3)	12 (5.2)	34 (19.4)	0 (0)	4 (6.2)	1 (6.7)	0 (0)	0 (0)	1 (16.7)	4 (8.0)	1 (6.7)	1 (2.0)
Diagnosis												
Bronchiolitis												
Yes	45 (11.1)	40 (17.2)	5 (2.9)	0 (0)	4 (6.2)	2 (13.3)	3 (15.8)	0 (0)	0 (0)	21 (42.0)	1 (6.7)	9 (18.0)
No	362 (88.9)	192 (82.8)	170 (97.1)	7 (100)	61 (93.8)	13 (86.7)	16 (84.2)	5 (100)	6 (100)	29 (58.0)	14 (93.3)	41 (82.0)
Pneumonia												
Yes	87 (21.4)	53 (22.8)	34 (19.4)	1 (14.3)	11 (16.9)	5 (33.3)	9 (47.4)	0 (0)	0 (0)	10 (20.0)	2 (15.4)	15 (30.0)
No	326 (78.6)	179 (77.2)	141 (80.6)	6 (85.7)	54 (83.1)	10 (66.7)	10 (52.6)	5 (100)	6 (100)	40 (80.0)	13 (84.6)	35 (70.0)
Respiratory tract infection												
Yes	106 (26.0)	65 (28.0)	41 (23.4)	5 (71.4)	25 (38.5)	3 (20.0)	7 (36.8)	1 (20.0)	1 (16.7)	7 (14.0)	5 (33.3)	11 (22.0)
No	301 (74.0)	167 (72.0)	134 (76.6)	2 (28.6)	40 (61.5)	12 (80.0)	12 (63.2)	4 (80.0)	5 (83.3)	43 (86.0)	10 (66.7)	39 (78.0)

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

Table 17 Clinical characteristics (symptoms) associated with specimens for all children with accessible medical record information, with duplicates (n=407)

	Number of Specimens (%)											
	Total (n=407)	**Positive (n=232)**	**Negative (n=175)**	**Ad (n=7)**	**HRV (n=65)**	**HBoV (n=15)**	**hMPV (n=19)**	**Flu A (n=5)**	**Flu B (n=6)**	**RSV (n=50)**	**All PIV [a] (n=15)**	**Coinfection (n=50)**
Fever												
Yes	222 (54.6)	133 (57.3)	89 (50.9)	6 (85.7)	28 (43.1)	8 (53.3)	18 (94.7)	5 (100)	6 (100)	24 (48.0)	5 (33.3)	28 (56.0)
No	185 (45.5)	99 (42.7)	86 (49.1)	1 (14.3)	37 (56.9)	7 (46.7)	1 (5.3)	0 (0)	0 (0)	26 (52.0)	10 (66.7)	22 (44.0)
Nasal												
Yes	164 (40.3)	114 (49.1)	50 (28.6)	5 (71.4)	30 (46.2)	6 (40.0)	10 (52.6)	4 (80.0)	3 (50.0)	22 (44.0)	5 (33.3)	29 (58.0)
No	243 (59.7)	118 (50.9)	125 (71.4)	2 (28.6)	35 (53.9)	9 (60.0)	9 (47.4)	1 (20.0)	3 (50.0)	28 (56.0)	10 (66.7)	21 (42.0)
Cough												
Yes	220 (54.1)	152 (65.5)	68 (38.9)	5 (71.4)	35 (53.9)	8 (53.3)	17 (89.5)	5 (100)	4 (66.7)	29 (58.0)	9 (60.0)	40 (80.0)
No	187 (46.0)	80 (34.5)	107 (61.1)	2 (28.6)	30 (46.2)	7 (46.7)	2 (10.5)	0 (0)	2 (33.3)	21 (42.0)	6 (40.0)	10 (20.0)
Wheeze												
Yes	74 (18.2)	62 (26.7)	12 (6.9)	1 (14.3)	18 (27.7)	5 (33.3)	5 (26.3)	1 (20.0)	0 (0)	16 (32.0)	2 (13.3)	14 (28.0)
No	333 (81.8)	170 (73.3)	163 (93.1)	6 (85.7)	47 (72.3)	10 (66.7)	14 (73.7)	4 (80.0)	6 (100)	34 (68.0)	13 (86.7)	36 (72.0)
Tachypnea												
Yes	30 (7.4)	21 (9.1)	9 (5.1)	0 (0)	5 (7.7)	3 (20.0)	3 (15.8)	0 (0)	0 (0)	4 (8.0)	2 (13.3)	4 (8.0)
No	377 (92.6)	211 (90.9)	166 (94.9)	7 (100)	60 (92.3)	12 (80.0)	16 (84.2)	5 (100)	6 (100)	46 (92.0)	13 (86.7)	46 (92.0)
Increased work of breathing												
Yes	98 (24.1)	66 (28.5)	32 (18.3)	1 (14.3)	20 (30.8)	4 (26.7)	5 (26.3)	0 (0)	0 (0)	19 (38.0)	4 (26.7)	13 (26.0)
No	309 (75.9)	166 (71.6)	143 (81.7)	6 (85.7)	45 (69.2)	11 (73.3)	14 (73.7)	5 (100)	6 (100)	31 (62.0)	11 (73.3)	46 (92.0)
Gastrointestinal												
Yes	128 (31.5)	80 (34.9)	47 (26.9)	2 (28.6)	18 (27.7)	2 (13.3)	10 (52.6)	2 (40.0)	2 (33.3)	24 (48.0)	4 (26.7)	17 (34.0)
No	279 (68.6)	151 (65.1)	128 (73.1)	5 (71.4)	47 (72.3)	13 (86.7)	9 (47.4)	3 (60.0)	4 (66.7)	26 (52.0)	11 (73.3)	33 (66.0)

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

Table 18 Clinical characteristics (medical history) associated with specimens for all children with accessible medical record information, without duplicates (n=407)

	Number of Specimens (%)											
	Total (n=407)	**Positive (n=232)**	**Negative (n=175)**	**Ad (n=7)**	**HRV (n=65)**	**HBoV (n=15)**	**hMPV (n=19)**	**Flu A (n=5)**	**Flu B (n=6)**	**RSV (n=50)**	**All PIV [a] (n=15)**	**Coinfection (n=50)**
Respiratory condition												
Any												
Yes	144 (35.4)	86 (37.1)	58 (33.1)	1 (14.3)	30 (46.2)	8 (53.3)	4 (21.1)	4 (80.0)	2 (33.3)	16 (32.0)	3 (20.0)	18 (36.0)
No	263 (64.6)	146 (62.9)	117 (66.7)	6 (85.7)	35 (53.9)	7 (46.7)	15 (79.0)	1 (20.0)	4 (66.7)	34 (68.0)	12 (80.0)	32 (64.0)
Asthma												
Yes	48 (11.8)	34 (14.7)	14 (8.00)	1 (14.3)	12 (18.5)	2 (13.3)	0 (0)	3 (60.0)	0 (0)	9 (18.0)	1 (6.7)	6 (12.0)
No	316 (77.6)	198 (85.3)	161 (92.0)	6 (85.7)	53 (81.5)	13 (86.7)	19 (100)	2 (40.0)	6 (100)	41 (82.0)	14 (93.3)	44 (88.0)
Structural defect												
Yes	79 (19.4)	49 (21.1)	30 (17.1)	0 (0)	17 (26.2)	5 (33.3)	3 (15.8)	0 (0)	0 (0)	10 (20.0)	2 (13.3)	12 (24.0)
No	328 (80.6)	183 (78.9)	145 (82.9)	7 (100)	48 (73.9)	10 (66.7)	16 (84.2)	5 (100)	6 (100)	40 (80.0)	13 (86.7)	38 (76.0)
Other medical condition												
Prematurity												
Yes	91 (22.4)	44 (19.0)	47 (26.9)	0 (0)	13 (20.0)	7 (46.7)	3 (15.8)	1 (20.0)	1 (16.7)	9 (18.0)	3 (20.0)	7 (14.0)
No	316 (77.6)	188 (81.0)	128 (73.1)	7 (100)	52 (80.0)	8 (53.3)	16 (84.2)	4 (80.0)	5 (83.3)	41 (82.0)	12 (80.0)	43 (86.0)
Cancer												
Yes	28 (6.9)	17 (7.3)	11 (6.3)	0 (0)	5 (7.7)	0 (0)	2 (10.5)	1 (20.0)	0 (0)	4 (8.0)	1 (6.7)	4 (8.00)
No	379 (93.1)	215 (92.7)	164 (93.7)	7 (100)	60 (92.3)	15 (100)	17 (89.5)	4 (80.0)	6 (100)	46 (92.0)	14 (93.3)	46 (92.0)
Transplant												
Yes	10 (2.5)	6 (2.6)	4 (2.3)	0 (0)	4(6.2)	0 (0)	0 (0)	0 (0)	1 (16.7)	0 (0)	0 (0)	1 (2.0)
No	397 (97.5)	226 (97.4)	171 (97.7)	7 (100)	61 (93.9)	15 (100)	19 (100)	5 (100)	5 (83.3)	50 (100)	15 (100)	49 (98.0)
Immunocompromised[b]												
Yes	121 (29.7)	70 (30.2)	51 (29.1)	1 (14.3)	19 (29.2)	1 (6.7)	8 (42.1)	1 (20.0)	3 (50.0)	15 (30.0)	2 (13.3)	20 (40.0)
No	286 (70.3)	162 (69.8)	124 (70.9)	6 (85.7)	46 (70.8)	14 (93.3)	11 (57.9)	4 (80.0)	3 (50.0)	35 (70.0)	13 (86.7)	30 (60.0)

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

[b] Includes history of cancer, transplant, and chronic conditions that may lead to increased risk of ARTI (see Table 2).

Table 19 Laboratory characteristics for all specimens with accessible medical record information, without duplicates (n=407)

	Number of Specimens (%)											
	Total (n=407)	**Positive (n=232)**	**Negative (n=175)**	**Ad (n=7)**	**HRV (n=65)**	**HBoV (n=15)**	**hMPV (n=19)**	**Flu A (n=5)**	**Flu B (n=6)**	**RSV (n=50)**	**All PIV[a] (n=15)**	**Coinfection (n=50)**
Month												
Mar 08	20 (4.9)	15 (6.5)	5 (2.9)	0 (0)	4 (6.2)	1 (6.7)	1 (5.3)	0 (0)	1 (16.7)	2 (4.0)	3 (20.0)	3 (6.0)
Apr 08 - Jun 08	82 (20.1)	52 (22.4)	30 (17.1)	2 (28.6)	13 (20.0)	5 (33.3)	8 (42.1)	0 (0)	0 (0)	3 (6.0)	5 (33.4)	16 (32.0)
Jul 08 - Sep 08	30 (7.4)	16 (6.9)	14 (8.0)	1 (14.3)	12 (18.5)	1 (6.7)	0 (0)	0 (0)	0 (0)	1 (2.0)	0 (0)	1 (2.0)
Oct 08 - Dec 08	76 (18.7)	33 (14.2)	43 (24.6)	2 (28.6)	10 (15.4)	3 (20.0)	1 (5.3)	0 (0)	0 (0)	7 (14.0)	1 (6.7)	9 (18.0)
Jan 09 - Mar 09	127 (31.2)	75 (32.3)	52 (29.7)	1 (14.3)	12 (18.5)	3 (20.0)	7 (36.8)	5 (100)	4 (66.7)	34 (68.0)	1 (6.7)	8 (16.0)
Apr 09 - Jun 09	72 (17.7)	41 (17.7)	31 (17.7)	1 (14.3)	14 (21.5)	2 (13.3)	2 (10.5)	0 (0)	1 (16.7)	3 (6.0)	5 (33.3)	13 (26.0)
Source												
Nasal wash	343 (85.8)	208 (90.8)	135 (79.0)	6 (85.7)	51 (81.0)	11 (78.6)	17 (89.5)	5 (100)	6 (100)	48 (96.0)	15 (100)	49 (98.0)
Bronch lavage	14 (3.5)	4 (1.8)	10 (5.9)	0 (0)	3 (4.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.0)
Trach aspirate	33 (8.3)	13 (5.7)	20 (11.7)	0 (0)	6 (9.5)	3 (21.4)	2 (10.5)	0 (0)	0 (0)	2 (4.0)	0 (0)	0 (0)
Other[b]	10 (2.5)	8 (3.5)	6 (3.5)	1 (14.3)	3 (4.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Missing	7	3	4	0	2	1	0	0	0	0	0	0

Note: Excludes 14 specimens for which medical record information was inaccessible. Percentages may not add to 100.0 due to rounding. Virus-specific estimates exclude coinfections.

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

[b] Other may include bronchial wash/biopsy, lung aspirate/biopsy, nasopharyngeal swab, nasal swab, THS, and tissue biopsy.

Table 20 Available demographic characteristics of children with accessible medical record information from eligible specimens excluded from study due to unavailability of specimen, without duplicates (n=100)

	Number of Specimens (%)								
	Total (n=100)	**Positive (n=74)**	**Negative (n=26)**	**Ad (n=2)**	**Flu A (n=3)**	**Flu B (n=5)**	**RSV (n=54)**	**All PIV[a] (n=8)**	**Coinfection (n=2)**
Gender									
Female	40 (40.0)	31 (41.9)	9 (34.6)	0 (0)	2 (66.7)	4 (80.0)	22 (40.7)	2 (25.0)	1 (50.0)
Male	60 (60.0)	43 (58.1)	17 (65.4)	2 (100)	1 (33.3)	1 (20.0)	32 (59.3)	6 (75.0)	1 (50.0)
Age (years)									
0 to < 0.5	41 (41.0)	33 (44.6)	8 (30.8)	0 (0)	1 (33.3)	0 (0)	29 (53.7)	1 (12.5)	0 (0)
0.5 to < 1	20 (20.0)	17 (23.0)	3 (11.5)	0 (0)	1 (33.3)	0 (0)	16 (29.6)	0 (0)	0 (0)
1 to < 5	29 (29.0)	20 (27.0)	9 (34.6)	0 (0)	1 (33.3)	3 (60.0)	9 (16.7)	5 (62.5)	0 (0)
≥ 5	10 (10.0)	4 (5.4)	6 (23.1)	2 (100)	0 (0)	2 (40.0)	0 (0)	2 (.25)	1 (100)
Race									
Caucasian	66 (75.0)	52 (81.3)	14 (58.3)	1 (50.0)	3 (100)	1 (25.0)	39 (82.9)	7 (100)	1 (100)
African-American	9 (10.2)	4 (6.3)	5 (20.8)	1 (50.0)	0 (0)	0 (0)	3 (6.4)	0 (0)	0 (0)
Hispanic	5 (5.7)	2 (3.1)	3 (12.5)	0 (0)	0 (0)	1 (25.0)	1 (2.1)	0 (0)	0 (0)
Other	8 (9.1)	6 (9.4)	2 (8.3)	0 (0)	0 (0)	2 (50)	4 (8.5)	0 (0)	0 (0)
Missing	12	10	2	0	0	0	7	1	1
Urban/Rural									
Urban	78 (78.0)	57 (77.0)	21 (80.8)	2 (100)	2 (66.7)	5 (100)	42 (77.8)	4 (50.0)	2 (100)
Large rural	8 (8.0)	7 (9.5)	1 (3.9)	0 (0)	0 (0)	0 (0)	4 (7.4)	3 (37.5)	0 (0)
Small rural	9 (9.0)	7 (9.5)	2 (7.7)	0 (0)	0 (0)	0 (0)	6 (11.1)	1 (12.5)	0 (0)
Isolated rural	5 (5.0)	3 (4.1)	2 (7.7)	0 (0)	1 (33.3)	0 (0)	2 (3.7)	0 (0)	0 (0)
Missing	0	0	0	0	0	0	0	0	0

Note: Excludes 3 specimens for which medical record information was inaccessible. Percentages may not add to 100.0 due to rounding. Virus-specific estimates exclude coinfections.

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

Table 21 Mean age of children with accessible medical record information from eligible specimens excluded from study due to unavailability of specimen, without duplicates (n=100)

	Total (n=100)	Positive (n=74)	Negative (n=26)	Ad (n=2)	Flu A (n=3)	Flu B (n=5)	RSV (n=54)	All PIV[a] (n=8)	Coinfection (n=2)
Age (years)									
Mean	1.64	1.34	2.50	2.42	1.65	5.24	0.66	3.36	0.39
Std deviation	2.16	1.77	2.90	0.35	2.00	2.09	0.80	2.06	0.12
Minimum	0.01	0.01	0.04	2.17	0.44	3.43	0.01	0.47	0.30
Maximum	8.53	7.62	8.53	2.67	3.97	7.62	4.75	6.41	0.47

Note: Excludes 3 specimens for which medical record information was inaccessible. Percentages may not add to 100.0 due to rounding. Virus-specific estimates exclude coinfections.

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

Table 22 Clinical characteristics (indicators of severity) associated with specimens with accessible medical record information from eligible children excluded from study due to unavailable specimen, without duplicates (n=100)

	Number of Specimens (%)								
	Total (n=100)	**Positive (n=74)**	**Negative (n=26)**	**Ad (n=2)**	**Flu A (n=3)**	**Flu B (n=5)**	**RSV (n=54)**	**All PIV[a] (n=8)**	**Coinfection (n=2)**
Inpatient									
Yes	44 (44.0)	33 (44.6)	11 (42.3)	2 (100)	1 (33.3)	0 (0)	23 (42.6)	7 (87.5)	0 (0)
No	56 (56.0)	41 (55.4)	15 (57.7)	0 (0)	2 (66.7)	5 (100)	31 (57.4)	1 (12.5)	2 (100)
ICU admission, if hospitalized									
Ever	12 (27.3)	6 (18.2)	6 (54.6)	0 (0)	0 (0)	NA	6 (26.1)	0 (0)	NA
Never	32 (72.7)	27 (81.8)	5 (45.5)	2 (100)	1 (100)	NA	17 (73.9)	7 (100)	NA

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

Table 23 Clinical characteristics (length of hospitalization) associated with specimens with accessible medical record information from eligible children excluded from study due to unavailable specimen, without duplicates (n=100)

	Total (n=100)	Positive (n=74)	Negative (n=26)	Ad (n=2)	Flu A (n=3)	Flu B (n=5)	RSV (n=54)	All PIV[a] (n=8)	Coinfection (n=2)
UIHC hospitalization Length of stay, days									
N	43	32	11	2	1	0	23	6	0
Median	2.00	2.00	11.00	3.00	2.00	NA	2.00	3.50	NA
Mean	9.37	7.31	15.36	3.00	2.00	NA	9.00	3.17	NA
Std deviation	17.47	16.80	18.81	2.83	NA	NA	19.64	1.94	NA
Minimum	<1.00	<1.00	1.00	1.00	2.00	NA	<1.00	1.00	NA
Maximum	93.00	93.00	63.00	5.00	2.00	NA	93.00	6.00	NA
Non-ICU days									
N	40	32	8	2	1	0	23	6	0
Median	2.00	2.00	1.50	3.00	2.00	NA	2.00	3.50	NA
Mean	4.28	3.78	6.25	3.00	2.00	NA	4.09	3.17	NA
Std deviation	6.41	5.24	10.07	2.83	NA	NA	6.09	1.94	NA
Minimum	<1.00	<1.00	1.00	1.00	2.00	NA	<1.00	1.00	NA
Maximum	65.00	28.00	29.00	5.00	2.00	NA	28.00	6.00	NA
ICU days									
N	12	6	6	0	0	0	6	0	0
Median	9.50	8.00	12.00	NA	NA	NA	8.00	NA	NA
Mean	19.33	18.83	19.83	NA	NA	NA	18.83	NA	NA
Std deviation	22.27	23.50	23.21	NA	NA	NA	23.50	NA	NA
Minimum	1.00	4.00	1.00	NA	NA	NA	4.00	NA	NA
Maximum	65.00	65.00	63.00	NA	NA	NA	65.00	NA	NA

Table 23 Continued

	Total (n=100)	Positive (n=74)	Negative (n=26)	Ad (n=2)	Flu A (n=3)	Flu B (n=5)	RSV (n=54)	All PIV[a] (n=8)	Coinfection (n=2)
Total hospitalization, days[b]									
N	43	32	11	2	1	0	23	6	0
Median	2.00	2.00	13.00	3.00	2.00	NA	2.00	3.50	NA
Mean	9.72	7.38	16.55	3.00	2.00	NA	9.09	3.17	NA
Std deviation	17.61	16.80	18.92	2.83	NA	NA	19.64	1.94	NA
Minimum	<1.00	<1.00	1.00	1.00	2.00	NA	<1.00	1.00	NA
Maximum	93.00	93.00	63.00	5.00	2.00	NA	93.00	6.00	NA

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

[b] Includes non-UIHC hospitalizations when applicable.

Table 24 Laboratory characteristics of clinical specimens with accessible medical record information from eligible children excluded from study due to unavailable specimen, without duplicates (n=100)

	Number of Specimens (%)								
	Total (n=100)	**Positive (n=74)**	**Negative (n=26)**	**Ad (n=2)**	**Flu A (n=3)**	**Flu B (n=5)**	**RSV (n=54)**	**All PIV[a] (n=8)**	**Coinfection (n=2)**
Month									
Mar 08	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Apr 08 - Jun 08	14 (14.0)	8 (10.8)	6 (23.1)	0 (0)	0 (0)	1 (20.0)	6 (11.1)	1 (12.5)	0 (0)
Jul 08 - Sep 08	2 (2.0)	0 (0)	2 (7.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Oct 08 - Dec 08	13 (13.0)	10 (13.5)	3 (11.5)	1 (50.0)	0 (0)	0 (0)	7 (13.0)	1 (12.5)	1 (50.0)
Jan 09 - Mar 09	47 (47.0)	45 (60.8)	2 (7.7)	0 (0)	2 (66.7)	4 (80.0)	36 (66.7)	2 (25.0)	1 (50.0)
Apr 09 - Jun 09	24 (24.0)	11 (14.9)	13 (50.0)	1 (50.0)	1 (33.3)	0 (0)	5 (9.3)	3 (37.5)	0 (0)
Source									
Bronch wash	1 (1.0)	1 (1.4)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.9)	0 (0)	0 (0)
NP swab	5 (5.0)	0 (0)	5 (19.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nasal swab	5 (5.0)	1 (1.4)	4 (15.4)	0 (0)	0 (0)	0 (0)	1 (1.9)	0 (0)	0 (0)
Nasal wash	84 (84.0)	70 (94.6)	14 (53.9)	2 (100)	3 (100)	5 (100)	51 (94.4)	7 (87.5)	2 (100)
Tissue biopsy	1 (1.0)	0 (0)	1 (3.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Trach aspirate	3 (3.0)	2 (2.7)	1 (3.9)	0 (0)	0 (0)	0 (0)	1 (1.9)	1 (12.5)	0 (0)
Pleural fluid	1 (1.0)	0 (0)	1 (3.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Note: Excludes 3 specimens for which medical record information was inaccessible. Percentages may not add to 100.0 due to rounding. Virus-specific estimates exclude coinfections.

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

Table 25 Demographic characteristics of children for HRV-tested specimens with accessible medical record information, without duplicates (n=407)

	Number of Specimens (%)					
	HRV-Positive (n=102)	HRV-Negative (n=305)	HRV A (n=29)	HRV C (n=31)	HRV Other[a] (n=5)	Coinfection with Any Virus (n=37)
Gender						
Female	44 (43.1)	143 (46.9)	11 (37.9)	19 (61.3)	1 (20.0)	13 (35.1)
Male	58 (56.9)	162 (53.1)	18 (62.1)	12 (38.7)	4 (80.0)	24 (64.9)
Age (years)						
0 to < 0.5	33 (32.4)	120 (39.3)	14 (48.3)	10 (32.3)	0 (0)	9 (24.3)
0.5 to < 1	20 (19.6)	29 (9.5)	3 (10.3)	7 (22.6)	1 (20.0)	9 (24.3)
1 to < 5	34 (33.3)	115 (37.7)	7 (24.1)	10 (32.3)	2 (40.0)	15 (40.5)
≥ 5	15 (14.7)	41 (13.4)	5 (17.2)	4 (12.9)	2 (40.0)	4 (10.8)
Race						
Caucasian	69 (75.0)	203 (72.2)	22 (84.6)	17 (60.7)	4 (80.0)	26 (78.9)
African-American	9 (9.8)	33 (11.7)	3 (11.5)	4 (14.3)	0 (0)	2 (6.1)
Hispanic	9 (7.6)	27 (9.6)	1 (3.9)	5 (17.9)	0 (0)	1 (3.0)
Other	7 (7.6)	18 (6.4)	0 (0)	2 (7.1)	1 (20.0)	4 (12.1)
Missing	10	24	3	3	0	4
Medicaid						
Yes	47 (46.1)	146 (48.3)	13 (44.8)	15 (48.4)	3 (60.0)	16 (43.2)
No	55 (53.9)	156 (51.7)	16 (55.2)	16 (51.6)	2 (40.0)	21 (56.8)
Missing	0	3	0	0	0	0
Urban/Rural						
Urban	64 (62.8)	180 (59.2)	20 (69.0)	19 (61.3)	4 (80.0)	21 (56.8)
Large rural	12 (11.8)	51 (16.8)	3 (10.3)	3 (9.7)	0 (0)	6 (16.2)
Small rural	13 (12.8)	36 (11.8)	4 (13.8)	3 (9.7)	1 (20.0)	5 (13.5)
Isolated rural	13 (12.8)	37 (12.2)	2 (6.9)	6 (19.4)	0 (0)	5 (13.5)
Missing	0	1	0	0	0	0

Table 25 Continued

	Number of Specimens (%)					
	HRV-Positive (n=102)	HRV-Negative (n=305)	HRV A (n=29)	HRV C (n=31)	HRV Other[a] (n=5)	Coinfection with Any Virus (n=37)
Smoke exposure						
None	28 (68.3)	82 (65.1)	6 (66.7)	9 (81.1)	1 (33.3)	12 (66.7)
Direct	4 (9.8)	14 (11.1)	0 (0)	1 (9.1)	0 (0)	3 (16.7)
Indirect	9 (22.0)	30 (23.8)	3 (33.3)	1 (9.1)	2 (66.7)	3 (16.7)
Missing	61	179	20	20	2	19

Note: Excludes 14 specimens for which medical record information was inaccessible. Percentages may not add to 100.0 due to rounding. Virus-specific estimates exclude coinfections.

[a] The category HRV Other includes 1 HRV B and 4 non-typeable HRVs.

Table 26 Mean age of children for HRV-tested specimens with accessible medical record information, without duplicates (n=407)

	HRV-Positive (n=102)	HRV-Negative (n=305)	HRV A (n=29)	HRV C (n=31)	HRV Other[a] (n=5)	Coinfection with Any Virus (n=37)
Age (years)						
Mean	2.07	2.07	2.01	1.91	4.70	1.90
Std deviation	2.58	2.50	2.41	2.47	3.95	2.52
Minimum	0.03	0	0.04	0.03	0.79	0.11
Maximum	9.73	9.80	8.15	9.73	9.29	9.62

Note: Excludes 14 specimens for which medical record information was inaccessible. Percentages may not add to 100.0 due to rounding. Virus-specific estimates exclude coinfections.

[a] The category HRV Other includes 1 HRV B and 4 non-typeable HRVs.

Table 27 Clinical characteristics (indicators of severity) associated with HRV-tested specimens with accessible medical record information, without duplicates (n=407)

	Number of Specimens (%)					
	HRV-Positive (n=102)	HRV-Negative (n=305)	HRV A (n=29)	HRV C (n=31)	HRV Other[a] (n=5)	Coinfection with Any Virus (n=37)
Inpatient						
Yes	77 (75.5)	236 (77.4)	25 (86.2)	21 (67.7)	4 (80.0)	27 (73.0)
No	25 (24.5)	69 (22.6)	4 (13.8)	10 (32.3)	1 (20.0)	10 (27.0)
ICU admission, if hospitalized						
Ever	19 (24.7)	103 (43.6)	10 (40.0)	5 (23.8)	0 (0)	4 (14.8)
Never	58 (75.3)	133 (56.4)	15 (60.0)	16 (76.2)	1 (100)	23 (85.2)
ICU at collection						
Yes	19 (24.7)	94 (39.8)	10 (40.0)	5 (23.8)	0 (0)	4 (14.8)
No	58 (75.3)	142 (60.2)	15 (60.0)	16 (76.2)	1 (100)	23 (85.2)
Mechanically ventilated						
Yes	8 (7.8)	61 (20.0)	6 (20.7)	1 (3.2)	0 (0)	1 (2.7)
No	94 (92.2)	244 (80.0)	23 (79.3)	30 (96.8)	5 (100)	36 (97.3)
Oxygen requirement						
Yes	36 (35.3)	145 (47.5)	12 (41.4)	7 (22.6)	2 (40.0)	15 (40.5)
No	66 (64.7)	160 (52.5)	17 (58.6)	24 (77.4)	3 (60.0)	22 (59.5)
Bronchodilator administered						
Yes	34 (33.3)	80 (26.2)	4 (13.8)	11 (35.5)	2 (40.0)	17 (46.0)
No	68 (66.7)	225 (73.8)	25 (86.2)	20 (64.5)	3 (60.0)	20 (54.1)
Oxygen saturation < 90%						
Yes	30 (29.4)	107 (35.1)	9 (31.0)	6 (19.4)	2 (40.0)	13 (35.1)
No	72 (70.6)	198 (64.9)	20 (69.0)	25 (80.7)	3 (60.0)	24 (64.9)

[a] The category HRV Other includes 1 HRV B and 4 non-typeable HRVs.

Table 28 Clinical characteristics (length of hospitalization) associated with HRV-tested specimens with accessible medical record information, without duplicates (n=407)

	HRV-Positive (n=102)	HRV-Negative (n=305)	HRV A (n=29)	HRV C (n=31)	HRV Other[a] (n=5)	Coinfection with Any Virus (n=37)
UIHC hospitalization Length of stay, days						
N	77	236	25	21	4	27
Median	3.00	6.00	4.00	2.00	3.50	3.00
Mean	11.88	25.31	18.80	5.90	6.00	11.00
Std deviation	31.65	50.04	42.62	11.78	6.06	32.55
Minimum	<1.00	<1.00	<1.00	<1.00	2.00	1.00
Maximum	204.00	377.00	204.00	53.00	15.00	172.00
Non-ICU days						
N	73	180	22	20	4	27
Median	3.00	3.00	3.00	2.00	3.50	3.00
Mean	5.81	7.28	7.45	2.55	6.00	6.85
Std deviation	11.95	28.04	16.08	2.39	6.06	12.91
Minimum	<1.00	<1.00	1.00	<1.00	2.00	1.00
Maximum	77.00	369.00	77.00	11.00	15.00	67.00
ICU days						
N	19	103	10	5	0	4
Median	4.00	18.00	7.00	4.00	0.00	2.50
Mean	25.84	45.30	30.60	14.60	NA	28.00
Std deviation	50.34	58.32	62.30	21.87	NA	51.34
Minimum	<1.00	1.00	<1.00	1.00	NA	2.00
Maximum	204.00	377.00	204.00	53.00	NA	105.00

Table 28 Continued

	HRV-Positive (n=102)	HRV-Negative (n=305)	HRV A (n=29)	HRV C (n=31)	HRV Other[a] (n=5)	Coinfection with Any Virus (n=37)
Total hospitalization, days[b]						
N	77	236	25	21	4	27
Median	3.00	6.00	4.00	2.00	3.50	3.00
Mean	14.08	25.65	25.40	6.00	6.00	11.07
Std deviation	37.59	50.00	54.62	11.76	6.06	32.73
Minimum	<1.00	<1.00	<1.00	<1.00	2.00	1.00
Maximum	204.00	377.00	204.00	53.00	15.00	173.00

[a] The category HRV Other includes 1 HRV B and 4 non-typeable HRVs.

[b] Includes non-UIHC hospitalizations when applicable.

Table 29 Clinical characteristics (antimicrobial use and inflammation markers) associated with HRV-tested specimens with accessible medical record information, without duplicates (n=407)

	Number of Specimens (%)					
	HRV-Positive (n=102)	HRV-Negative (n=305)	HRV A (n=29)	HRV C (n=31)	HRV Other[a] (n=5)	Coinfection with Any Virus (n=37)
Antimicrobial use						
Prior use						
Yes	33 (32.4)	88 (28.9)	13 (44.8)	7 (22.6)	2 (40.0)	11 (29.7)
No	69 (67.7)	217 (71.2)	16 (55.2)	24 (77.4)	3 (60.0)	26 (70.3)
UIHC administered						
Yes	56 (54.9)	187 (61.3)	18 (62.1)	14 (45.2)	3 (60.0)	21 (56.8)
No	46 (45.1)	118 (38.7)	11 (37.9)	17 (54.8)	2 (40.0)	16 (43.2)
Take-home prescription						
Yes	31 (30.4)	75 (24.6)	6 (20.7)	11 (35.5)	0 (0)	14 (37.8)
No	71 (69.6)	230 (75.4)	23 (79.3)	20 (64.5)	5 (100)	23 (62.2)
Leukopenia						
Yes	10 (13.5)	63 (26.5)	4 (16.7)	3 (15.0)	1 (25.0)	2 (7.7)
No	64 (86.5)	175 (73.5)	20 (83.3)	17 (85.0)	3 (75.0)	24 (92.3)
Missing	28	67	5	11	1	11
Leukocytosis						
Yes	19 (25.7)	62 (26.1)	3 (12.5)	8 (40.0)	2 (50.0)	6 (23.1)
No	55 (74.3)	176 (74.0)	21 (87.5)	12 (60.0)	2 (50.0)	20 (76.9)
Missing	28	67	5	11	1	11
CRP > 0.5 mg/dl						
Yes	34 (61.8)	138 (68.7)	12 (63.2)	10 (55.6)	2 (100)	10 (62.5)
No	21 (38.2)	63 (31.3)	7 (36.8)	8 (44.4)	0 (0)	6 (37.5)
Missing	47	104	10	13	3	21

[a] The category HRV Other includes 1 HRV B and 4 non-typeable HRVs.

Table 30 Clinical characteristics (diagnoses) associated with HRV-tested specimens with accessible medical record information, without duplicates (n=407)

	Number of Specimens (%)					
	HRV-Positive (n=102)	HRV-Negative (n=305)	HRV A (n=29)	HRV C (n=31)	HRV Other[a] (n=5)	Coinfection with Any Virus (n=37)
ARTI						
None	2 (2.0)	13 (4.3)	0 (0)	1 (3.2)	0 (0)	1 (2.7)
Physician diagnosed	54 (52.9)	136 (44.6)	16 (55.2)	16 (51.6)	1 (20.0)	21 (56.8)
Physician documented symptoms	41 (40.2)	115 (37.7)	12 (41.4)	11 (35.5)	4 (80.0)	14 (37.8)
Concern for ARTI without traditional symptoms	5 (4.9)	41 (13.4)	1 (3.5)	3 (9.7)	0 (0)	1 (2.7)
Diagnosis						
Bronchiolitis						
Yes	12 (11.8)	33 (10.8)	1 (3.4)	3 (9.7)	0 (0)	8 (21.6)
No	90 (88.2)	272 (89.2)	28 (96.6)	28 (90.3)	5 (100)	29 (78.4)
Pneumonia						
Yes	22 (21.6)	65 (21.3)	7 (24.1)	3 (9.7)	1 (20.0)	11 (29.7)
No	80 (78.4)	240 (78.7)	22 (75.9)	28 (90.3)	4 (80.0)	26 (70.3)
Respiratory tract infection						
Yes	34 (33.3)	72 (23.6)	13 (44.8)	12 (38.7)	0 (0)	9 (24.3)
No	68 (66.7)	233 (76.4)	16 (55.2)	19 (61.3)	5 (100)	28 (75.7)

[a] The category HRV Other includes 1 HRV B and 4 non-typeable HRVs.

Table 31 Clinical characteristics (symptoms) associated with HRV-tested specimens with accessible medical record information, without duplicates (n=407)

	Number of Specimens (%)					
	HRV-Positive (n=102)	HRV-Negative (n=305)	HRV A (n=29)	HRV C (n=31)	HRV Other[a] (n=5)	Coinfection with Any Virus (n=37)
Fever						
Yes	47 (46.1)	175 (57.4)	13 (44.8)	13 (41.9)	2 (40.0)	19 (51.4)
No	55 (53.9)	130 (42.6)	16 (55.2)	18 (58.1)	3 (60.0)	18 (48.7)
Nasal						
Yes	51 (50.0)	113 (37.1)	13 (44.8)	15 (48.4)	2 (40.0)	21 (56.8)
No	51 (50.0)	192 (63.0)	16 (55.2)	16 (51.6)	3 (60.0)	16 (43.2)
Cough						
Yes	65 (63.7)	155 (50.8)	12 (41.4)	20 (64.5)	3 (60.0)	30 (81.8)
No	37 (36.3)	150 (49.2)	17 (58.6)	11 (35.5)	2 (40.0)	7 (18.9)
Wheeze						
Yes	31 (30.4)	43 (14.1)	3 (10.3)	14 (45.2)	1 (20.0)	13 (35.1)
No	71 (69.6)	262 (85.9)	26 (89.7)	17 (54.8)	4 (80.0)	24 (64.9)
Tachypnea						
Yes	8 (7.8)	22 (7.2)	3 (10.3)	1 (3.2)	1 (20.0)	3 (8.1)
No	94 (92.2)	283 (92.8)	26 (89.7)	30 (96.8)	4 (80.0)	34 (91.9)
Increased work of breathing						
Yes	30 (29.4)	68 (22.3)	8 (27.6)	11 (35.5)	1 (20.0)	10 (27.0)
No	72 (70.6)	237 (77.7)	21 (72.4)	20 (64.5)	4 (80.0)	27 (73.0)
Gastrointestinal						
Yes	28 (27.5)	100 (32.8)	7 (24.1)	9 (29.0)	2 (40.0)	10 (27.0)
No	74 (72.6)	205 (67.2)	22 (75.9)	22 (71.0)	3 (60.0)	27 (73.0)

[a] The category HRV Other includes 1 HRV B and 4 non-typeable HRVs.

Table 32 Clinical characteristics (medical history) associated with HRV-tested specimens with accessible medical record information, without duplicates (n=407)

	Number of Specimens (%)					
	HRV-Positive (n=102)	HRV-Negative (n=305)	HRV A (n=29)	HRV C (n=31)	HRV Other[a] (n=5)	Coinfection with Any Virus (n=37)
Respiratory condition						
Any						
Yes	47 (46.1)	97 (31.8)	15 (51.7)	13 (41.9)	2 (40.0)	17 (46.0)
No	55 (53.9)	208 (68.2)	14 (48.3)	18 (58.1)	3 (60.0)	20 (54.1)
Asthma						
Yes	17 (16.7)	31 (10.2)	3 (10.3)	8 (25.8)	1 (20.0)	5 (13.5)
No	85 (83.3)	274 (89.8)	26 (89.7)	23 (74.2)	4 (80.0)	32 (86.5)
Structural defect						
Yes	29 (28.4)	50 (16.4)	9 (31.0)	6 (19.4)	2 (40.0)	12 (32.4)
No	73 (71.6)	255 (83.6)	20 (69.0)	25 (80.7)	3 (60.0)	25 (67.6)
Other medical condition						
Prematurity						
Yes	20 (19.6)	71 (23.3)	8 (27.6)	5 (16.1)	0 (0)	7 (18.9)
No	82 (80.4	234 (76.7)	21 (72.4)	26 (83.9)	5 (100)	30 (81.1)
Cancer						
Yes	8 (7.8)	20 (6.6)	3 (10.3)	2 (6.5)	0 (0)	3 (8.1)
No	94 (92.2)	285 (93.4)	26 (89.7)	29 (93.6)	5 (100)	34 (97.9)
Transplant						
Yes	5 (4.9)	5 (1.6)	3 (10.3)	1 (3.2)	0 (0)	1 (2.7)
No	97 (95.1)	300 (98.4)	26 (89.7)	30 (96.8)	5 (100)	36 (97.3)
Immunocompromised[b]						
Yes	35 (34.3)	86 (28.2)	10 (34.5)	6 (19.4)	2 (40.0)	17 (45.9)
No	67 (65.7)	219 (71.8)	19 (34.5)	25 (80.7)	3 (60.0)	20 (54.1)

[a] The category HRV Other includes 1 HRV B and 4 non-typeable HRVs.

[b] Includes history of cancer, transplant, and chronic conditions that may lead to increased risk of ARTI (see Table 2).

Table 33 Laboratory characteristics of HRV-tested specimens with accessible medical record information, without duplicates (n=407)

	Number of Specimens (%)					
	HRV-Positive (n=102)	HRV-Negative (n=305)	HRV A (n=29)	HRV C (n=31)	HRV Other[a] (n=5)	Coinfection with Any Virus (n=37)
Month						
Mar 08	6 (5.9)	14 (4.6)	2 (6.9)	2 (6.5)	0 (0)	2 (5.4)
Apr 08 - Jun 08	23 (22.6)	59 (19.3)	5 (17.2)	7 (22.6)	1 (20.0)	10 (27.0)
Jul 08 - Sep 08	12 (11.8)	18 (5.9)	9 (31.0)	3 (9.7)	0 (0)	0 (0)
Oct 08 - Dec 08	17 (16.7)	59 (19.3)	3 (10.3)	6 (19.4)	1 (20.0)	7 (18.9)
Jan 09 - Mar 09	19 (18.6)	108 (35.4)	1 (3.5)	8 (25.8)	3 (60.0)	7 (18.9)
Apr 09 - Jun 09	25 (24.5)	47 (15.4)	9 (31.0)	5 (16.1)	0 (0)	11 (29.7)
Source						
Nasal wash	88 (88.0)	255 (85.0)	20 (69.0)	26 (29.7)	5 (100)	37 (100)
Bronch lavage	3 (3.0)	11 (3.7)	1 (3.5)	2 (6.9)	0 (0)	0 (0)
Trach aspirate	6 (6.0)	27 (9.0)	6 (20.7)	0 (0)	0 (0)	0 (0)
Other[b]	3 (3.0)	7 (2.3)	2 (6.9)	1 (3.4)	0 (0)	0 (0)
Missing	2	5	0	2	0	0 (0)

Note: Excludes 14 specimens for which medical record information was inaccessible. Percentages may not add to 100.0 due to rounding. Virus-specific estimates exclude coinfections.

[a] The category HRV Other includes 1 HRV B and 4 non-typeable HRVs.

[b] Other may include bronchial wash/biopsy, lung aspirate/biopsy, nasopharyngeal swab, nasal swab, THS, tissue biopsy.

Table 34 Prevalence and odds ratio of viral coinfection by risk factor among children with confirmed or suspected ARTI, without duplicates[a]

Risk Factor	N	% Coinfected (95% CI)	OR (95% CI)	p	p trend
Gender					
Female	98	18.4 (11.3-27.5)	1.00		
Male	114	25.4 (17.8-34.5)	1.52 (0.78-2.94)	0.218	
Age (years)					
0 to < 0.5	66	18.1 (9.8-29.6)	1.00		0.558
0.5 to < 1	37	27 (13.8-44.1)	1.67 (0.64-4.34)	0.296	
1 to < 5	83	22.9 (14.4-33.4)	1.34 (0.60-3.00)	0.483	
> 5	26	23.1 (9.0-43.7)	1.35 (0.45-4.08)	0.595	
Race					
Caucasian	147	21.8 (15.4-29.3)	1.00		
African-American	20	15.0 (3.2-37.9)	0.63 (0.18-2.30)	0.488	
Hispanic	19	15.8 (3.4-39.6)	0.67 (0.19-2.46)	0.549	
Other	10	40.0 (12.2-73.8)	2.40 (0.64-9.01)	0.196	
Medicaid					
No	112	22.3 (15.0-31.2)	1.00		
Yes	98	22.5 (14.6-32.0)	1.01 (0.53-1.93)	0.982	
Urban/Rural					
Urban	128	20.3 (13.7-28.3)	1.00		0.391
Large rural	30	26.7 (12.3-45.9)	1.43 (0.57-3.57)	0.448	
Small rural	28	17.9 (6.1-36.9)	0.85 (0.30-2.46)	0.768	
Isolated rural	26	30.8 (14.3-51.8)	1.74 (0.68-4.45)	0.245	
History of chronic respiratory condition					
No	136	22.1 (15.4-30.0)	1.00		
Yes	76	22.4 (13.6-33.4)	1.02 (0.52-1.99)	0.958	

Table 34 Continued

Risk Factor	N	% Coinfected (95% CI)	OR (95% CI)	p	p trend
History of structural respiratory condition					
No	169	21.3 (15.4-28.3)	1.00		
Yes	43	25.6 (13.5-41.2)	1.27 (0.58-2.76)	0.547	
History of asthma					
No	180	22.8 (16.9-29.6)	1.00		
Yes	32	18.8 (7.2-36.4)	0.78 (0.30-2.03)	0.614	
History of cancer					
No	195	22.1 (16.4-28.5)	1.00		
Yes	17	23.5 (6.8-49.9)	1.08 (0.34-3.51)	0.888	
History of transplant					
No	207	22.2 (16.8-28.5)	1.00		
Yes	5	20.0 (0.5-71.6)	0.88 (0.10-8.02)	0.906	
History of any immunosuppressive condition[b]					
No	147	19.1 (13.1-26.3)	1.00		
Yes	65	29.2 (18.6-41.8)	1.76 (0.89-3.45)	0.102	
History of prematurity					
No	175	23.4 (17.4-30.4)	1.00		
Yes	37	16.2 (0.6-32.0)	0.63 (0.25-1.62)	0.340	
Smoke exposure					
None	61	22.9 (13.2-35.5)	1.00		0.828
Direct	9	44.4 (13.7-78.8)	2.69 (0.63-11.38)	0.180	
Indirect	26	26.9 (11.6-47.8)	1.24 (0.43-3.54)	0.692	
Missing	116				

[a] Bivariate analysis of selected risk factors and viral coinfection includes only virus-positive specimens from children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI with accessible medical records, without duplicates (n=212).

[b] Includes history of cancer, transplant, and chronic conditions that may lead to increased risk of ARTI (see Table 2).

Table 35 Adjusted odds ratio of viral coinfection by risk factor among children with confirmed or suspected ARTI, without duplicates[a]

Risk Factor	Adjusted OR (95% CI)	p
Gender		
Female	1.00	
Male	1.70 (0.83-3.46)	0.145
Age (years)		
0 to < 0.5	1.00	
0.5 to < 1	2.15 (0.75-6.19)	0.154
1 to < 5	1.59 (0.65-3.92)	0.313
> 5	1.67 (0.50-5.53)	0.403
History of any immunosuppressive condition[b]		
No	1.00	
Yes	2.05 (0.99-4.23)	0.052

[a] Multivariate analysis of selected risk factors and viral coinfection includes only virus-positive specimens from children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI with accessible medical records, without duplicates (n=212).

[b] Includes history of cancer, transplant, and chronic conditions that may lead to increased risk of ARTI (see Table 2).

Table 36 Prevalence and odds ratio of viral coinfection by risk factor among children with confirmed or suspected ARTI with complete tobacco smoke exposure data, without duplicates[a]

Risk Factor	N	% Coinfected (95% CI)	OR (95% CI)	p	p trend
Gender					
Female	44	18.2 (8.2-32.7)	1.00		
Male	52	32.7 (20.3-47.1)	2.17 (0.83-5.56)	0.111	
Age (years)					
0 to < 0.5	34	20.6 (8.7-37.9)	1.00		0.527
0.5 to < 1	16	31.3 (11.0-58.7)	1.75 (0.46-6.73)	0.413	
1 to < 5	38	29.0 (15.4-45.9)	1.57 (0.53-4.66)	0.415	
> 5	8	25.0 (3.2-65.1)	1.29 (0.21-7.80)	0.785	
Race					
Caucasian	70	24.3 (14.8-36.0)	1.00		
African-American	7	42.9 (0.10-81.6)	2.34 (0.48-11.51)	0.296	
Hispanic	9	11.1 (0.01-0.48.3)	0.39 (0.05-3.34)	0.390	
Other	1	100 (25.0-100)	NA	NA	
Medicaid					
No	44	20.5 (9.8-20.5)	1.00		
Yes	51	31.4 (19.1-45.9)	1.77 (0.69-4.56)	0.231	
Urban/Rural					
Urban	55	23.6 (13.2-37.0)	1.00		0.617
Large rural	22	31.8 (13.9-54.9)	1.51 (0.51-4.49)	0.461	
Small rural	7	14.3 (0.04-57.9)	0.54 (0.06-4.89)	0.582	
Isolated rural	12	33.3 (9.9-65.1)	1.62 (0.42-6.24)	0.487	
History of chronic respiratory condition					
No	59	22.0 (12.3-34.7)	1.00		
Yes	37	32.4 (18.0-49.8)	1.70 (0.68-4.28)	0.261	

Table 36 Continued

Risk Factor	N	% Coinfected (95% CI)	OR (95% CI)	p	p trend
History of structural respiratory condition					
No	78	24.4 (15.4-35.4)	1.00		
Yes	18	33.3 (0.13-59.0)	1.55 (0.51-4.70)	0.436	
History of asthma					
No	81	25.9 (16.8-36.9)	1.00		
Yes	15	26.7 (7.8-55.1)	1.04 (0.30-3.62)	0.952	
History of cancer					
No	95	26.3 (17.8-36.4)	1.00		
Yes	1	0 (0-97.5)	NA	NA	
History of transplant					
No	95	26.3 (17.8-36.4)	1.00		
Yes	1	0 (0-97.5)	NA	NA	
History of any immunosuppressive condition[b]					
No	82	24.4 (15.6-35.1)	1.00		
Yes	14	35.7 (12.8-64.9)	1.72 (0.52-5.74)	0.376	
History of prematurity					
No	77	27.3 (17.7-38.6)	1.00		
Yes	19	21.1 (6.1-45.6)	0.71 (0.21-2.39)	0.581	
Smoke exposure					
None	61	23.0 (13.2-35.5)	1.00		0.828
Direct	9	44.4 (13.7-78.8)	2.67 (0.63-11.38)	0.180	
Indirect	26	26.9 (11.6-47.8)	1.24 (0.43-3.54)	0.692	
Missing	0				

[a] Bivariate analysis of selected risk factors and viral coinfection includes only virus-positive specimens from children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI and with complete tobacco smoke exposure data, without duplicates (n=96).

[b] Includes history of cancer, transplant, and chronic conditions that may lead to increased risk of ARTI (see Table 2).

Table 37 Adjusted odds ratio of viral coinfection by risk factor among children with confirmed or suspected ARTI with complete tobacco smoke exposure data, without duplicates[a]

Risk Factor	Adjusted OR (95% CI)	p
Age (years)		
0 to < 0.5	1.00	
0.5 to < 1	3.27 (0.72-14.94)	0.126
1 to < 5	2.54 (0.72-8.90)	0.146
> 5	2.48 (0.34-18.25)	0.373
History of any immunosuppressive condition[b]		
No	1.00	
Yes	2.26 (0.63-8.15)	0.214
Smoke exposure		
None	1.00	
Direct	4.26 (0.88-20.67)	0.073
Indirect	1.60 (0.48-5.30)	0.439

[a] Multivariate analysis of selected risk factors and viral coinfection includes only virus-positive specimens from children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI and with complete tobacco smoke exposure data, without duplicates (n=96).

[b] Includes history of cancer, transplant, and chronic conditions that may lead to increased risk of ARTI (see Table 2).

Table 38 Prevalence and odds ratio of HRV-specific coinfection by risk factor among HRV-positive children with confirmed or suspected ARTI, without duplicates[a]

Risk Factor	N	% Coinfected (95% CI)	OR (95% CI)	p	p trend
Gender					
Female	40	30.0 (16.6-46.5)	1.00		
Male	55	41.8 (28.7-55.9)	1.67 (0.71-4.00)	0.240	
Age (years)					
0 to < 0.5	31	29.0 (14.2-48.0)	1.00		0.703
0.5 to < 1	17	47.1 (22.9-72.2)	2.17 (0.64-7.42)	0.216	
1 to < 5	33	42.4 (25.5-60.8)	1.80 (0.64-5.09)	0.267	
> 5	14	28.6 (8.4-58.1)	0.98 (0.24-3.95)	0.975	
Race					
Caucasian	65	38.5 (26.7-51.4)	1.00		
African-American	9	22.2 (2.8-60.0)	0.46 (0.09-2.38)	0.352	
Hispanic	7	14.3 (0.4-57.9)	0.27 (0.03-2.35)	0.234	
Other	5	60.0 (14.7-94.7)	2.40 (0.37-15.38)	0.356	
Medicaid					
No	51	39.2 (25.8-53.9)	1.00		
Yes	44	34.1 (20.5-49.9)	0.80 (0.35-1.86)	0.606	
Urban/Rural					
Urban	59	32.3 (20.6-45.6)	1.00		0.386
Large rural	12	50.0 (21.1-78.9)	2.11 (0.60-7.40)	0.246	
Small rural	12	41.7 (15.2-72.3)	1.50 (0.42-5.36)	0.529	
Isolated rural	12	41.7 (15.2-72.3)	1.50 (0.42-5.36)	0.529	
History of chronic respiratory condition					
No	52	36.5 (23.6-51.0)	1.00		
Yes	43	37.2 (22.9-53.3)	1.03 (0.45-2.38)	0.946	

Table 38 Continued

Risk Factor	N	% Coinfected (95% CI)	OR (95% CI)	p	p trend
History of structural respiratory condition					
No	68	35.3 (24.1-47.8)	1.00		
Yes	72	40.7 (22.4-61.2)	1.26 (0.51-3.15)	0.620	
History of asthma					
No	79	38.0 (27.3-49.6)	1.00		
Yes	16	31.3 (11.0-58.7)	0.74 (0.24-2.35)	0.612	
History of cancer					
No	87	36.8 (26.7-47.8)	1.00		
Yes	8	37.5 (8.5-75.5)	1.03 (0.23-4.61)	0.968	
History of transplant					
No	90	37.8 (27.8-48.6)	1.00		
Yes	5	20.0 (0.05-71.6)	0.41 (0.04-3.84)	0.436	
History of any immunosuppressive condition[b]					
No	61	32.8 (21.3-46.0)	1.00		
Yes	34	44.1 (27.2-62.1)	1.62 (0.68-3.83)	0.274	
History of prematurity					
No	77	37.7 (26.9-49.4)	1.00		
Yes	18	33.3 (13.3-59.0)	0.83 (0.28-2.44)	0.732	
Smoke exposure					
None	28	42.9 (24.5-62.8)	1.00		0.537
Direct	4	75.0 (19.4-99.4)	4.0 (0.37-43.38)	0.254	
Indirect	9	33.3 (7.5-70.1)	0.67 (0.14-3.22)	0.614	
Missing	54				

[a] Bivariate analysis of selected risk factors and viral coinfection includes only HRV-positive specimens from children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI with accessible medical record information, without duplicates (n=95).

[b] Includes history of cancer, transplant, and chronic conditions that may lead to increased risk of ARTI (see Table 2).

Table 39 Adjusted odds ratio of HRV-specific coinfection by risk factor among HRV-positive children with confirmed or suspected ARTI, without duplicates[a]

Risk Factor	Adjusted OR (95% CI)	p
Gender		
Female	1.00	
Male	1.89 (0.71-5.03)	0.202
Age (years)		
0 to < 0.5	1.00	
0.5 to < 1	3.70 (0.87-15.67)	0.076
1 to < 5	2.72 (0.80-9.21)	0.109
> 5	1.50 (0.30-7.44)	0.621
Urban/Rural		
Urban	1.00	
Large rural	3.17 (0.77-13.06)	0.110
Small rural	1.43 (0.36-5.60)	0.610
Isolated rural	1.24 (0.28-5.45)	0.779
History of any immunosuppressive condition[b]		
No	1.00	
Yes	2.24 (0.81-6.22)	0.121

[a] Bivariate analysis of selected risk factors and viral coinfection includes only HRV-positive specimens from children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI with accessible medical record information, without duplicates (n=95).

[b] Includes history of cancer, transplant, and chronic conditions that may lead to increased risk of ARTI (see Table 2).

Table 40 Prevalence and odds ratio of viral coinfection by risk factor among hospitalized children with confirmed or suspected ARTI, without duplicates[a]

Risk Factor	N	% Coinfected (95% CI)	OR (95% CI)	p
Gender				
Female	70	15.7 (8.1-26.4)	1.00	
Male	90	25.6 (16.9-35.8)	2.24 (0.24-1.21)	0.134
Age (years)[b]				
0 to < 1	79	19.0 (11.0-29.4)	1.00	
1 to < 5	63	22.2 (12.7-34.5)	1.22 (0.54-2.76)	0.635
> 5	18	27.8 (9.7-53.5)	1.64 (0.51-5.31)	0.408
Race (4 level)				
Caucasian	114	21.1 (14.0-29.7)	1.00	
African-American	15	20.0 (4.3-48.1)	0.94 (0.25-3.59)	0.925
Hispanic	14	14.3 (1.8-42.8)	0.63 (0.13-2.98)	0.556
Other	5	40.0 (5.3-85.3)	2.50 (0.40-15.82)	0.330
Race (2 level)				
Caucasian	114	16.2 (14.0-29.7)	1.00	
Other	34	20.6 (8.7-37.9)	0.97 (0.38-2.50)	0.954
Medicaid				
No	82	22.0 (13.6-32.5)	1.00	
Yes	77	20.8 (12.4-31.5)	0.93 (0.44-1.99)	0.857
Urban/Rural (4 level)[c]				
Urban	88	19.3 (11.7-29.1)	1.00	
Large rural	27	25.9 (11.1-46.3)	1.46 (0.53-4.02)	0.461
Small rural	25	20.0 (6.8-40.7)	1.04 (0.34-3.18)	0.939
Isolated rural	20	25.0 (8.7-49.1)	1.39 (0.44-4.36)	0.570
Urban/Rural (2 level)				
Urban	88	19.3 (11.7-29.1)	1.00	
Rural	72	23.6 (14.4-35.1)	1.29 (0.60-2.76)	0.510
History of chronic respiratory condition				
No	98	19.4 (12.1-28.6)	1.00	
Yes	62	24.2 (14.2-36.7)	1.33 (0.62-2.86)	0.470
History of structural respiratory condition				
No	119	20.2 (13.4-28.5)	1.00	
Yes	41	24.4 (12.4-40.3)	1.28 (0.55-2.96)	0.569
History of asthma				
No	135	20.7 (14.3-28.6)	1.00	
Yes	25	24.0 (9.4-45.1)	1.21 (0.44-3.31)	0.715
History of cancer				
No	144	20.8 (14.5-28.4)	1.00	
Yes	16	25.0 (7.3-52.4)	1.27 (0.38-4.21)	0.466
History of transplant				
No	155	21.3 (15.1-28.6)	1.00	
Yes	5	20.0 (0.0-71.6)	0.92 (0.10-8.55)	0.945

Table 40 Continued

Risk Factor	N	% Coinfected (95% CI)	OR (95% CI)	p
History of any immunosuppressive condition[d]				
No	103	17.5 (10.7-26.2)	1.00	
Yes	57	28.1 (17.0-41.5)	1.84 (0.85-3.98)	0.120
History of prematurity				
No	128	24.2 (17.1-32.6)	1.00	
Yes	32	9.4 (2.0-25.0)	0.32 (0.09-1.14)	0.078
Smoke exposure[e]				
None	46	21.7 (11.0-36.4)	1.00	
Direct	7	28.6 (3.7-71.0)	1.44 (0.24-8.57)	0.689
Indirect	22	27.3 (10.7-50.2)	1.35 (0.42-4.35)	0.615
Missing	85			
Prior antibiotic use				
No	106	19.8 (12.7-28.7)	1.00	
Yes	54	24.1 (13.5-37.6)	1.28 (0.59-2.82)	0.534
Leukocytosis				
No	107	22.5 (14.9-31.5)	1.00	
Yes	40	17.5 (7.3-32.8)	0.73 (0.29-1.87)	0.516
Missing	13			

[a] Bivariate analysis of selected risk factors and viral coinfection includes only virus-positive specimens from hospitalized children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI with accessible medical record information, without duplicates (n=160).

[b] p for trend 0.401

[c] p for trend 0.609

[d] Includes history of cancer, transplant, and chronic conditions that may lead to increased risk of ARTI (see Table 2).

[e] p for trend 0.652

Table 41 Prevalence and odds ratio of ICU admission by risk factor among hospitalized children with confirmed or suspected ARTI, without duplicates[a]

Risk Factor	N	% Admitted to ICU (95% CI)	OR (95% CI)	p
Gender				
Female	70	15.7 (8.1-26.4)	1.00	
Male	90	14.4 (16.9-35.8)	1.85 (0.83-4.17)	0.134
Age (years)[b]				
0 to < 1	79	26.6 (17.3-37.7)	1.00	
1 to < 5	63	17.5 (9.1-29.1)	0.58 (0.26-1.33)	0.199
> 5	18	11.1 (1.4-34.7)	0.35 (0.07-1.63)	0.179
Race (4 level)				
Caucasian	114	19.3 (12.5-27.8)	1.00	
African-American	15	20.0 (4.3-48.1)	1.05 (0.27-4.03)	0.949
Hispanic	14	14.3 (1.8-42.8)	0.70 (0.15-3.34)	0.652
Other	5	40.0 (5.3-85.3)	1.03 (0.44-17.71)	0.277
Race (2 level)				
Caucasian	114	20.6 (12.5-27.8)	1.00	
Other	34	19.3 (8.7-37.9)	1.08 (0.42-2.81)	0.868
Medicaid				
No	82	18.3 (10.6-28.4)	1.00	
Yes	77	23.4 (14.5-34.4)	1.36 (0.63-2.94)	0.431
Urban/Rural (4 level)[c]				
Urban	88	25.0 (16.4-35.4)	1.00	
Large rural	27	25.9 (11.1-46.3)	1.05 (0.40-2.82)	0.923
Small rural	25	20.0 (6.8-40.7)	0.75 (0.25-2.24)	0.606
Isolated rural	20	0 (0-16.8)	NA	NA
Urban/Rural (2 level)				
Urban	88	25.0 (16.4-35.4)	1.00	
Rural	72	16.7 (8.9-27.3)	1.62 (0.27-1.32)	0.203
History of chronic respiratory condition				
No	98	14.3 (8.0-22.8)	1.00	
Yes	62	32.3 (20.9-45.3)	2.86 (1.31-6.21)	0.008[†]
History of structural Respiratory Condition				
No	119	16.8 (10.6-24.8)	1.00	
Yes	41	34.2 (20.1-50.6)	2.57 (1.15-5.74)	0.022[†]
History of Asthma				
No	135	21.5 (14.9-29.4)	1.00	
Yes	25	20.0 (6.8-40.7)	0.91 (0.31-2.64)	0.868
History of Cancer				
No	144	22.9 (16.3-30.7)	1.00	
Yes	16	6.3 (0-30.2)	0.22 (0.03-1.76)	0.155
History of Transplant				
No	155	21.3 (15.1-28.6)	1.00	
Yes	5	20.0 (0-71.6)	0.92 (0.10-8.55)	0.945

Table 41 Continued

Risk Factor	N	% Admitted to ICU (95% CI)	OR (95% CI)	p
History of any immunosuppressive condition[d]				
No	103	21.4 (13.9-30.5)	1.00	
Yes	57	21.1 (11.4-33.9)	0.98 (0.45-2.17)	0.964
History of prematurity				
No	128	15.6 (9.8-23.1)	1.00	
Yes	32	43.8 (26.4-62.3)	4.20 (1.80-9.79)	0.001†
Smoke exposure[e]				
None	46	10.9 (3.6-23.6)	1.00	
Direct	7	42.9 (9.9-81.6)	6.15 (1.06-35.80)	0.043†
Indirect	22	27.3 (10.7-50.0)	3.08 (0.82-11.51)	0.095
Missing	85			
Prior antibiotic use				
No	106	20.8 (13.5-29.7)	1.00	
Yes	54	22.2 (12.0-35.6)	1.09 (0.49-2.42)	0.830
Leukocytosis				
No	107	15.9 (9.5-24.2)	1.00	
Yes	40	35.0 (20.6-51.7)	2.85 (1.24-6.55)	0.014†
Missing	13			

[a] Bivariate analysis of selected risk factors and ICU admission includes only virus-positive specimens from hospitalized children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI with accessible medical record information, without duplicates (n=160).

[b] p for trend 0.087

[c] p for trend 0.032

[d] Includes history of cancer, transplant, and chronic conditions that may lead to increased risk of ARTI (see Table 2).

[e] p for trend 0.030

† $p < 0.05$

Table 42 Adjusted odds ratio of ICU admission by risk factor among hospitalized children with confirmed or suspected ARTI, without duplicates[a]

Risk Factor	Adjusted OR (95% CI)	p
Coinfection		
No	1.00	
Yes	0.32 (0.08-1.27)	0.104
Gender		
Female	1.00	
Male	3.11 (1.20-8.06)	0.020†
Age (years)		
0 to < 1	1.00	
1 to < 5	0.52 (0.20-1.39)	0.192
> 5	0.27 (0.05-1.43)	0.124
History of any immunosuppressive condition[b]		
No	1.00	
Yes	3.20 (1.12-9.17)	0.030†
History of Prematurity		
No	1.00	
Yes	5.06 (1.61-15.93)	0.006†
Leukocytosis		
No	1.00	
Yes	4.44 (1.68-11.74)	0.003†

[a] Multivariate analysis of selected risk factors and ICU admission includes only virus-positive specimens from hospitalized children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI with accessible medical record information, without duplicates (n=160).

[b] Includes history of cancer, transplant, and chronic conditions that may lead to increased risk of ARTI (see Table 2).

† $p < 0.05$

Table 43 Prevalence and odds ratio of HRV-specific coinfection by risk factor among hospitalized HRV-positive children with confirmed or suspected ARTI, without duplicates[a]

Risk Factor	N	% Coinfected (95% CI)	OR (95% CI)	p
Gender				
Female	28	25.0 (10.7-44.9)	1.00	
Male	45	42.2 (27.7-57.9)	2.19 (0.77-6.21)	0.139
Age (years)[b]				
0 to < 1	35	34.3 (19.1-52.2)	1.00	
1 to < 5	27	37.0 (19.4-57.6)	1.23 (0.40-3.21)	0.822
> 5	11	36.4 (10.9-69.2)	1.10 (0.27-4.50)	0.900
Race (4 level)				
Caucasian	52	36.5 (23.6-51.0)	1.00	
African-American	6	33.3 (4.3-77.7)	0.87 (0.15-5.20)	0.877
Hispanic	6	16.7 (0-64.1)	0.35 (0.04-3.20)	0.351
Other	3	66.7 (9.4-99.2)	3.47 (0.30-40.9)	0.322
Race (2 level)				
Caucasian	52	36.5 (23.6-51.0)	1.00	
Other	15	33.3 (11.8-61.6)	0.87 (0.26-2.92)	0.820
Medicaid				
No	39	38.5 (23.4-55.4)	1.00	
Yes	34	32.4 (17.4-50.5)	0.77 (0.29-2.01)	0.587
Urban/Rural (4 level)[c]				
Urban	42	31.0 (17.6-47.1)	1.00	
Large rural	10	50.0 (18.7-81.3)	2.23 (0.55-9.06)	0.262
Small rural	11	45.5 (16.8-76.6)	1.86 (0.48-7.21)	0.370
Isolated rural	10	30.0 (6.7-65.3)	0.96 (0.21-4.30)	0.953
Urban/Rural (2 level)				
Urban	42	31.0 (24.6-60.9)	1.00	
Rural	31	41.9 (17.6-47.1)	1.61 (0.61-4.24)	0.334
History of chronic respiratory condition				
No	36	33.3 (18.6-51.0)	1.00	
Yes	37	37.8 (22.5-55.2)	1.22 (0.47-3.18)	0.688
History of structural respiratory condition				
No	47	34.0 (20.9-49.3)	1.00	
Yes	26	38.5 (20.2-59.4)	1.21 (0.45-3.27)	0.706
History of asthma				
No	60	35.0 (23.1-48.4)	1.00	
Yes	13	38.5 (13.9-68.4)	1.16 (0.34-4.00)	0.813
History of cancer				
No	66	34.9 (23.5-47.6)	1.00	
Yes	7	42.9 (9.9-81.6)	1.40 (0.29-6.81)	0.675
History of transplant				
No	68	36.8 (25.4-49.3)	1.00	
Yes	5	20.0 (0-71.6)	0.43 (0.05-4.06)	0.461

Table 43 Continued

Risk Factor	N	% Coinfected (95% CI)	OR (95% CI)	p
History of any immunosuppressive condition[d]				
No	44	29.6 (16.8-45.2)	1.00	
Yes	29	44.8 (26.5-64.3)	1.94 (0.73-5.15)	0.185
History of prematurity				
No	58	39.7 (27.1-53.4)	1.00	
Yes	15	20.0 (4.3-48.1)	0.38 (0.10-1.50)	0.167
Smoke exposure[e]				
None	20	40.0 (19.1-64.0)	1.00	
Direct	3	66.7 (9.4-99.2)	3.00 (0.23-38.88)	0.401
Indirect	8	37.5 (8.5-75.5)	0.90 (0.34-4.87)	0.903
Missing	42			
Prior antibiotic use				
No	45	37.8 (23.8-53.5)	1.00	
Yes	28	32.1 (15.9-52.4)	0.78 (0.29-2.11)	0.625
Leukocytosis				
No	46	37.0 (23.2-52.5)	1.00	
Yes	18	33.3 (13.3-59.0)	0.85 (0.27-2.69)	0.786
Missing	9			

[a] Bivariate analysis of selected risk factors and viral coinfection includes only HRV-positive specimens from hospitalized children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI with accessible medical record information, without duplicates (n=73).

[b] p for trend 0.854

[c] p for trend 0.671

[d] Includes history of cancer, transplant, and chronic conditions that may lead to increased risk of ARTI (see Table 2).

[e] p for trend 0.822

Table 44 Prevalence and odds ratio of ICU admission by risk factor among hospitalized HRV-positive children with confirmed or suspected ARTI, without duplicates[a]

Risk Factor	N	% Admitted to ICU (95% CI)	OR (95% CI)	p
Gender				
Female	28	17.9 (6.1-36.9)	1.00	
Male	45	24.4 (12.9-39.5)	1.49 (0.46-4.76)	0.510
Age (years)[b]				
0 to < 1	35	31.4 (16.9-49.3)	1.00	
1 to < 5	27	14.8 (4.1-33.7)	0.38 (0.11-1.36)	0.137
> 5	11	9.10 (0-41.3)	0.22 (0.03-1.92)	0.170
Race (4 level)				
Caucasian	52	15.4 (6.9-28.1)	1.00	
African-American	6	50.0 (11.8-88.2)	5.5 (0.94-32.25)	0.059
Hispanic	6	33.3 (4.3-77.7)	2.75 (0.43-17.61)	0.286
Other	3	33.3 (1.0-90.6)	2.75 (0.22-34.04)	0.431
Race (2 level)				
Caucasian	52	15.4 (6.9-28.1)	1.00	
Other	15	40.0 (16.3-67.7)	3.67 (1.02-13.17)	0.046[†]
Medicaid				
No	39	15.4 (5.9-30.5)	1.00	
Yes	34	29.4 (15.1-47.5)	2.29 (0.73-7.17)	0.154
Urban/Rural (4 level)[c]				
Urban	42	28.6 (15.7-44.6)	1.00	
Large rural	10	20.0 (2.5-55.6)	0.63 (0.12-3.38)	0.585
Small rural	11	18.2 (2.3-51.8)	0.56 (0.10-2.96)	0.491
Isolated rural	10	0 (0-30.9)	NA	NA
Urban/Rural (2 level)				
Urban	42	28.6 (15.7-44.6)	1.00	
Rural	31	28.6 (3.6-29.8)	0.37 (0.11-1.29)	0.118
History of chronic respiratory condition				
No	36	13.9 (4.7-29.5)	1.00	
Yes	37	29.7 (15.9-47.0)	2.62 (0.81-8.53)	0.109
History of structural respiratory condition				
No	47	17.0 (7.7-30.8)	1.00	
Yes	26	30.8 (14.3-51.8)	2.17 (0.70-6.69)	0.179
History of asthma				
No	60	23.3 (13.4-36.0)	1.00	
Yes	13	15.4 (1.9-45.5)	0.60 (0.12-3.02)	0.533
History of cancer				
No	66	24.2 (14.5-36.4)	1.00	
Yes	7	0 (0-41.0)	NA	NA
History of transplant				
No	68	22.1 (12.9-33.8)	1.00	
Yes	5	20.0 (0-71.6)	0.88 (0.09-8.51)	0.915

Table 44 Continued

Risk Factor	N	% Admitted to ICU (95% CI)	OR (95% CI)	p
History of any immunosuppressive condition[d]				
No	44	22.7 (11.5-37.8)	1.00	
Yes	29	20.7 (8.0-39.7)	0.89 (0.28-2.78)	0.837
History of prematurity				
No	58	15.5 (7.4-27.4)	1.00	
Yes	15	46.7 (21.3-73.4)	4.76 (1.38-16.44)	0.014[†]
Smoke exposure[e]				
None	20	5.0 (0-24.9)	1.00	
Direct	3	33.3 (0-90.6)	9.50 (0.42-217.61)	0.159
Indirect	8	25.0 (3.2-65.1)	6.33 (0.49-82.75)	0.159
Missing	42			
Prior antibiotic use				
No	45	20.0 (9.6-34.6)	1.00	
Yes	28	25.0 (10.7-44.9)	1.33 (0.43-4.11)	0.616
Leukocytosis				
No	46	17.4 (7.8-31.4)	1.00	
Yes	18	27.8 (9.7-53.5)	1.83 (0.51-6.59)	0.357
Missing	9			

[a] Bivariate analysis of selected risk factors and ICU admission includes only HRV-positive specimens from hospitalized children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI with accessible medical record information, without duplicates (n=73).

[b] p for trend 0.065

[c] p for trend 0.057

[d] Includes history of cancer, transplant, and chronic conditions that may lead to increased risk of ARTI (see Table 2).

[e] p for trend 0.207

[†] $p < 0.05$

Table 45 Adjusted odds ratio of ICU admission by risk factor among hospitalized HRV-positive children with confirmed or suspected ARTI, without duplicates[a]

Risk Factor	Adjusted OR (95% CI)	p
Coinfection		
No	1.00	
Yes	0.51 (0.09-2.80)	0.440
Gender		
Female	1.00	
Male	2.72 (0.55-13.3)	0.217
Age (years)		
0 to < 1	1.00	
1 to < 5	0.47 (0.08-2.92)	0.417
> 5	0.16 (0.01-1.91)	0.146
History of any immunosuppressive condition[b]		
No	1.00	
Yes	5.48 (0.79-38.05)	0.085
History of Prematurity		
No	1.00	
Yes	11.72 (0.81-169.35)	0.071
Urban/Rural		
Urban	1.00	
Rural	0.15 (0.03-0.83)	0.030[†]
Leukocytosis		
No	1.00	
Yes	4.84 (0.82-28.66)	0.082

[a] Multivariate analysis of selected risk factors and ICU admission includes only HRV-positive specimens from hospitalized children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI with accessible medical record information, without duplicates (n=73).

[b] Includes history of cancer, transplant, and chronic conditions that may lead to increased risk of ARTI (see Table 2).

[†] $p < 0.05$

Table 46 Prevalence and odds ratio of HRV-specific coinfection by risk factor among HRV-positive children with confirmed or suspected ARTI, without duplicates[a]

Risk Factor	N	% Coinfected (95% CI)	OR (95% CI)	p
Gender				
Female	40	30.0 (16.6-46.5)	1.00	
Male	55	41.8 (28.7-55.9)	1.67 (0.71-4.00)	0.240
Age (years)[b]				
0 to < 0.5	31	29.0 (14.2-48.0)	1.00	
0.5 to < 1	17	47.1 (22.9-72.2)	2.17 (0.64-7.42)	0.216
1 to < 5	33	42.4 (25.5-60.8)	1.80 (0.64-5.09)	0.267
> 5	14	28.6 (8.4-58.1)	0.98 (0.24-3.95)	0.975
Race (4 level)				
Caucasian	65	38.5 (26.7-51.4)	1.00	
African-American	9	22.2 (2.8-60.0)	0.46 (0.09-2.38)	0.352
Hispanic	7	14.3 (0.4-57.9)	0.27 (0.03-2.35)	0.234
Other	5	60.0 (14.7-94.7)	2.40 (0.37-15.38)	0.356
Race (2 level)				
Caucasian	65	38.5 (26.7-51.4)	1.00	
Other	21	28.6 (11.3-52.2)	0.64 (0.22-1.87)	0.414
Medicaid				
No	51	39.2 (25.8-53.9)	1.00	
Yes	44	34.1 (20.5-49.9)	0.80 (0.35-1.86)	0.606
Urban/Rural (4 level)[c]				
Urban	59	32.3 (20.6-45.6)	1.00	
Large rural	12	50.0 (21.1-78.9)	2.11 (0.60-7.40)	0.246
Small rural	12	41.7 (15.2-72.3)	1.50 (0.42-5.36)	0.529
Isolated rural	12	41.7 (15.2-72.3)	1.50 (0.42-5.36)	0.529
Urban/Rural (2 level)				
Urban	59	32.3 (20.6-45.6)	1.00	
Rural	36	44.4 (27.9-61.9)	1.68 (0.72-3.96)	0.232
History of chronic respiratory condition				
No	52	36.5 (23.6-51.0)	1.00	
Yes	43	37.2 (22.9-53.3)	1.03 (0.45-2.38)	0.946
History of structural respiratory condition				
No	68	35.3 (24.1-47.8)	1.00	
Yes	72	40.7 (22.4-61.2)	1.26 (0.51-3.15)	0.620
History of asthma				
No	79	38.0 (27.3-49.6)	1.00	
Yes	16	31.3 (11.0-58.7)	0.74 (0.24-2.35)	0.612
History of cancer				
No	87	36.8 (26.7-47.8)	1.00	
Yes	8	37.5 (8.5-75.5)	1.03 (0.23-4.61)	0.968
History of transplant				
No	90	37.8 (27.8-48.6)	1.00	
Yes	5	20.0 (0.05-71.6)	0.41 (0.04-3.84)	0.436

Table 46 Continued

Risk Factor	N	% Coinfected (95% CI)	OR (95% CI)	p
History of any immunosuppressive condition[d]				
No	61	32.8 (21.3-46.0)	1.00	
Yes	34	44.1 (27.2-62.1)	1.62 (0.68-3.83)	0.274
History of prematurity				
No	77	37.7 (26.9-49.4)	1.00	
Yes	18	33.3 (13.3-59.0)	0.83 (0.28-2.44)	0.732
Smoke exposure[e]				
None	28	42.9 (24.5-62.8)	1.00	
Direct	4	75.0 (19.4-99.4)	4.0 (0.37-43.38)	0.254
Indirect	9	33.3 (7.5-70.1)	0.67 (0.14-3.22)	0.614
Missing	54			
Prior antibiotic use				
No	63	39.7 (27.6-52.8)	1.00	
Yes	32	31.3 (16.1-50.0)	0.69 (0.28-1.70)	0.422

[a] Bivariate analysis of selected risk factors and HRV-specific coinfection includes only HRV-positive specimens from children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI with accessible medical record information, without duplicates (n=95).

[b] p for trend 0.703

[c] p for trend 0.386

[d] Includes history of cancer, transplant, and chronic conditions that may lead to increased risk of ARTI (see Table 2).

[e] p for trend 0.537

Table 47 Prevalence and odds ratio of bronchodilator administration by risk factor among HRV-positive children with confirmed or suspected ARTI, without duplicates[a]

Risk Factor	N	% Administered Bronchodilator (95% CI)	OR (95% CI)	p
Gender				
Female	40	27.5 (14.6-43.9)	1.00	0.209
Male	55	40.0 (27.0-54.1)	1.75 (0.73-4.17)	0.209
Age (years)[b]				
0 to <0.5	31	16.1 (5.5-33.7)	1.00	
0 .5 to < 1	17	64.7 (38.3-85.8)	9.53 (2.40-37.91)	0.001[†]
1 to < 5	33	39.4 (22.9-57.9)	3.38 (1.03-11.05)	0.044[†]
> 5	14	28.6 (8.4-58.1)	2.08 (0.46-9.35)	0.340
Race (4 level)				
Caucasian	65	35.4 (23.9-48.2)	1.00	
African-American	9	33.3 (7.5-70.1)	0.91 (0.21-4.00)	0.904
Hispanic	7	57.1 (18.4-90.1)	2.44 (0.50-11.83)	0.270
Other	5	20.0 (1.0-71.6)	0.46 (0.05-4.33)	0.495
Race (2 level)				
Caucasian	65	35.4 (23.9-48.2)	1.00	
Other	21	38.1 (18.1-61.6)	1.12 (0.41-3.11)	0.822
Medicaid				
No	51	27.5 (15.9-41.7)	1.00	
Yes	44	43.2 (28.4-59.0)	2.01 (0.85-4.73)	0.111
Urban/Rural (4 level)[c]				
Urban	59	33.9 (22.1-47.4)	1.00	
Large rural	12	33.3 (9.9-65.1)	0.98 (0.26-3.63)	0.970
Small rural	12	33.3 (9.9-65.1)	0.98 (0.26-3.63)	0.970
Isolated rural	12	41.7 (15.2-72.3)	1.39 (0.39-4.95)	0.609
Urban/Rural (2 level)				
Urban	59	33.9 (22.1-47.4)	1.00	
Rural	36	36.1 (20.8-53.8)	1.10 (0.46-2.63)	0.826
History of chronic respiratory condition				
No	52	25.0 (14.0-39.0)	1.00	
Yes	43	46.5 (31.2-62.3)	2.61 (1.10-6.21)	0.030[†]
History of structural respiratory condition				
No	68	29.4 (19.0-41.7)	1.00	
Yes	72	48.2 (28.7-68.1)	2.23 (0.89-5.58)	0.087
History of asthma				
No	79	29.1 (19.4-40.4)	1.00	
Yes	16	62.5 (35.4-84.8)	4.06 (1.32-12.47)	0.015[†]
History of cancer				
No	87	37.9 (27.7-49.0)	1.00	
Yes	8	0 (0-36.9)	NA	NA
History of transplant				
No	90	36.7 (26.8-47.5)	1.00	
Yes	5	0 (0-52.2)	NA	NA

Table 47 Continued

Risk Factor	N	% Administered Bronchodilator (95% CI)	OR (95% CI)	p
History of any immunosuppressive condition[d]				
No	61	45.9 (33.1-59.2)	1.00	
Yes	34	14.7 (5.0-31.1)	0.20 (0.07-0.60)	0.004[†]
History of prematurity				
No	77	31.2 (21.1-42.7)	1.00	
Yes	18	50.0 (26.0-74.0)	2.21 (0.78-6.26)	0.136
Smoke exposure[e]				
None	28	32.1 (15.9-52.4)	1.00	
Direct	4	75.0 (19.4-99.4)	6.33 (0.58-69.68)	0.131
Indirect	9	55.6 (21.2-86.3)	2.64 (0.57-12.25)	0.216
Missing	54			
Prior antibiotic use				
No	63	30.2 (19.2-43.0)	1.00	
Yes	32	43.8 (26.4-62.3)	1.80 (0.75-4.35)	0.191

[a] Bivariate analysis of selected risk factors and bronchodilator administration includes only HRV-positive specimens from children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI with accessible medical record information, without duplicates (n=95).

[b] p for trend 0.268

[c] p for trend 0.696

[d] Includes history of cancer, transplant, and chronic conditions that may lead to increased risk of ARTI (see Table 2).

[e] p for trend 0.278

[†] $p < 0.05$

Table 48 Adjusted odds ratio of bronchodilator administration by risk factor among HRV-positive children with confirmed or suspected ARTI, without duplicates[a]

Risk Factor	Adjusted OR (95% CI)	p
Coinfection		
No	1.00	
Yes	3.02 (1.06-8.65)	0.039[†]
Age (years)		
0 to < 0.5	1.00	
0.5 to < 1	5.70 (1.26-25.73)	0.024[†]
1 to < 5	2.29 (0.63-8.40)	0.211
> 5	0.92 (0.16-5.33)	0.922
History of asthma		
No	1.00	
Yes	6.62 (1.60-27.52)	0.009[†]
Race		
Caucasian	1.00	
Other	1.64 (0.49-5.54)	0.422

[a] Multivariate analysis of selected risk factors and bronchodilator administration includes only HRV-positive specimens from children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI with accessible medical record information, without duplicates (n=95).

[†] $p < 0.05$

Table 49 Virus-specific mono-infection and virus-bacteria coinfection prevalence estimates for specimens from children with any bacterial tests completed (not limited to respiratory sites) and hospitalized with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI, without duplicates (n=217)

	Mono-infection	Coinfection			
Virus	Virus, n (% Total Positive[a])	Virus+Virus n (% Total Positive[a])	Virus+ Bacteria n (% Total Positive[a])	2 Viruses + Bacteria n (% Total Positive[a])	Total Positive n (% Total Specimens[b])
Ad	5 (50.0)	3 (30.0)	1 (10.0)	1 (10.0)	10 (4.6)
HRV	22 (42.3)	11 (21.2)	12 (23.1)	7 (13.5)	52 (24.0)
HBoV	9 (42.9)	9 (42.9)	2 (9.5)	1 (4.8)	21 (9.7)
hMPV	10 (47.6)	2 (9.5)	7 (33.3)	2 (9.5)	21 (9.7)
Flu A	1 (100)	0 (0)	0 (0)	0 (0)	1 (0.5)
Flu B	0 (0)	0 (0)	1 (100)	0 (0)	1 (0.5)
RSV	14 (48.3)	6 (20.7)	8 (27.6)	1 (3.5)	29 (13.4)
PIV All	6 (37.5)	6 (37.5)	2 (12.5)	2 (12.5)	16 (7.4)
Total	67 (54.0)	71 (13.7)	33 (26.6)	7 (5.7)	124 (57.1)

Note: Flu A (influenza A virus), Flu B (influenza B virus), PIV All (parainfluenza virus 1-3 and not otherwise specified).

[a] Denominator is virus-specific total number of positive specimens.

[b] Denominator is total number of specimens, n=217.

[c] 95% binomial confidence interval associated with prevalence percent estimate for total number of positive specimen.

Table 50 Prevalence and odds ratio of virus-bacteria coinfection (any site) by risk factor among hospitalized virus-positive children with confirmed or suspected ARTI, without duplicates[a]

Risk Factor	N	% Coinfected[b] (95% CI)	OR (95% CI)	p
Gender				
Female	54	35.2 (22.7-49.4)	1.00	
Male	70	30.0 (19.6-42.1)	0.79 (0.37-1.68)	0.541
Age (years)[c]				
0 to < 1	56	42.9 (29.7-56.8)	1.00	
1 to < 5	52	21.2 (11.1-34.7)	0.36 (0.15-0.84)	0.018[†]
> 5	16	31.3 (11.0-58.7)	0.61 (0.19-1.98)	0.406
Race (4 level)				
Caucasian	87	28.7 (19.5-39.4)	1.00	
African-American	13	38.5 (13.9-68.4)	1.55 (0.46-5.20)	0.478
Hispanic	11	27.3 (6.0-61.0)	0.93 (0.23-3.79)	0.919
Other	4	75.0 (19.4-99.4)	7.44 (0.74-74.98)	0.089
Race (2 level)				
Caucasian	87	28.7 (19.5-39.4)	1.00	
Other	28	39.3 (21.5-59.4)	1.61 (0.66-3.91)	0.297
Medicaid				
No	62	27.4 (16.9-40.2)	1.00	
Yes	61	36.1 (24.2-49.4)	1.49 (0.70-3.21)	0.304
Urban/Rural (4 level)[d]				
Urban	67	25.4 (15.5-37.5)	1.00	
Large rural	20	50.0 (27.2-72.8)	2.94 (1.05-8.28)	0.041[†]
Small rural	22	45.5 (24.4-67.8)	2.45 (0.90-6.69)	0.080
Isolated rural	15	20.0 (4.3-48.1)	0.74 (0.19-2.92)	0.662
Urban/Rural (2 level)				
Urban	67	25.4 (27.6-54.2)	1.00	
Rural	57	40.4 (15.5-37.5)	1.99 (0.93-4.27)	0.077
History of chronic respiratory condition				
No	73	28.7 (18.8-40.6)	1.00	
Yes	51	37.3 (24.1-51.9)	1.47 (0.69-3.15)	0.321
History of structural respiratory condition				
No	91	29.7 (20.6-40.2)	1.00	
Yes	33	39.4 (22.9-57.9)	1.54 (0.67-3.54)	0.308
History of asthma				
No	102	33.3 (24.3-43.4)	1.00	
Yes	22	27.3 (10.7-50.2)	0.75 (0.27-2.09)	0.582
History of cancer				
No	109	35.8 (26.8-45.5)	1.00	
Yes	15	6.7 (0-32.0)	0.13 (0.02-1.01)	0.051
History of transplant				
No	120	33.3 (25.0-42.5)	1.00	
Yes	4	0 (0-60.2)	NA	NA

Table 50 Continued

Risk Factor	N	% Coinfected[b] (95% CI)	OR (95% CI)	p
History of any immunosuppressive condition[e]				
No	76	36.8 (26.1-48.7)	1.00	
Yes	48	25.0 (13.6-39.6)	0.57 (0.26-1.28)	0.172
History of prematurity				
No	100	26.0 (17.7-35.7)	1.00	
Yes	24	58.3 (36.6-77.9)	3.99 (1.58-10.06)	0.003†
Smoke exposure[f]				
None	31	22.6 (9.6-41.1)	1.00	
Direct	6	66.7 (22.3-95.7)	6.86 (1.03-45.60)	0.046†
Indirect	16	25.0 (7.3-52.4)	1.14 (0.28-4.68)	0.853
Missing	71			
Prior antibiotic use				
No	86	29.1 (19.8-39.9)	1.00	
Yes	38	39.5 (24.0-56.6)	1.59 (0.72-3.54)	0.255
Leukocytosis				
No	81	29.6 (20.0-40.8)	1.00	
Yes	35	42.9 (26.3-60.7)	1.78 (0.78-4.05)	0.169
Missing	8			

[a] Bivariate analysis of selected risk factors and virus-bacteria coinfection includes only virus-positive specimens from children with any bacterial tests completed (not limited to respiratory sites), accessible medical records, and hospitalized with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI, without duplicates (n=124).

[b] Coinfection is defined as infection with at least one virus and one bacterium. "No coinfection" is defined as infection with a single virus.

[c] p for trend 0.091

[d] p for trend 0.500

[e] Includes history of cancer, transplant, and chronic conditions that may lead to increased risk of ARTI (see Table 2).

[f] p for trend 0.856

† $p < 0.05$

Table 51 Prevalence and odds ratio of ICU admission by risk factor among hospitalized virus-positive children tested for bacterial infection (any site) with confirmed or suspected ARTI, without duplicates[a]

Risk Factor	N	% Admitted to ICU (95% CI)	OR (95% CI)	p
Gender				
Female	54	20.4 (10.6-33.5)	1.00	
Male	70	30.0 (19.6-42.1)	1.68 (0.73-3.86)	0.227
Age (years)[b]				
0 to < 1	56	33.9 (21.8-47.8)	1.00	
1 to < 5	52	21.2 (11.1-34.7)	0.52 (0.22-1.24)	0.142
> 5	16	12.5 (1.6-38.4)	0.28 (0.06-1.35)	0.113
Race (4 level)				
Caucasian	87	24.1 (15.6-34.5)	1.00	
African-American	13	15.4 (1.9-45.5)	0.57 (0.12-2.79)	0.489
Hispanic	11	18.2 (2.3-51.8)	0.70 (0.14-3.49)	0.662
Other	4	50.0 (6.8-93.2)	3.14 (0.42-23.71)	0.267
Race (2 level)				
Caucasian	87	24.1 (15.6-34.5)	1.00	
Other	28	21.4 (8.3-41.0)	0.86 (0.31-2.40)	0.769
Medicaid				
No	62	24.2 (14.2-36.7)	1.00	
Yes	61	26.2 (15.8-39.1)	1.11 (0.49-2.52)	0.795
Urban/Rural (4 level)[c]				
Urban	67	29.9 (19.3-42.3)	1.00	
Large rural	20	35.0 (15.4-59.2)	1.27 (0.44-3.64)	0.663
Small rural	22	22.7 (7.8-45.4)	0.69 (0.22-2.13)	0.520
Isolated rural	15	0 (0-21.8)	NA	NA
Urban/Rural (2 level)				
Urban	67	21.1 (11.4-33.9)	1.00	
Rural	57	29.9 (19.3-42.3)	0.63 (0.28-1.43)	0.267
History of chronic respiratory condition				
No	73	17.8 (9.8-28.5)	1.00	
Yes	51	37.3 (24.1-51.9)	2.74 (1.20-6.26)	0.017[†]
History of structural respiratory condition				
No	91	19.8 (12.2-29.5)	1.00	
Yes	33	42.4 (25.5-60.8)	2.99 (1.26-7.07)	0.013[†]
History of asthma				
No	102	26.5 (18.2-36.1)	1.00	
Yes	22	22.7 (7.8-45.4)	0.82 (0.28-2.43)	0.716
History of cancer				
No	109	28.4 (20.2-37.9)	1.00	
Yes	15	6.7 (0-32.0)	0.18 (0.02-1.43)	0.104
History of transplant				
No	120	25.8 (18.3-34.6)	1.00	
Yes	4	25.0 (0.1-80.6)	0.96 (0.10-9.55)	0.970

Table 51 Continued

Risk Factor	N	% Admitted to ICU (95% CI)	OR (95% CI)	p
History of any immunosuppressive condition[d]				
No	76	26.3 (16.9-37.7)	1.00	
Yes	48	25.0 (13.6-39.6)	0.93 (0.41-2.14)	0.871
History of prematurity				
No	100	19.0 (11.8-28.1)	1.00	
Yes	24	54.2 (32.8-74.5)	5.04 (1.96-12.97)	0.001†
Smoke exposure[e]				
None	31	16.1 (5.5-33.7)	1.00	
Direct	6	50.0 (11.8-88.2)	5.20 (0.81-33.56)	0.083
Indirect	16	25.0 (7.3-52.4)	1.73 (0.39-7.63)	0.467
Missing	71			
Prior antibiotic use				
No	86	23.3 (14.8-33.6)	1.00	
Yes	38	31.6 (17.5-48.7)	1.52 (0.65-3.56)	0.330
Leukocytosis				
No	81	19.8 (11.7-30.1)	1.00	
Yes	35	40.0 (23.9-57.9)	2.71 (1.14-6.46)	0.025†
Missing	8			

[a] Bivariate analysis of selected risk factors and ICU admission includes only virus-positive specimens from children with any bacterial tests completed (not limited to respiratory sites), accessible medical records, and hospitalized with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI, without duplicates (n=124).

[b] p for trend 0.048

[c] p for trend 0.037

[d] Includes history of cancer, transplant, and chronic conditions that may lead to increased risk of ARTI (see Table 2).

[e] p for trend 0.687

† $p < 0.05$

Table 52 Adjusted odds ratio of ICU admission by risk factor among hospitalized virus-positive children tested for bacterial infection (any site) with confirmed or suspected ARTI, without duplicates[a]

Risk Factor	Adjusted OR (95% CI)	p
Coinfection[b]		
No	1.00	
Yes	5.58 (1.95-15.96)	0.001[†]
Age (years)		
0 to < 1	1.00	
1 to < 5	0.77 (0.26-2.25)	0.632
> 5	0.33 (0.04-1.46)	0.121
Leukocytosis		
No	1.00	
Yes	2.52 (0.87-7.28)	0.089
History of Prematurity		
No	1.00	
Yes	3.17 (1.03-9.77)	0.045[†]
Urban/Rural		
Urban	1.00	
Rural	0.41 (0.14-1.26)	0.118

[a] Multivariate analysis of selected risk factors and ICU admission includes only virus-positive specimens from children with any bacterial tests completed (not limited to respiratory sites), accessible medical records, and hospitalized with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI, without duplicates (n=124).

[b] Coinfection is defined as infection with at least one virus and one bacterium. "No coinfection" is defined as infection with a single virus.

[†] $p < 0.05$

Table 53 Virus-specific mono-infection and virus-bacteria coinfection prevalence estimates for specimens from children with any respiratory bacterial tests completed and hospitalized with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI, without duplicates (n=93)

	Mono-infection	Coinfection			
Virus	Virus, n (% Total Positive[a])	Virus+Virus n (% Total Positive[a])	Virus+ Bacteria n (% Total Positive[a])	2 Viruses + Bacteria n (% Total Positive[a])	Total Positive n (% Total Specimens[b])
Ad	1 (25.0)	3 (75.0)	0 (0)	0 (0)	4 (4.3)
HRV	10 (37.0)	10 (37.0)	4 (14.8)	3 (11.1)	27 (29.0)
HBoV	4 (44.4)	4 (44.4)	0 (0)	1 (11.1)	9 (9.7)
hMPV	5 (38.5)	2 (15.4)	4 (30.8)	2 (15.4)	13 (14.0)
Flu B	1 (100)	0 (0)	0 (0)	0 (0)	1 (1.1)
RSV	7 (41.2)	6 (35.3)	4 (23.5)	0 (0)	17 (18.3)
PIV All	4 (50.0)	4 (50.0)	0 (0)	0 (0)	8 (8.6)
Total	32 (53.3)	13 (21.7)	12 (20.0)	3 (5.0)	60 (64.5)

Note: Flu A (influenza A virus), Flu B (influenza B virus), PIV All (parainfluenza virus 1-3 and not otherwise specified).

[a] Denominator is virus-specific total number of positive specimens.

[b] Denominator is total number of specimens, n=93.

[c] 95% binomial confidence interval associated with prevalence percent estimate for total number of positive specimen.

Table 54 Prevalence and odds ratio of virus-bacteria coinfection (respiratory site) by risk factor among hospitalized virus-positive children with confirmed or suspected ARTI, without duplicates[a]

Risk Factor	N	% Coinfected[b] (95% CI)	OR (95% CI)	p
Gender				
Female	26	30.8 (14.3-51.8)	1.00	
Male	34	20.6 (8.7-37.9)	0.58 (0.18-5.56)	0.369
Age (years)[c]				
0 to < 1	26	26.9 (11.6-47.8)	1.00	
1 to < 5	29	24.1 (10.3-43.5)	0.86 (0.26-2.91)	0.813
> 5	5	20.0 (0.1-71.6)	0.68 (0.06-7.16)	0.747
Race (4 level)				
Caucasian	40	25.0 (12.7-41.2)	1.00	
African-American	8	12.5 (0.3-52.7)	0.43 (0.05-3.92)	0.453
Hispanic	4	25.0 (0.6-80.6)	1.00 (0.09-10.74)	1.00
Other	2	50.0 (1.3-98.7)	3.00 (0.17-52.53)	0.452
Race (2 level)				
Caucasian	40	25.0 (12.7-41.2)	1.00	
Other	14	21.4 (4.7-50.8)	0.82 (0.19-3.54)	0.788
Medicaid				
No	28	21.4 (8.3-41.0)	1.00	
Yes	32	28.1 (13.8-46.8)	1.44 (0.44-4.70)	0.551
Urban/Rural (4 level)[d]				
Urban	27	29.6 (13.8-50.2)	1.00	
Large rural	14	21.4 (4.7-50.8)	0.65 (0.14-2.96)	0.576
Small rural	12	33.3 (9.9-65.1)	1.19 (0.28-5.10)	0.817
Isolated rural	7	0 (0-41.0)	NA	NA
Urban/Rural (2 level)				
Urban	27	29.6 (13.8-50.2)	1.00	
Rural	33	21.2 (9.0-38.9)	0.64 (0.20-2.07)	0.455
History of chronic respiratory condition				
No	31	19.4 (7.5-37.5)	1.00	
Yes	29	31.0 (15.3-50.8)	1.88 (0.57-6.15)	0.300
History of structural respiratory condition				
No	38	23.7 (11.4-40.2)	1.00	
Yes	22	27.3 (10.7-50.2)	1.21 (0.36-4.01)	0.757
History of asthma				
No	50	20.0 (10.0-33.7)	1.00	
Yes	10	50.0 (18.7-81.3)	4.00 (0.97-16.55)	0.056
History of cancer				
No	55	27.3 (16.1-41.0)	1.00	
Yes	5	0 (0-52.2)	NA	NA
History of transplant				
No	60	25.0 (14.7-37.9)	1.00	
Yes	0	0 (0)	NA	NA

Table 54 Continued

Risk Factor	N	% Coinfected[b] (95% CI)	OR (95% CI)	p
History of any immunosuppressive condition[e]				
No	36	27.8 (14.2-45.2)	1.00	
Yes	24	20.8 (7.1-42.2)	0.68 (0.20-2.33)	0.544
History of prematurity				
No	46	23.9 (12.6-38.8)	1.00	
Yes	14	28.6 (8.4-58.1)	1.27 (0.33-4.88)	0.725
Smoke exposure[f]				
None	12	16.7 (2.1-48.4)	1.00	
Direct	4	25.0 (0.6-80.6)	1.67 (0.11-25.44)	0.713
Indirect	10	20.0 (2.5-55.6)	1.25 (0.14-10.94)	0.840
Missing	34			
Prior antibiotic use				
No	39	23.1 (11.1-39.3)	1.00	
Yes	21	28.6 (11.3-52.2)	1.33 (0.40-4.45)	0.640
Leukocytosis				
No	38	23.7 (11.4-40.2)	1.00	
Yes	19	31.6 (12.6-56.6)	1.49 (0.44-5.05)	0.525
Missing	3			

[a] Bivariate analysis of selected risk factors and virus-bacteria coinfection includes only virus-positive specimens from children with any respiratory bacterial tests completed, accessible medical records, and hospitalized with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI, without duplicates (n=60).

[b] Coinfection is defined as infection with at least one virus and one bacterium. “No coinfection” is defined as infection with a single virus.

[c] p for trend 0.724

[d] p for trend 0.294

[e] Includes history of cancer, transplant, and chronic conditions that may lead to increased risk of ARTI (see Table 2).

[f] p for trend 0.916

Table 55 Prevalence and odds ratio of ICU admission by risk factor among hospitalized virus-positive children tested for bacterial infection (respiratory site) with confirmed or suspected ARTI, without duplicates[a]

Risk Factor	N	% Admitted to ICU (95% CI)	OR (95% CI)	p
Gender				
Female	26	23.1 (9.0-43.7)	1.00	
Male	34	26.5 (12.9-44.4)	1.20 (0.37-3.94)	0.764
Age (years)[b]				
0 to < 1	26	34.6 (17.2-55.7)	1.00	
1 to < 5	29	20.7 (8.0-39.7)	0.49 (0.15-1.65)	0.251
> 5	5	0 (0-52.2)	NA	NA
Race (4 level)				
Caucasian	40	25.0 (12.7-41.2)	1.00	
African-American	8	12.5 (0.3-52.7)	0.43 (0.05-3.92)	0.453
Hispanic	4	25.0 (0.6-80.6)	1.00 (0.09-10.74)	1.00
Other	2	0 (0-84.2)	NA	NA
Race (2 level)				
Caucasian	40	25.0 (12.7-41.2)	1.00	
Other	14	14.3 (1.8-42.8)	0.50 (0.10-2.63)	0.413
Medicaid				
No	28	28.6 (13.2-48.7)	1.00	
Yes	32	21.9 (9.3-40.0)	0.70 (0.22-2.26)	0.551
Urban/Rural (4 level)[c]				
Urban	27	33.3 (16.5-54.0)	1.00	
Large rural	14	14.3 (1.8-42.8)	0.33 (0.06-1.82)	0.205
Small rural	12	33.3 (9.9-65.1)	1.00 (0.24-4.23)	1.00
Isolated rural	7	0 (0-41.0)	NA	NA
Urban/Rural (2 level)				
Urban	27	33.3 (16.5-54.0)	1.00	
Rural	33	18.2 (7.0-35.5)	0.44 (0.14-1.47)	0.183
History of chronic respiratory condition				
No	31	16.1 (5.5-33.7)	1.00	
Yes	29	34.5 (17.9-54.3)	2.74 (0.80-9.32)	0.107
History of structural respiratory condition				
No	38	26.3 (13.4-43.1)	1.00	
Yes	22	22.7 (7.8-45.4)	0.82 (0.24-2.82)	0.757
History of asthma				
No	50	24.0 (13.1-38.2)	1.00	
Yes	10	30.0 (6.7-65.3)	1.36 (0.30-6.08)	0.690
History of cancer				
No	55	27.3 (16.1-41.0)	1.00	
Yes	5	0 (0-52.2)	NA	NA
History of transplant				
No	60	25.0 (14.7-37.9)	1.00	
Yes	0	0 (0)	NA	NA

Table 55 Continued

Risk Factor	N	% Admitted to ICU (95% CI)	OR (95% CI)	p
History of any immunosuppressive condition[d]				
No	36	25.0 (12.1-42.2)	1.00	
Yes	24	25.0 (9.8-46.7)	1.00 (0.30-3.30)	1.00
History of prematurity				
No	46	21.7 (11.0-36.4)	1.00	
Yes	14	35.7 (12.8-64.9)	2.00 (0.55-7.33)	0.295
Smoke exposure[e]				
None	12	8.3 (0.2-38.5)	1.00	
Direct	4	50.0 (6.8-93.2)	11.0 (0.65-187.09)	0.097
Indirect	10	20.0 (2.5-55.6)	2.75 (0.21-35.82)	0.440
Missing	34			
Prior antibiotic use				
No	39	25.6 (13.0-42.1)	1.00	
Yes	21	23.8 (8.2-47.2)	0.91 (0.26-3.12)	0.876
Leukocytosis				
No	38	18.4 (7.7-34.3)	1.00	
Yes	19	36.8 (16.3-61.6)	2.58 (0.75-8.94)	0.134
Missing	3			

[a] Bivariate analysis of selected risk factors and virus-bacteria coinfection includes only virus-positive specimens from children with any respiratory bacterial tests completed, accessible medical records, and hospitalized with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI, without duplicates (n=60).

[b] p for trend 0.777

[c] p for trend 0.184

[d] Includes history of cancer, transplant, and chronic conditions that may lead to increased risk of ARTI (see Table 2).

[e] p for trend 0.826

CHAPTER 5 – DISCUSSION

Polymicrobial infections were common in our study of hospital-based pediatric inpatients and outpatients with acute respiratory tract infections. We conducted a retrospective study of 559 archived respiratory specimens from 421 children under the age of 10 years collected between March 28, 2008 and June 30, 2009. This population was comprised mostly of very young (86.2% under the age of 5 years, mean age 2.07 years), Caucasian (72.9%) children many of whom relied on Medicaid as a primary payor for medical services (47.8%). This study included several children who resided in rural areas (39.9%). A large proportion of the children were hospitalized (76.9%), and of those that were hospitalized, 36.1% were patients in an intensive care unit at the time of specimen collection.

A virus was identified in 61.3% of 349 respiratory specimens from children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI. HRV (27.5%), RSV (18.9%), HBoV (8.3%), hMPV (7.7%), and PIV (6.6%) were the most common viruses detected. Of the 96 HRV-positive specimens, HRV A was the most common group detected (46.3%) followed by HRV C (41.1%), and non-typeable HRVs (12.6%). A viral coinfection was identified in 21.5% of the 214 virus-positive specimens and was most often detected for Ad (53.3% of 15 Ad-positive specimens), HBoV (51.7% of 29 HBoV-positive specimens), PIV (43.5% of 23 PIV-positive specimens), HRV (35.4% of 96 HRV-positive specimens), and RSV (34.8% of 66 RSV-positive specimens). Among the 46 specimens with dual or triple viral coinfections detected, the most frequent virus-virus combinations were HRV-RSV (n=12), HRV-HBoV (n=6), and HRV-PIV 3 (n=4). Among the 96 HRV-positive specimens, 58.3% of the non-

typeable HRV specimens, 36.4% of the HRV A specimens, and 30.8% of the HRV C specimens were involved in coinfections.

These results are similar to previously published studies. Coinfection rates vary widely among these studies and are estimated to account for between 8.4% and 36.1% of ARTIs for which at least one virus was detected [3, 4, 6, 7, 9, 14-16, 19, 20]. Direct comparison of results from this study to previous studies is made difficult due to the number of design factors that vary from study to study, such as differences in patient population (e.g., ages included, inclusion of inpatients and/or outpatients, hospital or community source), definition of ARTI (e.g., lower or upper ARTI, pneumonia only, bronchiolitis only), timing of the study (e.g., season), diagnostic methods used (e.g., cell culture or molecular assays such as PCR), and pathogens under review (e.g., viral and/or bacterial, inclusion or exclusion of newly recognized agents such as HBoV).

We hypothesized that certain host-specific risk factors were associated with the likelihood of viral coinfection (Specific aim 2). While none of the covariates in our final model were significant, the results were suggestive. Male gender (OR 1.70, 95% CI 0.83-3.46), age between 6 months to 1 year (as compared to children less than 6 months old, OR 2.15, 95% CI 0.75-6.19), and history of any chronic condition that may result in immunosuppression (OR 2.05, 95% CI 0.99-4.23) were each associated with increased odds of viral coinfection ($p > 0.05$). Similar results were observed when limiting the analysis to viral coinfections that included HRV; in addition to male gender (OR 1.89, 95% CI 0.71-5.03), age between 6 months to 1 year (as compared to children less than 6 months old, OR 3.70, 95% CI 0.87-15.67), and history of any chronic condition that may result in immunosuppression (OR 2.24, 95% CI 0.81-6.22), children residing in large rural areas, as compared to those residing in urban areas, also

had greater odds of HRV-specific coinfection (OR 3.17, 95% 0.77-13.10) though this increase was not statistically significant ($p > 0.05$).

Few studies have made an effort to identify host factors that may predispose a child to respiratory coinfections. In a study of 316 pediatric patients (less than 14 years old) hospitalized for either upper or lower ARTI in China, Peng et al. noted that coinfection was more common in children aged 3 to 6 years [14]. In a study of viruses in community-acquired pneumonia in hospitalized and non-hospitalized children aged less than 3 years old, Cilla et al. noted that children aged less than 12 months were more likely than older children to have a viral coinfection [7].

We also hypothesized that children with viral coinfections would be more likely to have severe ARTI (requiring hospitalization or greater medical intervention such as bronchodilator administration, supplemental oxygen requirement, or need for mechanical ventilation) than those children with single virus infections (Specific aim 3). No significant association was identified between any virus-virus coinfection and the following indicators of severity – hospitalization, bronchodilator administration, oxygen saturation less than 90% (hypoxemia), requirement for supplemental oxygen, requirement for mechanical ventilation, or total length of hospitalization. The unadjusted odds ratio for ICU admission associated with virus-virus coinfection was marginally significant (OR 0.30, 95% CI 0.09-1.04). After controlling for gender, age, history of any chronic condition that may result in immunosuppression, history of prematurity, and leukocytosis, the OR was no longer marginally significant (OR 0.32, 95%CI 0.08-1.27).

With respect to virus-virus coinfections, our results are similar to studies that have found no significant association between coinfection and severity of illness [6, 9, 10, 12, 14]. However, these studies did not use multivariate

regression modeling to test hypotheses regarding severity of illness, and they do not report any measures of association (e.g., odds ratio). In our study, children with a viral coinfection were less likely to be admitted to the intensive care unit than children with a single virus infection, though this association was not statistically significant (OR 0.32, 95% CI 0.08-1.27) after controlling for potential confounders.

With respect to reasons for hospitalization and ICU admission in cases of pediatric ARTI, a number of factors may be considered, but oftentimes no set algorithm is in place and decisions regarding admission are made at the physician's discretion based upon the evidence at hand. We hypothesized that perhaps the observed reduced likelihood of admission to the ICU associated with virus-virus coinfections was an artifact associated with physician behavior when deciding what child is admitted to the ICU and when they are admitted. Most studies focusing on the need for major medical intervention in pediatric populations with ARTI have focused on bronchiolitis and RSV. Parker et al. identified 4 factors associated with major intervention (i.e., oxygen administration, IV fluid bolus, any treatment for apnea, or admission to critical care unit) in infants with bronchiolitis; these factors were severe retractions on arrival, baseline oxygen saturation 92% or less, increased respiratory rate, and history of poor fluid intake [112]. Weigl et al. identified young age, presence of underlying condition, pneumonia or bronchiolitis, prematurity, and retractions as factors that increased the duration of hospitalization in children under 2 years old admitted with ARTI [113]. In a study of dual viral infection in infants with severe bronchiolitis, Richard et al. identified young age, prematurity, underlying illness, and male gender as factors associated with admission to a pediatric intensive care unit [114]. Factors such as age, oxygen saturation, work of breathing, ability of the guardians to monitor the child at home, ability to feed, dehydration,

complexity of care, and pre-existing conditions (i.e., underlying heart or pulmonary disease) are often considered by the evaluating physician at the University of Iowa Hospital and Clinics (personal communication with Dr. Jody Murph). We assessed the importance of several of these variables in our analyses. However, even after controlling for potential confounders, the direction of effect remained consistent in several sub-analyses (data not shown).

We next hypothesized that perhaps concurrent bacterial infections were playing a role in influencing the paradoxical viral coinfection data. We limited secondary analyses to hospitalized children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI for whom any bacterial test (not limited to respiratory sites) had been ordered during the same hospitalization that a viral test had been ordered and for whom a virus was detected (n=124). A virus-bacteria coinfection was identified for 33 children, and a virus-virus-bacteria coinfection was identified in 7 children. Children with virus-bacteria coinfection, as compared to children with viral mono-infection, were more likely to be admitted to an intensive care unit (OR 5.58, 95% CI 1.95-15.96) even after controlling for potential confounders including age, history of prematurity, urban/rural residence, and leukocytosis. Similar results were observed when further limiting the population to children with respiratory bacterial tests ordered, though the sample size was insufficient to allow for control of confounding through multivariate logistic regression modeling (crude OR 9.75, 95% CI 2.54-37.40).

Given these data, we hypothesize the following explanation for the observed decreased likelihood of ICU admission among children with virus-virus coinfection as compared to children with viral mono-infection. The 33 children with single virus/single bacterium coinfections (26.6% of the children with virus-positive specimens) would have been classified as having a viral mono-infection

in the primary analyses limiting exposure to virus-virus coinfection (no bacterial data included). It is also likely that a number of children not tested for bacterial pathogens may have had a concurrent bacterial infection. Though these cases would likely be distributed between viral mono-infection and virus-virus coinfections, we suspect that a higher proportion of viral mono-infections would also be positive for bacterial pathogens as evidenced by the data presented in Table 49 (virus-bacteria coinfections represented 26.6% of virus-positive specimens whereas virus-virus-bacteria coinfections represented only 5.7% of virus-positive specimens). Given that 33 of the 40 children with these virus-bacteria coinfections would have been classified as having viral mono-infections in our primary analyses and that our secondary analyses suggest these children are at increased risk of ICU admission compared to viral mono-infections, children with virus-virus coinfections would appear to be less likely to be admitted to the ICU as compared to children with viral mono-infections when bacterial coinfections are not accounted for. When the children with virus-bacteria coinfections were removed from the analysis of virus-virus coinfection versus virus mono-infection, the observed odds ratio estimating the association between viral coinfection and ICU admission moved closer to the null hypothesis (OR 0.53, 95% CI 0.11-2.49). This suggests that at least part of the observed protective effect of virus-virus coinfection ($p > 0.05$) can be explained by virus-bacteria coinfection, and that perhaps undetected bacterial coinfections could account for the remaining effect.

Examples of coinfecting bacterial and viral pathogens are common in the literature, but reports tend to be virus-specific [115]. For example, most deaths associated with epidemics of influenza are associated with secondary bacterial infections including *Streptococcus pneumoniae* and *Haemophilus influenzae*. In children, RSV has been associated with *S. pneumoniae*, *Bordetella pertussis*,

and *Staphylococcus aureus*. Additionally, associations between adenovirus and *B. pertussis* have been noted in severe respiratory disease in children. The body of evidence describing the importance of viral and bacterial cooperation in cases of pneumonia is growing [116]. Jennings et al. conducted a study among 304 patients admitted to the hospital with community-acquired pneumonia (CAP) and demonstrated that HRV-pneumococcal coinfection was independently associated with severe pneumonia [11]. Templeton et al. included both inpatients and outpatients in their study of CAP and demonstrated that individuals with HRV-bacterial or coronavirus-bacterial coinfections were independently association with severe pneumonia [17]. Additional evidence of the interaction between bacterial and viral pathogens comes from animal studies [115]. Several mechanisms have been postulated to further explain this interaction [115]. Viruses may increase the ability of bacteria to infect or adhere to mucosal surfaces through changes induced in host cell membranes. It has also been postulated that perhaps exudates on mucosal surfaces resulting from viral infection may increase bacterial growth. The host immune defense against bacteria could also be affected by viral infection through the inhibition of nonspecific phagocytosis by neutrophils and macrophages. It has also been postulated that perhaps viral infection can exacerbate the effect of bacterial toxins.

The original intent of this study was to focus attention on coinfections involving HRV, HBoV, and Ad. Our sample size was insufficient to examine hypotheses regarding illness severity in the cases of HBoV-specific and Ad-specific coinfections. With respect to HRV-specific coinfections, our results are similar to other published studies. Recent studies report HRV coinfection rates ranging from 17.7% to 47% [47, 52, 54-59]. In our sample of 349 children with confirmed (physician diagnosed) or suspected (physician-documented

symptoms) ARTI, 96 children (27.5%) were HRV-positive, 35.4% of which were co-infected with HRV and at least one other virus. Some studies have suggested that coinfection with HRV leads to more severe disease manifestations such as lower respiratory tract infections, requirement for supplemental oxygen, and longer stays in the hospital [54, 58, 59]. In the current study, no significant association was identified between coinfection involving HRV (as compared to HRV mono-infection) and the following indicators of severity – hospitalization, ICU admission, oxygen saturation less than 90% (hypoxemia), requirement for supplemental oxygen, requirement for mechanical ventilation. However, children with coinfection involving HRV (as compared to HRV mono-infection) were significantly more likely to be administered a bronchodilator (OR 3.02, 95% CI 1.06-8.65) even after controlling for age, history of asthma, and race. Like RSV, HRVs have been known to be associated with wheezing and asthma exacerbations in children [49, 117]. The most common combination among detected coinfections involving HRV was HRV-RSV (47% of 34 coinfections). We hypothesize that it is dual infection with RSV that drives the increased likelihood of bronchodilator administration in children with HRV-specific coinfections as compared to HRV mono-infections.

We must acknowledge the limitations of this study. The use of archived respiratory specimens proves to be problematic with respect to biases associated with sampling and exposure misclassification. First, not all individuals with ARTIs may be symptomatic; and furthermore, not all symptomatic individuals with ARTI may seek medical care. Thus, only those individuals who sought medical care were eligible for inclusion into this study. Additionally, not every individual who seeks medical care for an ARTI will have a viral respiratory test ordered. Therefore, it is likely that certain cases of ARTI (e.g., symptomatic infections requiring medical attention or more severe infections eliciting increased effort to

identify an etiologic agent) may be overrepresented in the sample population. Indeed, over 75% of our population was hospitalized.

An additional limitation was the unavailability of all eligible specimens collected during the study period. Specimens were not available for the following reasons: (1) the specimen tested negative for all viruses and was not archived because the entire volume of sample was used for clinical testing, (2) the specimen tested positive for at least one virus and the laboratory technician decided not to archive the remaining volume of the sample, or (3) the remaining volume of the sample was retained for in-house validation studies. Compared to those children for whom specimens were included in the study, children for whom specimens were unavailable (n=105) were significantly younger (p=0.035), were more likely to reside in an urban area (p=0.009), and were less likely to be admitted to the hospital (p<0.001). If children whose specimens were excluded were more likely to be coinfected than those children whose specimens were included (a large proportion were RSV-positive), then our observed measures of association between coinfection and severity of illness, specifically ICU admission, would be biased away from the null hypothesis of no association.

Underestimation of respiratory coinfections likely occurred for several reasons. First, every possible respiratory pathogen was not included in the respiratory panel so this study was limited to coinfections involving influenza A and B, parainfluenza 1, 2, and 3, respiratory syncytial virus, adenovirus, rhinovirus, human bocavirus, and human metapneumovirus. However, those viruses included are the most common respiratory viral pathogens infecting children. Second, if a clinician ordered a virus-specific DFA in addition to a viral culture panel and the DFA was positive, viral culture would not be completed. Case in point - among the 105 specimens not included in this study, which were therefore limited to UIHC routine testing procedures alone, only 2 viral

coinfections were detected. Third, additional coinfections may have been missed as the viral culture and DFA methods utilized for influenza A and B, parainfluenza 1, 2, and 3, respiratory syncytial virus, and adenovirus are less sensitive than the molecular methods utilized for rhinovirus, human bocavirus, human metapneumovirus, and adenovirus. Finally, only a limited proportion of our sample had information regarding bacterial pathogens. When available in the patient medical record, information regarding results from additional bacterial tests performed by the UIHC Clinical Microbiology Laboratory or the University Hygienic Laboratory (UHL) on other specimens (collected at the time a specimen for viral culture was collected) was included in secondary analyses.

This was a cross-sectional study using archived respiratory specimens that were collected as a part of routine medical care. As such, we are unable to establish causality with regard to coinfections and severe ARTI in children as we cannot firmly establish a temporal sequence of events.

It is likely that further under-ascertainment of coinfections occurred as a result of the disconnect between the timing of potential coinfection and specimen collection; for example, a patient may be infected with a single pathogen at time A, then infected with a second pathogen at time B, and at time C the first infection has resolved but the second has not. Sampling at time A, B, or C may therefore produce different results with respect to the presence of a coinfection. Unless multiple samples were taken over the duration of the illness, little can be done to address to this problem or to identify the significance of concurrent versus consecutive infections.

Over-estimation of respiratory coinfections due to co-detection of asymptomatic viral shedding post-infection and acute infection with a second virus may have also occurred. Among the 407 children for whom medical records were available, 3.5% of virus-positive children did not have a

symptomatic ARTI. Molecular methods may have over-estimated the presence of viable virus through detection of viral particles or nonviable virus. Some would argue that co-detection is a more appropriate term for what we define as coinfection in this study. Some studies have attempted to address this concern by measuring viral load in respiratory specimens with quantitative, real-time PCR assays. The underlying assumption is that high viral loads represent acute infection whereas low viral loads may represent shedding of virus from a previous infection. Due to financial constraints, we were unable to use these methods for this study.

Data quality and completeness was expected to vary among covariates selected for abstraction from electronic medical records. Attempts were made to correct inaccurate or incomplete data. Any misclassification of clinical covariates is expected to be non-differential as the investigator was blinded to coinfection and illness severity status at the time of abstraction. Exclusion of incomplete information from analysis may lead to biased estimates of association as this assumes that the observations with complete data are representative of all observations. Furthermore, exclusion of observations may result in an insufficient sample size for subsequent analyses. Some specimens originated from children outside the UIHC medical system (e.g., tests could not be conducted at local hospital and were sent to the UIHC Clinical Microbiology Laboratory) and were not accompanied by additional data from the patient medical record. These samples were excluded from the analysis.

Finally, our sample size may have been insufficient to detect certain measures of association. Though we began with 559 archived respiratory specimens, the effective sample size was whittled down as children with multiple specimens were limited to the first specimen collected during the first episode of ARTI, children without accessible medical records were excluded, children not

meeting the primary or secondary definition of ARTI were excluded, and as outpatients were excluded from analyses focused on ICU admission, requirement for mechanical ventilation, and length of hospitalization.

Despite these limitations, the methodology of the current study sets it apart from earlier studies. Unlike many of its predecessors, this study was designed with an *a priori* hypothesis in mind concerning a role for coinfections in severe ARTI. Furthermore, few studies have attempted to control for potential confounders, and to our knowledge, none have explored the role of potential effect modifiers.

The University of Iowa Hospital and Clinics is a comprehensive academic medical center and regional referral center. Our results may not be applicable to other hospital-based settings due to the composition of the patients seeking care at UIHC and the behavior of the physicians providing care; however, the underlying biological theory suggests that an association could still exist if virus-bacteria coinfections do in fact result in more severe illness, though the measure of association may be attenuated.

Further studies are needed to elucidate the clinical significance of polymicrobial infections, particularly with respect to severity of illness and the role of certain viruses as they occur in coinfections, such as HRV, HBoV, and Ad. Many of the studies published thus far have been retrospective in nature, relying on archived respiratory specimens. Those that do rely on prospective collection of respiratory specimens and accompanying medical record data are often limited by small sample sizes and do not attempt to estimate a measure of association (either odds ratio or risk ratio) for severity of illness as it relates to coinfection. Those that do generate a measure of association often do not control for important confounders. Future studies should include both viral and bacterial pathogens for consideration. *S. pneumoniae*, *Streptococcus pyogenes*,

H. influenzae, *Staphylococcus aureus*, *B. pertussis*, *Moraxella catarrhalis*, *Mycoplasma pneumonia*, and *Chlamydophila pneumoniae* have been identified as bacterial pathogens of the respiratory tract in immunocompetent children [118] and their role in virus-bacteria coinfections should warrant further consideration.

In summary, the results of this study suggest that polymicrobial infections are common in this pediatric population and that these infections, particularly those involving bacteria, may lead to more severe disease outcomes. It is our hope that this study will inform medical and public health professionals with regard to the epidemiology of polymicrobial infections and their potential importance as a cause of severe acute respiratory tract infection in children. Furthermore, the results of this study could contribute to the ongoing discussion of the importance of diagnostic ability to reliably detect multiple concurrent pathogens in a single patient.

APPENDIX

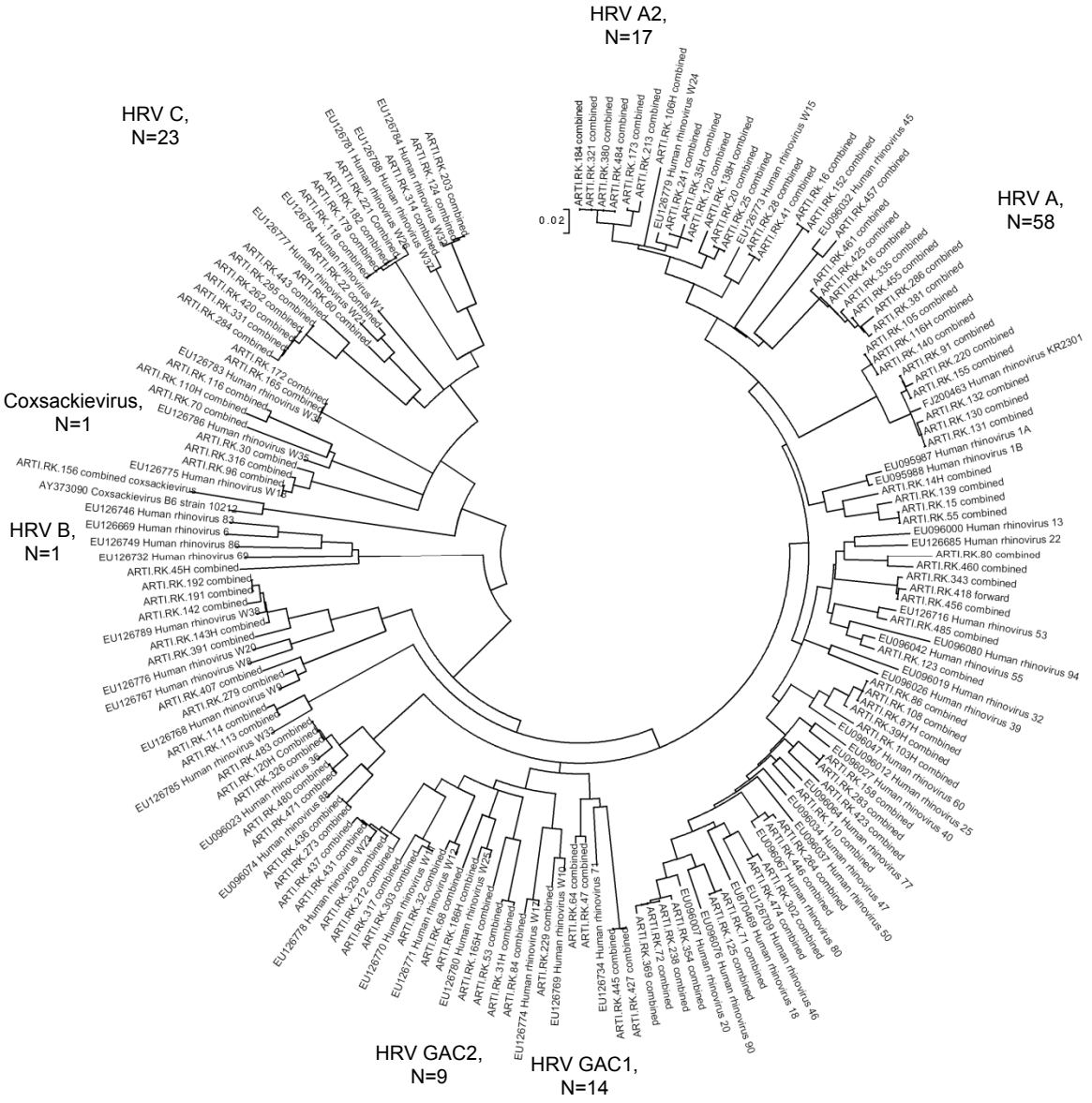

Figure A1. Evolutionary relationships of 174 HRV taxa (5'NCR protocol). The evolutionary history was inferred using the Neighbor-Joining method [1]. The bootstrap consensus tree inferred from 1000 replicates [2] is taken to represent the evolutionary history of the taxa analyzed [2]. Branches corresponding to partitions reproduced in less than 50% bootstrap replicates are collapsed. The percentage of replicate trees in which the associated taxa clustered together in the bootstrap test (1000 replicates) are shown next to the branches [2]. The tree is drawn to scale, with branch lengths in the same units as those of the evolutionary distances used to infer the phylogenetic tree. The evolutionary distances were computed using the Maximum Composite Likelihood method [3] and are in the units of the number of base substitutions per site. All positions containing gaps and missing data were eliminated from the dataset (Complete deletion option). There were a total of 174 positions in the final dataset. Phylogenetic analyses were conducted in MEGA4 [4]. Prefix ARTI.RK denotes study specimens.

Source: 1. Saitou N & Nei M (**1987**) The neighbor-joining method: A new method for reconstructing phylogenetic trees. *Molecular Biology and Evolution* **4**:406-425.

2. Felsenstein J (**1985**) Confidence limits on phylogenies: An approach using the bootstrap. *Evolution* **39**:783-791.

3. Tamura K, Nei M & Kumar S (**2004**) Prospects for inferring very large phylogenies by using the neighbor-joining method. *Proceedings of the National Academy of Sciences* (*USA*) **101**:11030-11035.

4. Tamura K, Dudley J, Nei M & Kumar S (**2007**) MEGA4: Molecular Evolutionary Genetics Analysis (MEGA) software version 4.0. *Molecular Biology and Evolution* **24**:1596-1599.

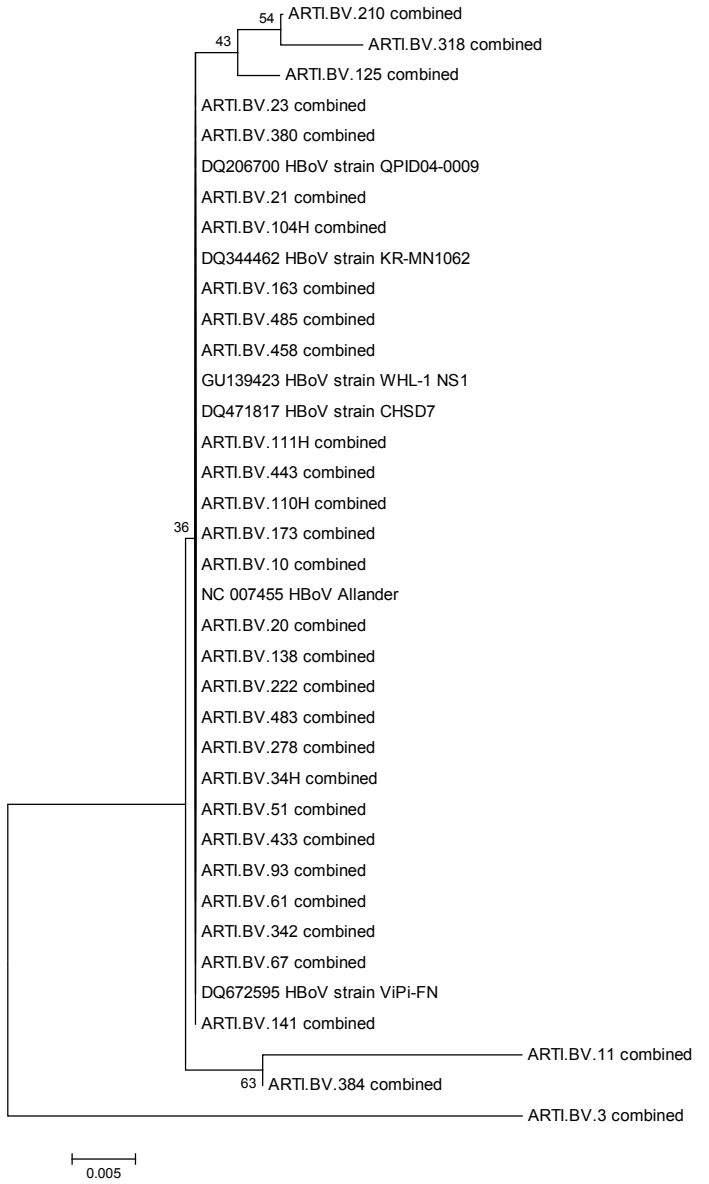

Figure A2. Evolutionary relationships of 37 HBoV taxa. The evolutionary history was inferred using the Neighbor-Joining method [1]. The bootstrap consensus tree inferred from 1000 replicates [2] is taken to represent the evolutionary history of the taxa analyzed [2]. Branches corresponding to partitions reproduced in less than 50% bootstrap replicates are collapsed. The percentage of replicate trees in which the associated taxa clustered together in the bootstrap test (1000 replicates) are shown next to the branches [2]. The tree is drawn to scale, with branch lengths in the same units as those of the evolutionary distances used to infer the phylogenetic tree. The evolutionary distances were computed using the Maximum Composite Likelihood method [3] and are in the units of the number of base substitutions per site. All positions containing gaps and missing data were eliminated from the dataset (Complete deletion option). There were a total of 151 positions in the final dataset. Phylogenetic analyses were conducted in MEGA4 [4]. Prefix ARTI.BV denotes study specimens.

Source: 1. Saitou N & Nei M (**1987**) The neighbor-joining method: A new method for reconstructing phylogenetic trees. *Molecular Biology and Evolution* **4**:406-425.

2. Felsenstein J (**1985**) Confidence limits on phylogenies: An approach using the bootstrap. *Evolution* **39**:783-791.

3. Tamura K, Nei M & Kumar S (**2004**) Prospects for inferring very large phylogenies by using the neighbor-joining method. *Proceedings of the National Academy of Sciences* (*USA*) **101**:11030-11035.

4. Tamura K, Dudley J, Nei M & Kumar S (**2007**) MEGA4: Molecular Evolutionary Genetics Analysis (MEGA) software version 4.0. *Molecular Biology and Evolution* **24**:1596-1599.

Table A1 Virus-specific mono-infection and coinfection prevalence estimates for all specimens, with duplicates (n=559)

Virus	Mono-infection, n (% Total Positive[a])	Co-infection, n (% Total Positive[a])	Total Positive, n (% Total Specimens[b])	95% CI[c]
Ad[d]	10 (50.0)	10 (50.0)	20 (3.6)	2.2-5.5
HRV	87 (66.9)	43 (33.1)	130 (23.3)	19.8-27.0
HBoV	18 (48.7)	19 (51.3)	37 (6.6)	4.7-9.0
hMPV	24 (70.6)	10 (29.4)	34 (6.1)	4.3-8.4
CoxS	1 (50.0)	1 (50.0)	2 (0.4)	0.0-1.3
Flu A	8 (88.9)	1 (11.1)	9 (1.6)	0.7-3.0
Flu B	6 (100)	0 (0)	6 (1.1)	0.4-2.3
RSV	64 (66.7)	32 (33.3)	96 (17.2)	14.1-20.6
PIV 1	1 (100)	0 (0)	1 (0.2)	0-1.0
PIV 2	1 (33.3)	2 (66.7)	3 (0.5)	0.1-1.6
PIV 3	21 (70.0)	9 (30.0)	30 (5.4)	3.7-7.6
PIV NOS	0 (0)	4 (100)	4 (0.7)	0.2-1.8
Total	241 (79.5)	62 (20.5)	303 (54.2)	50.0-58.4

Note: CoxS (coxsackievirus), Flu A (influenza A virus), Flu B (influenza B virus), PIV NOS (parainfluenza virus not otherwise specified).

[a] Denominator is virus-specific total number of positive specimens.

[b] Denominator is total number of specimens, n=559.

[c] 95% binomial confidence interval associated with prevalence percent estimate for total number of positive specimens.

[d] Ad genotypes include Ad1 (n=1, 0% coinfected), Ad2 (n=6, 66.7% coinfected), Ad3 (n=8, 50.0% coinfected), Ad5 (n=1, 0% coinfected), Ad41 (n=1, 100% coinfected), and non-typeable (n=2, 50.0% coinfected).

Table A2 Frequency of viral coinfections for all specimens, with duplicates (n=559)

Co-detected Viruses	**N**
2 Viruses	
HRV + RSV	17
HRV + HBoV	7
HRV + PIV3	5
HRV + hMPV	4
HBoV + RSV	3
Ad + RSV	3
Ad + HRV	3
PIV NOS + RSV	2
PIV 3 + HBoV	2
PIV 2 + HBoV	2
PIV 3 + RSV	1
PIV 3 + hMPV	1
hMPV + RSV	1
hMPV + CoxS	1
HBoV + Flu A	1
HBoV + Ad	1
3 Viruses	
Ad + HRV + HBoV	2
HRV + HBoV + hMPV	1
HRV + HBoV + RSV	1
HRV + hMPV + RSV	1
HRV + PIV NOS + RSV	1
hMPV + PIV NOS + RSV	1
Ad + HRV + RSV	1
Total	61

Note: CoxS (coxsackievirus), Flu A (influenza A virus), PIV NOS (parainfluenza virus not otherwise specified).

Table A3 Virus-specific mono-infection and coinfection prevalence estimates for specimens from eligible children excluded from study due to unavailable specimen, with duplicates (n=116)

Virus[a]	Mono-infection, n (% Total Positive[b])	Co-infection, n (% Total Positive[b])	Total Positive, n (% Total Specimens[c])	95% CI[d]
Ad[e]	2 (66.7)	1 (33.3)	3 (2.6)	0.5-7.4
Flu A	3 (100)	0 (0)	3 (2.6)	0.5-7.4
Flu B	5 (100)	0 (0)	5 (4.31)	1.4-9.8
RSV	57 (96.6)	2 (3.4)	59 (50.9)	41.4-60.3
PIV 1	0 (0)	0 (0)	0 (0)	NA
PIV 2	2 (66.7)	1 (33.3)	3 (2.6)	0.5-7.4
PIV 3	6 (100)	0 (0)	6 (5.2)	1.9-10.9
PIV NOS	0 (0)	0 (0)	0 (0)	NA
Total	75 (97.4)	2 (2.6)	77 (66.4)	57.0-74.9

Note: CoxS (coxsackievirus), Flu A (influenza A virus), Flu B (influenza B virus), PIV NOS (parainfluenza virus not otherwise specified).

[a] Limited to UIHC Clinical Microbiology Laboratory virological assays.

[b] Denominator is virus-specific total number of positive specimens.

[c] Denominator is total number of specimens, n=116.

[d] 95% binomial confidence interval associated with prevalence percent estimate for total number of positive specimens.

[e] Ad genotypes not determined.

Table A4 Frequency of viral coinfections for specimens from eligible children excluded from study due to unavailable specimen, with duplicates (n=116)

Co-detected Viruses	**N**
RSV + Ad	1
RSV + PIV 2	1
Total	2

Table A5 Demographic characteristics of children for all specimens with accessible medical record information, with duplicates (n=529)

	Number of Specimens (%)												
	Total (n=529)	**Positive (n=295)**	**Negative (n=234)**	**Ad (n=10)**	**HRV (n=84)**	**HBoV (n=17)**	**hMPV (n=22)**	**CoxS (n=1)**	**Flu A (n=8)**	**Flu B (n=6)**	**RSV (n=62)**	**All PIV (n=23)**	**Coinfection (n=62)**
Gender													
Female	247 (46.7)	135 (45.8)	112 (47.9)	4 (40.0)	41 (48.8)	7 (41.2)	12 (54.6)	0 (0)	2 (25.0)	1 (16.7)	30 (48.4)	11 (47.8)	27 (43.6)
Male	282 (53.3)	160 (54.2)	122 (52.1)	6 (60.0)	43 (51.2)	10 (58.8)	10 (45.5)	1 (100)	6 (75.0)	5 (83.3)	32 (51.6)	12 (52.2)	35 (56.5)
Age (years)													
0 to < 0.5	181 (34.2)	83 (28.1)	98 (41.9)	1 (10.0)	26 (31.0)	3 (17.7)	6 (27.3)	0 (0)	0 (0)	1 (16.7)	25 (40.3)	6 (26.1)	14 (22.6)
0.5 to < 1	86 (16.3)	59 (20.0)	27 (11.5)	3 (30.0)	15 (17.9)	4 (23.5)	6 (27.3)	0 (0)	2 (25.0)	0 (0)	14 (22.6)	1 (4.3)	14 (22.6)
1 to < 5	196 (37.1)	117 (39.7)	79 (33.8)	4 (40.0)	29 (34.5)	8 (47.1)	8 (36.4)	0 (0)	5 (62.5)	2 (33.3)	21 (33.9)	12 (52.2)	28 (45.2)
≥ 5	66 (12.5)	36 (12.2)	30 (12.8)	2 (20.0)	14 (16.7)	2 (11.8)	2 (9.1)	1 (100)	1 (12.5)	3 (50.0)	2 (3.2)	4 (17.4)	6 (9.7)
Race													
Caucasian	342 (71.9)	195 (72.0)	147 (71.1)	4 (44.4)	55 (72.4)	11 (64.7)	17 (85.0)	0 (0)	7 (87.5)	6 (100)	36 (64.3)	17 (81.0)	42 (73.7)
African-American	53 (11.1)	31 (11.4)	22 (10.7)	4 (44.4)	9 (11.8)	3 (17.7)	1 (5.0)	1 (100)	0 (0)	0 (0)	9 (16.1)	1 (4.8)	3 (5.3)
Hispanic	47 (9.9)	27 (10.0)	20 (9.8)	0 (0)	8 (10.5)	2 (11.8)	2 (10.0)	0 (0)	1 (12.5)	0 (0)	6 (10.7)	2 (9.5)	6 (10.5)
Other	34 (7.1)	18 (6.6)	16 (7.8)	1 (11.1)	4 (5.3)	1 (5.9)	0 (0)	0 (0)	0 (0)	0 (0)	5 (8.9)	1 (4.8)	6 (10.5)
Missing	53	24	29	1	8	0	2	0	0	0	6	2	5
Medicaid													
Yes	262 (50.0)	139 (47.4)	123 (53.3)	2 (22.2)	41 (48.8)	7 (41.2)	12 (54.6)	0 (0)	3 (37.5)	2 (33.3)	33 (54.1)	10 (43.5)	29 (46.8)
No	262 (50.0)	154 (52.6)	108 (46.8)	7 (77.8)	43 (51.2)	10 (58.5)	10 (45.5)	1 (100)	5 (62.5)	4 (66.7)	28 (45.9)	13 (56.5)	33 (53.2)
Missing	5	2	3	1	0	0	0	0	0	0	1	0	0
Urban/Rural													
Urban	309 (58.5)	176 (59.7)	133 (57.1)	7 (70.0)	55 (65.5)	11 (64.7)	8 (36.4)	1 (100)	5 (62.5)	2 (33.3)	41 (66.1)	13 (56.5)	33 (53.2)
Large rural	82 (15.5)	38 (12.9)	44 (18.9)	1 (10.0)	6 (7.1)	1 (5.9)	8 (36.4)	0 (0)	0 (0)	2 (33.3)	6 (9.7)	2 (8.7)	12 (19.4)
Small rural	72 (13.6)	43 (14.6)	29 (12.5)	1 (10.0)	12 (14.3)	3 (17.7)	3 (13.6)	0 (0)	0 (0)	0 (0)	12 (19.4)	5 (21.7)	7 (11.3)
Isolated rural	65 (12.3)	38 (12.9)	27 (11.6)	1 (10.0)	11 (13.1)	2 (11.8)	3 (13.6)	0 (0)	3 (37.5)	2 (33.3)	3 (4.8)	3 (13.0)	10 (16.1)
Missing	1	0	1	0	0	0	0	0	0	0	0	0	0

Table A5 Continued

	Number of Specimens (%)												
	Total (n=529)	**Positive (n=295)**	**Negative (n=234)**	**Ad (n=10)**	**HRV (n=84)**	**HBoV (n=17)**	**hMPV (n=22)**	**CoxS (n=1)**	**Flu A (n=8)**	**Flu B (n=6)**	**RSV (n=62)**	**All PIV [a] (n=23)**	**Coinfection (n=62)**
Smoke exposure													
None	135 (63.7)	76 (61.8)	59 (66.3)	3 (75.0)	20 (64.5)	5 (62.5)	3 (37.5)	0 (0)	2 (50.0)	1 (50.0)	17 (65.4)	8 (80.0)	17 (56.7)
Direct	24 (11.3)	12 (9.8)	12 (13.5)	0 (0)	2 (6.5)	0 (0)	2 (25.0)	0 (0)	0 (0)	1 (50.0)	2 (7.7)	0 (0)	5 (16.7)
Indirect	53 (25.0)	35 (28.5)	18 (20.2)	1 (25.0)	9 (29.0)	3 (37.5)	3 (37.5)	0 (0)	2 (50.0)	0 (0)	7 (26.9)	2 (20.0)	8 (26.7)
Missing	317	172	145	6	53	9	14	1	4	4	36	13	32

Note: Excludes 30 specimens for which medical record information was inaccessible. Percentages may not add to 100.0 due to rounding. Virus-specific estimates exclude coinfections.

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

Table A6 Mean age of children for all specimens with accessible medical record information, with duplicates (n=529)

	Total (n=529)	Positive (n=295)	Negative (n=234)	Ad (n=10)	HRV (n=84)	HBoV (n=17)	hMPV (n=22)	CoxS (n=1)	Flu A (n=8)	Flu B (n=6)	RSV (n=62)	All PIV[a] (n=23)	Coinfection (n=62)
Age (years)													
Mean	2.02	2.05	1.97	2.77	2.26	1.84	1.80	0.37	3.15	4.35	1.28	2.72	1.99
Std deviation	2.40	2.31	2.52	3.29	2.62	1.89	1.86	NA	2.67	2.85	1.56	2.21	2.31
Minimum	0.00	0.01	0.00	0.01	0.03	0.20	0.13	0.37	0.67	0.31	0.02	0.06	0.10
Maximum	9.98	9.98	9.80	8.93	9.98	6.94	6.13	0.37	8.59	7.31	7.44	6.71	9.62

Note: Excludes 30 specimens for which medical record information was inaccessible. Percentages may not add to 100.0 due to rounding. Virus-specific estimates exclude coinfections.

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

Table A7 Clinical characteristics (indicators of severity) associated with specimens for all children with accessible medical record information, with duplicates (n=529)

	Number of Specimens (%)												
	Total (n=529)	**Positive (n=295)**	**Negative (n=234)**	**Ad (n=10)**	**HRV (n=84)**	**HBoV (n=17)**	**hMPV (n=22)**	**CoxS (n=1)**	**Flu A (n=8)**	**Flu B (n=6)**	**RSV (n=62)**	**All PIV[a] (n=23)**	**Coinfection (n=62)**
Inpatient													
Yes	420 (79.4)	227 (77.0)	193 (82.5)	8 (80.0)	67 (79.8)	17 (100)	22 (100)	1 (100)	4 (50.0)	1 (16.7)	47 (75.8)	18 (78.3)	42 (67.7)
No	109 (20.6)	68 (23.0)	41 (17.5)	2 (20.0)	17 (20.2)	0 (0)	0 (0)	0 (0)	4 (50.0)	5 (83.3)	15 (24.2)	5 (21.7)	20 (32.3)
ICU admission, if hospitalized													
Ever	174 (41.4)	61 (26.9)	113 (58.6)	1 (12.5)	20 (29.9)	8 (47.1)	5 (22.7)	0 (0)	0 (0)	1 (100)	20 (42.6)	1 (5.6)	5 (11.9)
Never	246 (58.6)	166 (73.1)	80 (41.5)	7 (87.5)	47 (70.2)	9 (52.9)	17 (77.3)	1 (100)	4 (100)	0 (0)	27 (57.5)	17 (94.4)	37 (88.1)
ICU at collection													
Yes	160 (38.1)	59 (26.0)	113 (58.6)	1 (12.5)	20 (29.9)	7 (41.2)	4 (18.2)	0 (0)	0 (0)	1 (100)	20 (42.6)	1 (5.6)	5 (11.9)
No	260 (61.9)	168 (74.0)	80 (41.5)	7 (87.5)	47 (70.2)	10 (58.8)	18 (81.8)	1 (100)	4 (100)	0 (0)	27 (57.5)	17 (94.4)	37 (88.1)
Mechanically ventilated													
Yes	96 (18.2)	30 (10.2)	66 (28.2)	1 (10.0)	10 (11.9)	4 (23.5)	3 (13.6)	0 (0)	0 (0)	0 (0)	10 (16.3)	1 (4.3)	1 (1.6)
No	433 (81.9)	265 (89.8)	168 (71.8)	9 (90.0)	74 (88.1)	13 (76.5)	19 (86.4)	1 (100)	8 (100)	6 (100)	52 (83.9)	22 (95.7)	61 (98.4)
Oxygen requirement													
Yes	248 (46.9)	119 (40.3)	129 (55.1)	3 (30.0)	31 (36.9)	14 (82.4)	13 (59.1)	0 (0)	0 (0)	1 (16.7)	29 (46.8)	6 (26.1)	22 (35.5)
No	281 (53.1)	176 (59.7)	105 (44.9)	7 (70.0)	53 (63.1)	3 (17.7)	9 (40.9)	1 (100)	8 (100)	5 (83.3)	33 (53.2)	17 (73.9)	40 (64.5)
Bronchodilator administered													
Yes	150 (28.4)	110 (37.3)	40 (17.1)	2 (20.0)	25 (29.8)	11 (64.7)	8 (36.4)	0 (0)	2 (25.0)	0 (0)	30 (48.4)	5 (21.7)	27 (43.6)
No	379 (71.6)	185 (62.7)	194 (82.9)	8 (80.0)	59 (70.2)	6 (35.3)	14 (63.6)	1 (100)	6 (75.0)	6 (100)	32 (51.6)	18 (78.3)	35 (56.5)
Oxygen saturation < 90%													
Yes	186 (35.2)	95 (32.2)	91 (38.9)	2 (20.0)	27 (32.1)	8 (47.1)	9 (40.9)	0 (0)	0 (0)	1 (16.7)	24 (38.7)	5 (21.7)	19 (30.7)
No	343 (64.8)	200 (67.8)	143 (61.1)	8 (80.0)	27 (32.1)	9 (52.9)	13 (59.1)	1 (100)	8 (100)	5 (83.3)	38 (61.3)	18 (78.3)	43 (69.4)

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

Table A8 Clinical characteristics (length of hospitalization) associated with specimens for all children with accessible medical record information, with duplicates (n=529)

	Total (n=529)	Positive (n=295)	Negative (n=234)	Ad (n=10)	HRV (n=84)	HBoV (n=17)	hMPV (n=22)	CoxS (n=1)	Flu A (n=8)	Flu B (n=6)	RSV (n=62)	All PIV[a] (n=23)	Coinfection (n=62)
UIHC hospitalization Length of stay, days													
N	420	227	193	8	67	17	22	1	4	1	47	18	42
Median	5.00	3.00	9.00	3.50	3.00	6.00	5.00	4.00	3.00	153.00	3.00	3.00	3.00
Mean	29.05	17.24	42.94	3.75	10.67	21.47	30.55	4.00	3.25	153.00	28.49	15.06	8.38
Std deviation	55.44	43.83	63.94	2.66	27.49	38.76	83.04	NA	1.50	NA	48.04	50.67	26.22
Minimum	< 1.00	< 1.00	1.00	1.00	< 1.00	< 1.00	1.00	4.00	2.00	153.00	1.00	1.00	1.00
Maximum	377.00	369.00	377.00	9.00	204.00	140.00	369.00	4.00	5.00	153.00	172.00	2.18	172.00
Non-ICU days													
N	339	209	130	1	61	14	21	1	4	0	41	18	42
Median	3.00	3.00	4.00	3.00	2.00	3.00	4.00	4.00	3.00	NA	2.00	3.00	3.00
Mean	7.99	7.51	8.78	3.57	5.34	3.93	25.33	4.00	3.25	NA	7.37	4.11	5.67
Std deviation	22.63	27.23	12.08	2.82	10.52	3.85	79.48	NA	1.50	NA	14.49	4.48	10.53
Minimum	< 1.00	< 1.00	1.00	1.00	< 1.00	< 1.00	1.00	4.00	2.00	NA	1.00	1.00	1.00
Maximum	369.00	369.00	67.00	9.00	77.00	12.00	369.00	4.00	5.00	NA	67.00	21.00	67.00
ICU days													
N	174	61	113	1	20	8	5	0	0	1	20	1	5
Median	30.00	11.00	43.00	5.00	3.50	9.00	9.00	NA	NA	153.00	28.00	197.00	2.00
Mean	54.57	38.43	63.28	5.00	19.40	38.75	28.00	NA	NA	153.00	51.85	197.00	22.80
Std deviation	65.96	54.34	70.15	NA	45.76	52.51	49.94	NA	NA	NA	50.09	NA	45.95
Minimum	< 1.00	< 1.00	1.00	5.00	< 1.00	< 1.00	1.00	NA	NA	153.00	2.00	197.00	2.00
Maximum	377.00	204.00	377.00	5.00	204.00	140.00	117.00	NA	NA	153.00	140.00	197.00	105.00

Table A8 Continued

	Total (n=529)	Positive (n=295)	Negative (n=234)	Ad (n=10)	HRV (n=84)	HBoV (n=17)	hMPV (n=22)	CoxS (n=1)	Flu A (n=8)	Flu B (n=6)	RSV (n=62)	All PIV[a] (n=23)	Coinfection (n=62)
Total hospitalization, days[b]													
N	420	227	193	8	67	17	22	1	4	1	47	18	42
Median	5.00	3.00	10.00	4.00	3.00	6.00	5.00	4.00	3.00	153.00	4.00	3.00	3.00
Mean	29.70	18.18	43.24	4.00	13.15	22.06	30.64	4.00	3.25	153.00	28.77	15.89	8.48
Std deviation	56.00	45.31	63.93	2.78	35.08	38.80	83.02	NA	1.50	NA	48.07	50.62	26.36
Minimum	< 1.00	< 1.00	1.00	1.00	< 1.00	< 1.00	1.00	4.00	2.00	153.00	1.00	1.00	1.00
Maximum	377.00	369.00	377.00	9.00.00	204.00	140.00	369.00	4.00	5.00	153.00	173.00	218.00	173.00

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

[b] Includes non-UIHC hospitalizations when applicable.

Table A9 Clinical characteristics (antimicrobial use and inflammation markers) associated with specimens for all children with accessible medical record information, with duplicates (n=529)

	Number of Specimens (%)												
	Total (n=529)	**Positive (n=295)**	**Negative (n=234)**	**Ad (n=10)**	**HRV (n=84)**	**HBoV (n=17)**	**hMPV (n=22)**	**CoxS (n=1)**	**Flu A (n=8)**	**Flu B (n=6)**	**RSV (n=62)**	**All PIV[a] (n=23)**	**Coinfection (n=62)**
Antimicrobial use													
Prior use[b]													
Yes	153 (28.9)	83 (28.1)	70 (29.9)	5 (50.0)	26 (31.0)	5 (29.4)	6 (27.3)	0 (0)	1 (12.5)	0 (0)	19 (30.7)	2 (8.7)	19 (30.7)
No	376 (71.1)	212 (71.9)	164 (70.1)	5 (50.0)	58 (69.0)	12 (70.6)	16 (72.7)	1 (100)	7 (87.5)	6 (100)	43 (69.4)	21 (91.3)	43 (69.4)
UIHC administered													
Yes	328 (62.0)	173 (58.6)	155 (66.2)	7 (70.0)	49 (58.3)	13 (76.5)	15 (68.2)	1 (100)	3 (37.5)	3 (50.0)	34 (54.8)	14 (60.9)	34 (54.8)
No	201 (38.0)	122 (41.4)	79 (33.8)	3 (30.0)	35 (41.7)	4 (23.5)	7 (31.8)	0 (0)	5 (62.5)	3 (50.0)	28 (45.2)	9 (39.1)	28 (45.2)
Take-home prescription													
Yes	133 (25.1)	86 (29.2)	187 (79.9)	2 (20.0)	23 (27.4)	6 (35.3)	9 (40.9)	0 (0)	3 (37.5)	1 (16.7)	11 (17.7)	8 (34.8)	23 (37.1)
No	396 (74.9)	209 (70.9)	47 (20.1)	8 (80.0)	61 (72.6)	11 (64.7)	13 (59.1)	1 (100)	5 (62.5)	5 (83.3)	51 (82.3)	15 (65.2)	39 (62.9)
Leukopenia													
Yes	102 (24.5)	58 (25.7)	44 (23.0)	3 (33.3)	10 (15.2)	2 (12.5)	5 (23.8)	0 (0)	4 (66.7)	0 (0)	8 (18.6)	9 (52.9)	8 (18.8)
No	315 (75.5)	168 (74.3)	147 (77.0)	6 (66.7)	56 (84.9)	14 (87.5)	16 (76.2)	1 (100)	2 (33.3)	3 (100)	35 (81.4)	8 (47.1)	35 (81.8)
Missing	112	69	43	1	18	1	1	0	2	3	19	6	18
Leukocytosis													
Yes	114 (27.3)	60 (26.6)	54 (28.3)	3 (33.3)	23 (34.9)	9 (56.3)	7 (33.3)	0 (0)	0 (0)	3 (100)	12 (27.9)	2 (11.8)	10 (22.7)
No	303 (72.7)	166 (73.5)	137 (71.7)	6 (66.7)	43 (65.2)	7 (43.8)	14 (66.7)	1 (100)	6 (100)	0 (0)	31 (72.1)	15 (88.2)	34 (77.3)
Missing	112	69	43	1	18	1	1	0	2	3	19	6	18
CRP > 0.5 mg/dl													
Yes	235 (68.5)	124 (70.9)	111 (66.1)	6 (100)	39 (69.6)	13 (86.7)	13 (72.2)	0 (0)	0 (0)	2 (100)	19 (55.9)	10 (76.9)	19 (70.4)
No	108 (31.5)	51 (29.1)	57 (33.9)	0 (0)	17 (30.4)	2 (13.3)	5 (27.8)	1 (100)	3 (100)	0 (0)	15 (44.1)	3 (23.1)	8 (29.6)
Missing	186	120	66	4	28	2	4	0	5	4	28	10	35

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

[b] Denotes antibiotics used prior to UIHC episode during which specimen was collected.

Table A10 Clinical characteristics (diagnoses) associated with specimens for all children with accessible medical record information, with duplicates (n=529)

	Number of Specimens (%)												
	Total (n=529)	**Positive (n=295)**	**Negative (n=234)**	**Ad (n=10)**	**HRV (n=84)**	**HBoV (n=17)**	**hMPV (n=22)**	**CoxS (n=1)**	**Flu A (n=8)**	**Flu B (n=6)**	**RSV (n=62)**	**All PIV[a] (n=23)**	**Coinfection (n=62)**
ARTI													
None	19 (3.6)	9 (3.1)	10 (4.3)	0 (0)	1 (1.2)	1 (5.9)	0 (0)	0 (0)	0 (0)	0 (0)	3 (4.8)	1 (4.3)	3 (4.8)
Physician diagnosed	234 (44.2)	166 (56.3)	68 (29.1)	6 (60.0)	43 (51.2)	9 (52.9)	17 (77.3)	1 (100)	5 (62.5)	1 (16.7)	39 (62.9)	6 (26.1)	39 (62.9)
Physician documented symptoms	207 (39.1)	107 (36.3)	100 (42.7)	4 (40.0)	36 (42.9)	6 (35.3)	5 (22.7)	0 (0)	3 (37.5)	4 (66.7)	15 (24.2)	15 (65.2)	19 (30.7)
Concern for ARTI without traditional symptoms	69 (13.0)	13 (4.4)	56 (23.9)	0 (0)	4 (4.8)	1 (5.9)	0 (0)	0 (0)	0 (0)	1 (16.7)	5 (8.1)	1 (4.3)	1 (1.6)
Diagnosis													
Bronchiolitis													
Yes	51 (9.6)	46(15.6)	5 (0.9)	0 (0)	4 (4.8)	2 (11.8)	3 (13.6)	0 (0)	0 (0)	0 (0)	24 (38.7)	1 (4.3)	12 (19.4)
No	478 (90.4)	249 (84.4)	229 (99.1)	10 (100)	80 (95.2)	15 (88.2)	19 (86.4)	1 (100)	8 (100)	6 (100)	38 (61.3)	22 (95.7)	50 (80.6)
Pneumonia													
Yes	109 (20.7)	64 (21.7)	45 (19.2)	2 (20.0)	13 (15.5)	7 (41.2)	10 (45.5)	0 (0)	0 (0)	0 (0)	11 (17.7)	3 (13.0)	18 (29.0)
No	420 (79.3)	231 (78.3)	189 (80.8)	8 (80.0)	71 (84.5)	10 (58.8)	12 (54.5)	1 (100)	8 (100)	6 (100)	51 (82.3)	20 (87.0)	44 (71.0)
Respiratory tract infection													
Yes	132 (25.0)	86 (29.2)	122 (47.9)	6 (60.0)	35 (41.7)	3 (17.6)	8 (36.4)	1 (100)	3 (37.5)	1(16.7)	8 (12.9)	6 (26.1)	15 (24.2)
No	397 (75.0)	209 (70.8)	112 (52.1)	4 (40.0)	49 (58.3)	14 (82.4)	14 (63.6)	0 (0)	5 (62.5)	5 (83.3)	54 (87.1)	17 (73.4)	47 (75.8)

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

Table A11 Clinical characteristics (symptoms) associated with specimens for all children with accessible medical record information, with duplicates (n=529)

	Number of Specimens (%)												
	Total (n=529)	**Positive (n=295)**	**Negative (n=234)**	**Ad (n=10)**	**HRV (n=84)**	**HBoV (n=17)**	**hMPV (n=22)**	**CoxS (n=1)**	**Flu A (n=8)**	**Flu B (n=6)**	**RSV (n=62)**	**All PIV[a] (n=23)**	**Coinfection (n=62)**
Fever													
Yes	289 (54.6)	170 (57.6)	119 (50.9)	8 (80.0)	38 (45.2)	10 (58.8)	20 (90.9)	1 (100)	8 (100)	6 (100)	30 (48.4)	15 (65.2)	34 (54.8)
No	240 (45.4)	125 (42.4)	115 (49.2)	2 (20.0)	46 (54.8)	7 (41.2)	2 (9.1)	0 (0)	0 (0)	0 (0)	32 (51.6)	8 (34.8)	28 (45.2)
Nasal													
Yes	205 (38.8)	142 (48.1)	63 (26.9)	7 (70.0)	40 (47.6)	7 (41.2)	11 (50.0)	1 (100)	3 (37.5)	3 (50.0)	23 (37.1)	11 (47.8)	34 (54.8)
No	324 (61.3)	153 (51.9)	171 (73.1)	3 (30.0)	44 (52.4)	10 (58.8)	11 (50.0)	0 (0)	5 (62.5)	3 (50.0)	39 (62.9)	12 (52.2)	28 (45.2)
Cough													
Yes	288 (54.4)	200 (67.8)	88 (37.6)	8 (80.0)	50 (59.5)	9 (52.9)	20 (90.9)	1 (100)	7 (87.5)	4 (66.7)	35 (56.5)	15 (65.2)	51 (82.3)
No	241 (45.6)	95 (32.2)	146 (62.4)	2 (20.0)	34 (40.5)	8 (47.1)	2 (9.1)	0 (0)	1 (12.5)	2 (33.3)	27 (43.6)	8 (34.8)	11 (17.7)
Wheeze													
Yes	97 (18.3)	78 (26.4)	19 (8.1)	1 (10.0)	22 (26.2)	6 (35.3)	5 (22.7)	0 (0)	1 (12.5)	0 (0)	22 (35.5)	3 (13.0)	18 (29.0)
No	432 (81.7)	217 (73.6)	215 (91.9)	9 (90.0)	62 (73.8)	11 (64.7)	17 (77.3)	1 (100)	7 (87.5)	6 (100)	40 (64.5)	20 (87.0)	44 (71.0)
Tachypnea													
Yes	41 (7.8)	26 (8.8)	15 (6.4)	1 (10.0)	8 (9.5)	3 (17.7)	3 (13.6)	0 (0)	0 (0)	0 (0)	4 (6.5)	2 (9.5)	5 (8.1)
No	488 (92.3)	269 (91.2)	219 (93.6)	9 (90.0)	76 (90.5)	14 (82.4)	19 (86.4)	1 (100)	8 (100)	6 (100)	58 (93.6)	21 (90.5)	57 (91.9)
Increased work of breathing													
Yes	122 (23.1)	75 (25.4)	47 (20.1)	1 (10.0)	21 (25.0)	4 (23.5)	7 (31.8)	0 (0)	0 (0)	0 (0)	23 (37.1)	4 (17.4)	15 (24.2)
No	407 (76.9)	220 (74.6)	187 (79.9)	9 (90.0)	63 (75.0)	13 (76.5)	15 (68.2)	1 (100)	8 (100)	6 (100)	39 (62.9)	19 (82.6)	47 (75.8)
Gastrointestinal													
Yes	164 (31.0)	105 (35.6)	59 (25.2)	5 (50.0)	26 (31.0)	3 (17.7)	10 (45.5)	0 (0)	4 (50.0)	2 (33.3)	27 (43.6)	5 (21.7)	23 (37.1)
No	365 (69.0)	190 (64.4)	175 (74.8)	5 (50.0)	58 (69.0)	14 (82.4)	12 (54.5)	1 (100)	4 (50.0)	4 (66.7)	35 (56.5)	18 (78.3)	39 (62.9)

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

Table A12 Clinical characteristics (medical history) associated with specimens for all children with accessible medical record information, with duplicates (n=529)

	Number of Specimens (%)												
	Total (n=529)	**Positive (n=295)**	**Negative (n=234)**	**Ad (n=10)**	**HRV (n=84)**	**HBoV (n=17)**	**hMPV (n=22)**	**CoxS (n=1)**	**Flu A (n=8)**	**Flu B (n=6)**	**RSV (n=62)**	**All PIV[a] (n=23)**	**Coinfection (n=62)**
Respiratory condition													
Any													
Yes	209 (39.5)	119 (40.3)	90 (38.5)	1 (10.0)	46 (54.8)	10 (58.8)	6 (27.3)	0 (0)	4 (50.0)	2 (33.3)	18 (29.0)	5 (21.7)	27 (43.6)
No	320 (60.5)	176 (59.7)	144 (61.5)	9 (90.0)	38 (45.2)	7 (41.2)	16 (72.7)	1 (100)	4 (50.0)	4 (66.7)	44 (71.0)	18 (78.3)	35 (56.5)
Asthma													
Yes	68 (12.9)	47 (15.9)	21 (9.0)	1 (10.0)	17 (20.2)	3 (17.7)	0 (0)	0 (0)	3 (37.5)	0 (0)	11 (17.7)	2 (8.7)	10 (16.1)
No	461 (87.2)	248 (84.1)	213 (91.0)	9 (90.0)	67 (79.8)	14 (82.4)	22 (100)	1 (100)	5 (62.5)	6 (100)	51 (82.3)	21 (91.3)	52 (83.9)
Structural defect													
Yes	122 (23.1)	71 (24.1)	51 (21.8)	0 (0)	28 (33.3)	6 (35.3)	5 (22.7)	0 (0)	0 (0)	0 (0)	11 (17.7)	2 (8.7)	19 (30.7)
No	407 (76.9)	224 (75.9)	183 (78.2)	10 (100)	56 (66.7)	11 (64.7)	17 (77.3)	1 (100)	8 (100)	6 (100)	51 (82.3)	21 (91.3)	43 (69.4)
Other medical condition													
Prematurity													
Yes	135 (25.5)	61 (20.7)	74 (31.6)	0 (0)	20 (23.8)	7 (41.2)	4 (18.2)	0 (0)	1 (12.5)	1 (16.7)	11 (17.7)	4 (17.4)	13 (21.0)
No	394 (74.5)	234 (79.3)	160 (68.4)	10 (100)	64 (76.2)	10 (58.8)	18 (81.8)	1 (100)	7 (87.5)	5 (83.3)	51 (82.3)	19 (82.6)	49 (79.0)
Cancer													
Yes	40 (7.6)	27 (9.2)	13 (5.6)	0 (0)	6 (7.1)	0 (0)	2 (9.1)	0 (0)	2 (25.0)	0 (0)	5 (8.1)	7 (30.4)	5 (8.1)
No	489 (92.4)	268 (90.9)	221 (94.4)	10 (100)	78 (92.9)	17 (100)	20 (90.9)	1 (100)	6 (75.0)	6 (100)	57 (91.9)	16 (69.6)	57 (91.9)
Transplant													
Yes	20 (3.8)	10 (3.4)	10 (4.3)	1 (10.0)	5 (6.0)	0 (0)	0 (0)	0 (0)	1 (12.5)	1 (16.7)	1 (1.6)	0 (0)	1 (1.6)
No	509 (96.2)	285 (96.6)	224 (95.7)	9 (90.0)	79 (94.1)	17 (100)	22 (100)	1 (100)	7 (87.5)	5 (83.3)	61 (98.4)	23 (100)	61 (98.4)
Immunocompromised[b]													
Yes	182 (34.4)	107 (36.3)	75 (32.0)	4 (40.0)	27 (32.1)	3 (17.7)	10 (45.5)	1 (100)	2 (25.0)	3 (50.0)	23 (37.1)	9 (39.1)	25 (40.3)
No	347 (65.6)	188 (63.7)	159 (68.0)	6 (60.0)	57 (97.9)	14 (82.4)	12 (54.5)	0 (0)	6 (75.0)	3 (50.0)	39 (62.9)	14 (60.9)	37 (59.7)

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

[b] Includes history of cancer, transplant, and chronic conditions that may lead to increased risk of ARTI (see Table 2).

Table A13 Laboratory characteristics for all specimens with accessible medical record information, with duplicates (n=529)

	Number of Specimens (%)												
	Total (n=529)	**Positive (n=295)**	**Negative (n=234)**	**Ad (n=10)**	**HRV (n=84)**	**HBoV (n=17)**	**hMPV (n=22)**	**CoxS (n=1)**	**Flu A (n=8)**	**Flu B (n=6)**	**RSV (n=62)**	**All PIV[a] (n=23)**	**Coinfection (n=62)**
Month													
Mar 08	21 (3.9)	16 (5.4)	5 (2.1)	0 (0)	4 (4.8)	1 (5.9)	1 (4.6)	0 (0)	0 (0)	1 (16.7)	3 (4.8)	3 (13.0)	3 (4.8)
Apr 08 - Jun 08	97 (18.3)	56 (19.0)	41 (17.5)	2 (20.0)	15 (17.9)	5 (29.4)	8 (36.4)	0 (0)	0 (0)	0 (0)	3 (4.8)	6 (26.1)	17 (27.4)
Jul 08 - Sep 08	41 (7.8)	20 (6.8)	21 (9.0)	3 (30.0)	14 (16.7)	1 (5.9)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.6)	0 (0)	1 (1.6)
Oct 08 - Dec 08	96 (18.2)	45 (15.2)	51 (21.8)	2 (20.0)	16 (19.0)	4 (23.5)	1 (4.6)	1 (100)	0 (0)	0 (0)	10 (16.1)	1 (0.4)	10 (16.1)
Jan 09 - Mar 09	172 (32.5)	102 (34.6)	70 (29.9)	1 (10.0)	17 (20.2)	4 (23.5)	9 (40.9)	0 (0)	8 (100)	4 (66.7)	42 (67.7)	4 (17.4)	13 (21.0)
Apr 09 - Jun 09	102 (19.3)	56 (19.0)	46 (19.7)	2 (20.0)	18 (21.4)	2 (11.8)	3 (13.6)	0 (0)	0 (0)	1 (16.7)	3 (4.8)	9 (39.1)	18 (29.0)
Source													
Nasal wash	438 (84.2)	266 (91.1)	172 (75.4)	8 (80.0)	66 (80.5)	13 (81.3)	20 (90.9)	1 (100)	8 (100)	6 (100)	60 (96.8)	23 (100)	61 (98.4)
Bronch lavage	21 (4.0)	5 (1.7)	16 (7.0)	0 (0)	4 (4.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.6)
Trach aspirate	45 (8.6)	15 (5.14)	30 (13.2)	0 (0)	8 (9.8)	3 (18.7)	2 (9.1)	0 (0)	0 (0)	0 (0)	2 (3.2)	0 (0)	0 (0)
Other[b]	16 (3.1)	6 (2.1)	10 (4.4)	2 (20.0)	4 (4.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Missing	9	3	6	0	2	1	0	0	0	0	0	0	0

Note: Excludes 30 specimens for which medical record information was inaccessible. Percentages may not add to 100.0 due to rounding. Virus-specific estimates exclude coinfections.

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

[b] Other may include bronchial wash/biopsy, lung aspirate/biopsy, nasopharyngeal swab, nasal swab, THS, tissue biopsy.

Table A14 Demographic characteristics of children with accessible medical record information and confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI, without duplicates (n=346)

	Number of Specimens (%)											
	Total (n=346)	**Positive (n=212)**	**Negative (n=134)**	**Ad (n=7)**	**HRV (n=60)**	**HBoV (n=13)**	**hMPV (n=19)**	**Flu A (n=5)**	**Flu B (n=5)**	**RSV (n=43)**	**All PIV[a] (n=13)**	**Coinfection (n=47)**
Gender												
Female	158 (45.7)	98 (46.2)	60 (44.8)	3 (42.9)	28 (46.7)	7 (53.9)	11 (57.9)	2 (40.0)	1 (20.0)	22 (51.2)	6 (46.2)	18 (38.3)
Male	188 (54.3)	114 (53.7)	74 (55.2)	4 (57.1)	32 (53.3)	6 (46.2)	8 (42.1)	3 (60.0)	4 (80.0)	21 (48.8)	7 (53.8)	29 (61.7)
Age (years)												
0 to < 0.5	111 (32.1)	66 (31.1)	45 (33.6)	1 (14.3)	22 (36.7)	0 (0)	6 (31.6)	0 (0)	1 (20.0)	19 (44.2)	5 (38.5)	12 (25.5)
0.5 to < 1	44 (12.7)	37 (17.5)	7 (5.2)	3 (42.9)	9 (15.0)	4 (30.8)	5 (26.3)	0 (0)	0 (0)	5 (11.6)	1 (7.7)	10 (21.3)
1 to < 5	142 (41.0)	83 (39.2)	59 (44.0)	2 (28.6)	19 (31.7)	7 (53.9)	6 (31.6)	4 (80.0)	2 (40.0)	17 (39.5)	7 (53.8)	19 (40.4)
≥ 5	49 (14.2)	26 (12.3)	23 (17.1)	1 (14.3)	10 (16.7)	2 (15.4)	2 (10.5)	1 (20.0)	2 (40.0)	2 (4.7)	0 (0)	6 (12.8)
Race												
Caucasian	233 (73.3)	147 (75.0)	86 (70.5)	4 (66.7)	40 (72.7)	9 (69.2)	15 (88.2)	4 (80.0)	5 (100)	28 (68.3)	10 (83.3)	32 (76.2)
African-American	35 (11.0)	20 (10.2)	15 (12.3)	2 (33.3)	7 (12.7)	2 (15.4)	1 (5.9)	0 (0)	0 (0)	5 (12.2)	0 (0)	3 (7.1)
Hispanic	30 (9.4)	19 (9.7)	11 (9.0)	0 (0)	6 (10.9)	1 (7.7)	1 (5.9)	1 (20.0)	0 (0)	5 (12.2)	2 (16.7)	3 (7.1)
Other	20 (6.3)	10 (5.1)	10 (8.2)	0 (0)	2 (3.6)	1 (7.7)	0 (0)	0 (0)	0 (0)	3 (7.3)	0 (0)	4 (9.5)
Missing	28	16	12	1	5	0	2	0	0	2	1	5
Medicaid												
Yes	162 (47.2)	98 (46.7)	64 (48.1)	1 (16.7)	29 (48.3)	4 (30.8)	10 (52.6)	0 ()	1 (20.0)	23 (54.8)	8 (61.5)	22 (46.8)
No	181 (52.7)	112 (53.3)	69 (51.9)	5 (83.3)	31 (51.7)	9 (69.2)	9 (47.4)	5 (100)	4 (80.0)	19 (45.2)	5 (38.5)	25 (53.2)
Missing	3	2	1	1	0	0	0	0	0	1	0	0
Urban/Rural												
Urban	207 (60.0)	128 (60.4)	79 (59.4)	4 (57.1)	40 (66.7)	9 (69.2)	7 (36.8)	5 (100)	2 (40.0)	29 (67.4)	6 (46.2)	26 (55.3)
Large rural	55 (15.9)	30 (14.2)	25 (18.8)	1 (14.3)	6 (10.0)	0 (0)	7 (36.8)	0 (0)	1 (20.0)	5 (11.6)	2 (15.4)	8 (17.0)
Small rural	42 (12.2)	28 (13.2)	14 (10.5)	1 (14.3)	7 (11.7)	2 (15.4)	3 (15.8)	0 (0)	0 (0)	7 (16.3)	3 (23.1)	5 (10.6)
Isolated rural	41 (11.9)	26 (12.3)	15 (11.3)	1 (14.3)	7 (11.7)	2 (15.4)	2 (10.5)	0 (0)	2 (40.0)	2 (4.7)	2 (15.4)	8 (17.0)
Missing	1	0	1	0	0	0	0	0	0	0	0	0

Table A14 Continued

	Number of Specimens (%)											
	Total (n=346)	**Positive (n=212)**	**Negative (n=134)**	**Ad (n=7)**	**HRV (n=60)**	**HBoV (n=13)**	**hMPV (n=19)**	**Flu A (n=5)**	**Flu B (n=5)**	**RSV (n=43)**	**All PIV [a] (n=13)**	**Coinfection (n=47)**
Smoke exposure												
None	98 (67.6)	61 (63.5)	37 (75.5)	3 (75.0)	16 (69.6)	3 (50.0)	3 (37.5)	2 (66.7)	1 (50.0)	13 (72.2)	6 (85.7)	14 (56.0)
Direct	15 (10.3)	9 (9.4)	6 (12.2)	0 (0)	1 (4.4)	0 (0)	2 (25.0)	0 (0)	1 (50.0)	1 (5.6)	0 (0)	4 (16.0)
Indirect	32 (22.1)	26 (27.1)	6 (12.2)	1 (25.0)	6 (26.1)	3 (50.0)	3 (37.5)	1 (33.3)	0 (0)	4 (22.2)	1 (14.3)	7 (28.0)
Missing	201	116	85	3	37	7	11	2	3	25	6	22

Note: Excludes 3 specimens for which medical record information was inaccessible. Percentages may not add to 100.0 due to rounding. Virus-specific estimates exclude coinfections.

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

Table A15 Mean age of children for specimens with accessible medical record information and confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI, without duplicates (n=346)

	Total (n=346)	Positive (n=212)	Negative (n=134)	Ad (n=7)	HRV (n=60)	HBoV (n=13)	hMPV (n=19)	Flu A (n=5)	Flu B (n=5)	RSV (n=43)	All PIV [a] (n=13)	Coinfection (n=47)
Age (years)												
Mean	2.21	2.02	2.51	2.04	2.17	2.23	1.87	4.44	3.76	1.39	1.49	2.11
Std deviation	2.49	2.29	2.75	2.99	2.51	1.99	1.97	2.60	2.75	1.65	1.35	2.59
Minimum	0.00	0.01	0.00	0.01	0.07	0.64	0.13	1.51	0.31	0.04	0.06	0.10
Maximum	9.79	9.62	9.80	8.64	9.29	6.94	6.13	8.59	6.99	7.44	4.30	9.62

Note: Excludes 3 specimens for which medical record information was inaccessible. Percentages may not add to 100.0 due to rounding. Virus-specific estimates exclude coinfections.

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

Table A16 Clinical characteristics (indicators of severity) associated with all specimens with accessible medical record information from children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI, without duplicates (n=346)

	Number of Specimens (%)											
	Total (n=346)	**Positive (n=212)**	**Negative (n=134)**	**Ad (n=7)**	**HRV (n=60)**	**HBoV (n=13)**	**hMPV (n=19)**	**Flu A (n=5)**	**Flu B (n=5)**	**RSV (n=43)**	**All PIV [a] (n=13)**	**Coinfection (n=47)**
Inpatient												
Yes	264 (76.3)	160 (75.5)	104 (77.6)	6 (85.7)	47 (78.3)	13 (100)	19 (100)	1 (20.0)	1 (20.0)	30 (69.8)	9 (69.2)	34 (72.3)
No	82 (23.7)	52 (24.5)	30 (22.4)	1 (14.3)	13 (21.7)	0 (0)	0 (0)	4 (80.0)	4 (80.0)	13 (30.2)	4 (30.8)	13 (27.7)
ICU admission, if hospitalized												
Ever	82 (31.1)	36 (22.5)	46 (44.2)	1 (16.7)	13 (27.7)	6 (46.2)	4 (21.1)	0 (0)	1 (100)	8 (26.7)	0 (0)	3 (8.8)
Never	182 (68.9)	124 (77.5)	58 (55.8)	5 (83.3)	34 (72.3)	7 (53.9)	15 (79.0)	1 (100)	0 (0)	22 (73.3)	9 (100)	31 (91.2)
ICU at collection												
Yes	74 (28.0)	34 (21.3)	40 (38.5)	1 (16.7)	13 (27.7)	5 (38.5)	3 (15.8)	0 (0)	1 (100)	8 (26.7)	0 (0)	3 (8.8)
No	190 (72.0)	126 (78.8)	64 (61.5)	5 (83.3)	34 (72.3)	8 (61.5)	16 (84.2)	1 (100)	0 (0)	22 (73.3)	9 (100)	31 (91.2)
Mechanically ventilated												
Yes	47 (13.6)	19 (9.0)	28 (20.9)	1 (14.3)	7 (11.7)	3 (23.1)	2 (10.5)	0 (0)	0 (0)	5 (11.6)	0 (0)	1 (2.1)
No	299 (86.4)	193 (91.0)	106 (79.1)	6 (85.7)	53 (88.3)	10 (76.9)	17 (89.5)	5 (100)	5 (100)	38 (88.4)	13 (100)	46 (97.9)
Oxygen requirement												
Yes	143 (41.3)	82 (38.7)	61 (45.5)	2 (28.6)	20 (33.3)	10 (76.9)	10 (52.6)	0 (0)	1 (20.0)	19 (44.2)	3 (23.1)	17 (36.2)
No	203 (58.7)	130 (61.3)	73 (54.5)	5 (71.4)	40 (66.7)	3 (23.1)	9 (47.4)	5 (100)	4 (80.0)	24 (55.8)	10 (76.9)	30 (63.8)
Bronchodilator administered												
Yes	112 (32.4)	85 (40.1)	27 (20.2)	1 (14.3)	16 (26.7)	9 (69.2)	8 (42.1)	2 (40.0)	0 (0)	27 (62.8)	2 (15.4)	20 (42.6)
No	234 (67.6)	127 (59.9)	107 (79.9)	6 (85.7)	44 (73.3)	4 (30.8)	11 (57.9)	3 (60.0)	5 (100)	16 (37.2)	11 (84.6)	27 (57.5)
Oxygen saturation < 90%												
Yes	108 (31.2)	63 (29.7)	45 (33.6)	1 (14.3)	16 (26.7)	7 (53.9)	6 (31.6)	0 (0)	1 (20.0)	16 (37.2)	3 (23.1)	14 (29.8)
No	238 (68.8)	149 (70.3)	89 (66.4)	6 (85.7)	44 (73.3)	6 (46.2)	13 (68.4)	5 (100)	4 (80.0)	27 (62.8)	10 (76.9)	33 (70.2)

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

Table A17 Clinical characteristics (length of hospitalization) associated with all specimens with accessible medical record information from children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI, without duplicates (n=346)

	Total (n=346)	Positive (n=212)	Negative (n=134)	Ad (n=7)	HRV (n=60)	HBoV (n=13)	hMPV (n=19)	Flu A (n=5)	Flu B (n=5)	RSV (n=43)	All PIV [a] (n=13)	Coinfection (n=47)
UIHC hospitalization Length of stay, days												
N	264	160	104	6	47	13	19	1	1	30	9	34
Median	4.00	3.00	6.00	3.50	3.00	3.00	6.00	5.00	153.00	2.00	2.00	2.00
Mean	18.27	14.12	24.66	3.17	12.64	18.70	34.58	5.00	153.00	8.30	2.89	9.21
Std deviation	45.39	42.04	49.63	1.83	32.43	39.24	88.90	NA	NA	20.51	1.76	29.13
Minimum	<1.00	<1.00	1.00	1.00	<1.00	<1.00	1.00	5.00	153.00	1.00	1.00	1.00
Maximum	377.00	369.00	377.00	5.00	204.00	140.00	369.00	5.00	153.00	112.00	6.00	172.00
Non-ICU days												
N	227	150	77	5	43	11	18	1	1	29	9	34
Median	3.00	2.00	3.00	3.00	2.00	3.00	5.00	5.00	153.00	2.00	2.00	2.00
Mean	6.89	7.41	5.86	2.80	5.40	3.55	28.78	5.00	153.00	2.55	2.89	6.00
Std deviation	25.77	31.21	7.98	1.79	11.83	3.70	85.69	NA	NA	2.23	1.76	11.65
Minimum	<1.00	<1.00	1.00	1.00	<1.00	<1.00	1.00	5.00	153.00	1.00	1.00	1.00
Maximum	369.00	369.00	55.00	5.00	77.00	12.00	369.00	5.00	153.00	11.00	6.00	67.00
ICU days												
N	82	36	46	1	13	6	4	0	0	8	0	3
Median	10.00	5.50	19.50	5.00	5.00	3.50	10.00	NA	NA	9.00	NA	2.00
Mean	39.79	31.86	46.00	5.00	27.85	34.00	54.97	NA	NA	21.88	NA	36.33
Std deviation	61.51	52.11	67.89	NA	55.53	55.06	2.00	NA	NA	37.13	NA	59.47
Minimum	<1.00	<1.00	1.00	5.00	<1.00	1.00	2.00	NA	NA	2.00	NA	2.00
Maximum	377.00	204.00	377.00	5.00	204.00	140.00	117.00	NA	NA	112.00	NA	105.00

Table A17 Continued

	Total (n=346)	Positive (n=212)	Negative (n=134)	Ad (n=7)	HRV (n=60)	HBoV (n=13)	hMPV (n=19)	Flu A (n=5)	Flu B (n=5)	RSV (n=43)	All PIV [a] (n=13)	Coinfection (n=47)
Total hospitalization, days[b]												
N	264	160	104	6	47	13	19	1	1	30	9	34
Median	4.00	3.00	6.00	4.00	3.00	3.00	6.00	5.00	153.00	2.00	2.00	3.00
Mean	19.09	15.36	24.84	3.50	16.00	19.46	34.68	5.00	153.00	8.60	4.56	9.32
Std deviation	46.61	44.26	49.70	2.17	41.39	39.35	88.95	NA	NA	20.48	6.00	29.28
Minimum	<1.00	<1.00	1.00	1.00	<1.00	<1.00	1.00	5.00	153.00	1.00	1.00	1.00
Maximum	377.00	369.00	377.00	6.00	204.00	140.00	369.00	5.00	153.00	112.00	20.00	173.00

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

[b] Includes non-UIHC hospitalizations when applicable.

Table A18 Clinical characteristics (antimicrobial use and inflammation markers) associated with all specimens with accessible medical record information from children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI, without duplicates (n=346)

	Number of Specimens (%)											
	Total (n=346)	**Positive (n=212)**	**Negative (n=134)**	**Ad (n=7)**	**HRV (n=60)**	**HBoV (n=13)**	**hMPV (n=19)**	**Flu A (n=5)**	**Flu B (n=5)**	**RSV (n=43)**	**All PIV [a] (n=13)**	**Coinfection (n=47)**
Antimicrobial use												
Prior use[b]												
Yes	104 (30.1)	64 (30.2)	40 (29.9)	3 (42.9)	22 (36.7)	4 (30.8)	5 (26.3)	1 (20.0)	0 (0)	11 (25.6)	2 (15.4)	16 (34.0)
No	242 (69.9)	148 (69.8)	94 (70.2)	4 (57.1)	38 (63.3)	9 (69.2)	14 (73.7)	4 (80.0)	5 (100)	32 (74.4)	11 (84.6)	31 (66.0)
UIHC administered												
Yes	203 (58.7)	119 (56.1)	84 (62.7)	4 (57.1)	32 (53.3)	10 (76.9)	13 (68.4)	2 (40.0)	2 (40.0)	20 (46.5)	8 (61.5)	28 (59.6)
No	143 (41.3)	93 (43.9)	50 (37.3)	3 (42.9)	28 (46.7)	3 (23.1)	6 (31.6)	3 (60.0)	3 (60.0)	23 (53.5)	5 (38.5)	19 (40.4)
Take-home prescription												
Yes	99 (28.6)	67 (31.6)	32 (23.9)	2 (28.6)	15 (25.0)	4 (30.8)	8 (42.1)	2 (40.0)	1 (20.0)	10 (23.3)	6 (46.2)	19 (40.4)
No	247 (71.4)	145 (68.4)	102 (76.1)	5 (71.4)	45 (75.0)	9 (69.2)	11 (57.9)	3 (60.0)	4 (80.0)	33 (76.7)	7 (53.8)	28 (59.6)
Leukopenia												
Yes	58 (22.0)	34 (21.7)	24 (22.4)	1 (16.7)	7 (15.6)	0 (0)	5 (27.8)	1 (33.3)	2 (100)	8 (28.6)	1 (11.1)	7 (21.2)
No	206 (78.0)	123 (78.3)	83 (77.6)	5 (83.3)	38 (84.4)	13 (100)	13 (72.2)	2 (66.7)	0 (0)	20 (71.4)	8 (88.9)	26 (78.8)
Missing	82	55	27	1	15	0	1	2	3	15	2	14
Leukocytosis												
Yes	71 (26.9)	40 (25.5)	31 (29.0)	2 (33.3)	12 (26.7)	8 (61.5)	5 (27.8)	0 (0)	0 (0)	5 (17.9)	1 (11.1)	7 (21.2)
No	193 (73.1)	117 (74.7)	76 (71.0)	4 (66.7)	33 (73.3)	5 (38.5)	13 (72.2)	3 (100)	2 (100)	23 (82.1)	8 (88.9)	26 (78.8)
Missing	82	55	27	1	15	0	1	2	3	15	2	14
CRP > 0.5 mg/dl												
Yes	147 (68.7)	87 (71.3)	60 (65.2)	5 (100)	24 (66.7)	10 (83.3)	11 (73.3)	1 (100)	1 (100)	14 (60.9)	7 (87.5)	14 (66.7)
No	67 (31.3)	35 (28.7)	32 (34.8)	0 (0)	12 (33.3)	2 (16.7)	4 (26.7)	0 (0)	0 (0)	9 (39.1)	1 (12.5)	7 (33.3)
Missing	132	90	42	2	24	1	4	4	4	20	5	26

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

[b] Denotes antibiotics used prior to UIHC episode during which specimen was collected.

Table A19 Clinical characteristics (diagnoses) associated with all specimens with accessible medical record information from children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI, without duplicates (n=346)

	Number of Specimens (%)											
	Total (n=346)	**Positive (n=212)**	**Negative (n=134)**	**Ad (n=7)**	**HRV (n=60)**	**HBoV (n=13)**	**hMPV (n=19)**	**Flu A (n=5)**	**Flu B (n=5)**	**RSV (n=43)**	**All PIV [a] (n=13)**	**Coinfection (n=47)**
ARTI												
None	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Physician diagnosed	156 (45.1)	134 (63.2)	78 (58.2)	5 (71.4)	33 (55.0)	7 (53.9)	15 (79.0)	3 (60.0)	1 (20.0)	35 (81.4)	5 (38.5)	30 (63.8)
Physician documented symptoms	190 (54.9)	78 (36.8)	56 (41.8)	2 (28.6)	27 (45.0)	6 (46.2)	4 (21.1)	2 (40.0)	4 (80.0)	8 (18.6)	8 (61.5)	17 (36.2)
Concern for ARTI without traditional symptoms	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Diagnosis												
Bronchiolitis												
Yes	45 (13.0)	40 (18.9)	5 (3.7)	0 (0)	4 (6.7)	2 (15.4)	3 (15.8)	0 (0)	0 (0)	21 (48.8)	1 (7.7)	9 (19.2)
No	301 (87.0)	172 (81.1)	129 (96.3)	7 (100)	56 (93.3)	11 (84.6)	16 (84.2)	5 (100)	5 (100)	22 (51.2)	12 (92.3)	38 (80.9)
Pneumonia												
Yes	87 (25.1)	53 (25.0)	34 (25.4)	1 (14.3)	11 (18.3)	5 (38.5)	9 (47.4)	0 (0)	0 (0)	10 (23.3)	1 (7.7)	15 (31.9)
No	259 (74.9)	159 (75.0)	100 (74.6)	6 (85.7)	49 (81.7)	8 (61.5)	10 (52.6)	5 (100)	5 (100)	33 (76.7)	12 (92.3)	32 (68.1)
Respiratory tract infection												
Yes	106 (30.6)	65 (30.7)	41 (30.6)	5 (71.4)	25 (41.7)	3 (23.1)	7 (36.8)	1 (20.0)	1 (20.0)	7 (16.3)	5 (38.5)	11 (23.4)
No	240 (69.4)	147 (69.3)	93 (69.4)	2 (28.6)	35 (58.3)	10 (76.9)	12 (63.2)	4 (80.0)	4 (80.0)	36 (83.7)	8 (61.5)	36 (76.6)

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

Table A20 Clinical characteristics (symptoms) associated with all specimens with accessible medical record information from children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI, without duplicates (n=346)

	Number of Specimens (%)											
	Total (n=346)	**Positive (n=212)**	**Negative (n=134)**	**Ad (n=7)**	**HRV (n=60)**	**HBoV (n=13)**	**hMPV (n=19)**	**Flu A (n=5)**	**Flu B (n=5)**	**RSV (n=43)**	**All PIV [a] (n=13)**	**Coinfection (n=47)**
Fever												
Yes	203 (58.7)	125 (59.0)	78 (58.2)	6 (85.7)	26 (43.3)	7 (53.9)	18 (94.7)	5 (100)	5 (100)	22 (51.2)	4 (30.8)	27 (57.5)
No	143 (41.3)	87 (41.0)	56 (41.8)	1 (14.3)	34 (56.7)	6 (46.2)	1 (5.3)	0 (0)	0 (0)	21 (48.8)	9 (69.2)	20 (42.6)
Nasal												
Yes	163 (47.1)	114 (53.8)	49 (36.6)	5 (71.4)	30 (50.0)	6 (46.2)	10 (52.6)	4 (80.0)	3 (60.0)	22 (51.2)	5 (38.5)	29 (61.7)
No	183 (52.9)	98 (46.2)	85 (63.4)	2 (28.6)	30 (50.0)	7 (53.9)	9 (47.4)	1 (20.0)	2 (40.0)	21 (48.8)	8 (61.5)	18 (38.3)
Cough												
Yes	214 (61.9)	149 (70.3)	65 (48.5)	5 (71.4)	34 (56.7)	8 (61.5)	17 (89.5)	5 (100)	4 (80.0)	28 (65.1)	9 (69.2)	39 (83.0)
No	132 (38.2)	63 (29.7)	69 (51.5)	2 (28.6)	26 (43.3)	5 (38.5)	2 (10.5)	0 (0)	1 (20.0)	15 (34.9)	4 (30.8)	8 (17.0)
Wheeze												
Yes	73 (21.1)	61 (28.8)	12 (9.0)	1 (14.3)	17 (28.3)	5 (38.5)	5 (26.3)	1 (20.0)	0 (0)	16 (37.2)	2 (15.4)	14 (29.8)
No	273 (78.9)	151 (71.2)	122 (91.0)	6 (85.7)	43 (71.7)	8 (61.5)	14 (73.7)	4 (80.0)	5 (100)	27 (62.8)	11 (84.6)	33 (70.2)
Tachypnea												
Yes	28 (8.1)	20 (9.4)	8 (6.0)	0 (0)	5 (8.3)	3 (23.1)	3 (15.8)	0 (0)	0 (0)	3 (7.0)	2 (15.4)	4 (8.5)
No	318 (91.9)	192 (90.6)	126 (94.0)	7(100)	55 (91.7)	10 (76.9)	16 (84.2)	5 (100)	5 (100)	40 (93.0)	11 (84.6)	43 (91.5)
Increased work of breathing												
Yes	89 (25.7)	63 (29.7)	26 (19.4)	1 (14.3)	18 (30.0)	4 (30.8)	5 (26.3)	0 (0)	0 (0)	18 (41.9)	4 (30.8)	13 (27.7)
No	257 (74.3)	149 (70.3)	108 (80.6)	6 (85.7)	42 (70.0)	9 (69.2)	14 (73.7)	5 (100)	5 (100)	25 (58.1)	9 (69.2)	34 (72.3)
Gastrointestinal												
Yes	122 (35.3)	80 (37.7)	42 (31.3)	2 (28.6)	18 (30.0)	2 (15.4)	10 (52.6)	2 (40.0)	2 (40.0)	23 (53.5)	4 (30.8)	17 (36.2)
No	224 (64.7)	132 (62.3)	92 (68.7)	5 (71.4)	42 (70.0)	11 (84.6)	9 (47.4)	3 (60.0)	3 (60.0)	20 (46.5)	9 (69.2)	30 (63.8)

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

Table A21 Clinical characteristics (medical history) associated with all specimens with accessible medical record information from children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI, without duplicates (n=346)

	Number of Specimens (%)											
	Total (n=346)	**Positive (n=212)**	**Negative (n=134)**	**Ad (n=7)**	**HRV (n=60)**	**HBoV (n=13)**	**hMPV (n=19)**	**Flu A (n=5)**	**Flu B (n=5)**	**RSV (n=43)**	**All PIV [a] (n=13)**	**Coinfection (n=47)**
Respiratory condition												
Any												
Yes	119 (34.4)	76 (35.9)	43 (32.1)	1 (14.3)	27 (45.0)	6 (46.2)	4 (21.1)	4 (80.0)	1 (20.0)	13 (30.2)	3 (23.1)	17 (36.2)
No	227 (65.6)	136 (64.2)	91 (67.9)	6 (85.7)	33 (55.0)	7 (53.9)	15 (79.0)	1 (20.0)	4 (80.0)	30 (69.8)	10 (76.9)	30 (63.8)
Asthma												
Yes	46 (13.3)	32 (15.1)	14 (10.5)	1 (14.3)	11 (18.3)	2 (15.4)	0 (0)	3 (60.0)	0 (0)	8 (18.6)	1 (7.7)	6 (12.8)
No	300 (86.7)	180 (84.9)	120 (89.6)	6 (85.7)	49 (81.7)	11 (84.6)	19 (100)	2 (40.0)	5 (100)	35 (81.4)	12 (92.3)	41 (87.2)
Structural defect												
Yes	61 (17.6)	43 (20.3)	18 (13.4)	0 (0)	16 (26.7)	4 (30.8)	3 (15.8)	0 (0)	0 (0)	7 (16.3)	2 (15.4)	11 (23.4)
No	285 (82.4)	169 (79.7)	116 (86.6)	7 (100)	44 (73.3)	9 (69.2)	16 (84.2)	5 (100)	5 (100)	36 (83.7)	11 (84.6)	36 (76.6)
Other medical condition												
Prematurity												
Yes	64 (18.5)	37 (17.5)	27 (20.2)	0 (0)	12 (20.0)	6 (46.2)	3 (15.8)	1 (20.0)	1 (20.0)	5 (11.6)	3 (23.1)	6 (12.8)
No	282 (81.5)	175 (82.6)	107 (79.9)	7 (100)	48 (80.0)	7 (53.9)	16 (84.2)	4 (80.0)	4 (80.0)	38 (88.4)	10 (76.9)	41 (87.2)
Cancer												
Yes	28 (8.1)	17 (8.0)	11 (8.2)	0 (0)	5 (8.3)	0 (0)	2 (10.5)	1 (20.0)	0 (0)	4 (9.3)	1 (7.7)	4 (8.5)
No	318 (91.9)	195 (92.0)	123 (91.8)	7 (100)	55 (91.7)	13 (100)	17 (89.5)	4 (80.0)	5 (100)	39 (90.7)	12 (92.3)	43 (91.5)
Transplant												
Yes	9 (2.6)	5 (2.4)	4 (3.0)	0 (0)	4 (6.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.1)
No	337 (97.4)	207 (97.6)	130 (97.0)	7 (100)	56 (93.3)	13 (100)	19 (100)	5 (100)	5 (100)	43 (100)	13 (100)	46 (97.8)
Immunocompromised[b]												
Yes	108 (31.2)	65 (30.7)	43 (32.1)	1 (14.3)	19 (31.7)	1 (7.7)	8 (42.1)	1 (20.0)	3 (60.0)	12 (27.9)	2 (15.4)	19 (40.4)
No	238 (68.8)	147 (69.3)	91 (67.9)	6 (85.7)	41 (68.3)	12 (92.3)	11 (57.9)	4 (80.0)	2 (40.0)	31 (72.1)	11 (84.6)	28 (59.6)

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

[b] Includes history of cancer, transplant, and chronic conditions that may lead to increased risk of ARTI (see Table 2).

Table A22 Laboratory characteristics of specimens with accessible medical record information from children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI, without duplicates (n=346)

	Number of Specimens (%)											
	Total (n=346)	**Positive (n=212)**	**Negative (n=134)**	**Ad (n=7)**	**HRV (n=60)**	**HBoV (n=13)**	**hMPV (n=19)**	**Flu A (n=5)**	**Flu B (n=5)**	**RSV (n=43)**	**All PIV[a] (n=13)**	**Coinfection (n=47)**
Month												
Mar 08	19 (5.5)	14 (6.6)	5 (3.7)	0 (0)	4 (6.7)	1 (7.7)	1 (5.3)	0 (0)	1 (20.0)	2 (4.7)	3 (23.1)	2 (4.3)
Apr 08 - Jun 08	73 (21.1)	48 (22.6)	25 (18.7)	2 (28.6)	12 (20.0)	3 (23.1)	8 (42.1)	0 (0)	0 (0)	3 (7.0)	4 (30.8)	16 (34.0)
Jul 08 - Sep 08	24 (6.9)	14 (6.6)	10 (7.5)	1 (14.3)	11 (18.3)	1 (7.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.1)
Oct 08 - Dec 08	61 (17.6)	29 (13.7)	32 (23.9)	2 (28.6)	9 (15.0)	3 (23.1)	1 (5.3)	0 (0)	0 (0)	5 (11.6)	1 (7.7)	8 (17.0)
Jan 09 - Mar 09	112 (32.4)	71 (33.5)	41 (30.6)	1 (14.3)	11 (18.3)	3 (23.1)	7 (36.8)	5 (100)	4 (80.0)	31 (72.1)	1 (7.7)	8 (17.0)
Apr 09 - Jun 09	57 (16.5)	36 (17.0)	21 (15.7)	1 (14.3)	13 (21.7)	2 (15.4)	2 (10.5)	0 (0)	0 (0)	2 (4.7)	4 (30.8)	12 (25.5)
Source												
Nasal wash	297 (87.4)	192 (91.9)	105 (80.2)	6 (85.7)	48 (82.8)	10 (83.3)	17 (89.5)	5 (100)	5 (100)	41 (95.4)	13 (100)	47 (100)
Bronch lavage	10 (2.9)	2 (1.0)	8 (6.1)	0 (0)	2 (3.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Trach aspirate	27 (7.9)	12 (5.7)	15 (11.5)	0 (0)	6 (10.3)	2 (16.7)	2 (10.5)	0 (0)	0 (0)	2 (4.7)	0 (0)	0 (0)
Other[b]	6 (1.8)	3 (1.4)	4 (3.1)	1 (14.3)	2 (3.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Missing	6	3	3	0	2	1	0	0	0	0	0	0

Note: Excludes 3 specimens for which medical record information was inaccessible. Percentages may not add to 100.0 due to rounding. Virus-specific estimates exclude coinfections.

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

[b] Other may include bronchial wash/biopsy, nasal swab, THS, tissue biopsy.

Table A23 Demographic characteristics of children with accessible medical record information and confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI or concern for ARTI in the absence of traditional symptoms, without duplicates (n=392)

	Number of Specimens (%)											
	Total (n=392)	**Positive (n=224)**	**Negative (n=168)**	**Ad (n=7)**	**HRV (n=64)**	**HBoV (n=14)**	**hMPV (n=19)**	**Flu A (n=5)**	**Flu B (n=6)**	**RSV (n=47)**	**All PIV[a] (n=14)**	**Coinfection (n=48)**
Gender												
Female	180 (45.9)	102 (45.5)	78 (46.4)	3 (42.9)	30 (46.9)	7 (50.0)	11 (57.9)	2 (40.0)	1 (16.7)	22 (46.8)	7 (50.0)	19 (39.6)
Male	212 (54.1)	122 (54.5)	90 (53.6)	4 (57.1)	34 (53.1)	7 (50.0)	8 (42.1)	3 (60.0)	5 (83.3)	25 (53.2)	7 (50.0)	29 (60.4)
Age (years)												
0 to < 0.5	146 (37.2)	73 (32.6)	73 (43.5)	1 (14.3)	24 (37.5)	1 (7.1)	6 (31.6)	0 (0)	1 (16.7)	23 (48.9)	5 (35.7)	12 (25.0)
0.5 to < 1	45 (11.5)	38 (17.0)	7 (4.2)	3 (42.9)	10 (15.6)	4 (28.6)	5 (26.3)	0 (0)	0 (0)	5 (10.6)	1 (7.1)	10 (20.8)
1 to < 5	147 (37.5)	84 (37.5)	63 (37.5)	2 (28.6)	19 (29.7)	7 (50.0)	6 (31.6)	4 (80.0)	2 (33.3)	17 (36.2)	7 (50.0)	20 (41.7)
≥ 5	54 (13.8)	29 (13.0)	25 (14.9)	1 (14.3)	11 (17.2)	2 (14.3)	2 (10.5)	1 (20.0)	3 (50.0)	2 (4.3)	1 (7.1)	6 (12.5)
Race												
Caucasian	261 (72.5)	153 (73.9)	108 (70.6)	4 (66.7)	42 (72.4)	10 (71.4)	15 (88.2)	4 (80.0)	6 (100)	29 (64.4)	11 (84.6)	32 (74.4)
African-American	41 (11.4)	22 (10.6)	19 (12.4)	2 (33.3)	7 (12.1)	2 (14.3)	1 (5.9)	0 (0)	0 (0)	7 (15.6)	0 (0)	3 (7.0)
Hispanic	34 (9.4)	20 (9.7)	14 (9.2)	0 (0)	6 (10.3)	1 (7.1)	1 (5.9)	1 (20.0)	0 (0)	6 (13.3)	2 (15.4)	3 (7.0)
Other	24 (6.7)	12 (5.8)	12 (7.8)	0 (0)	3 (5.2)	1 (7.1)	0 (0)	0 (0)	0 (0)	3 (6.7)	0 (0)	5 (11.6)
Missing	32	17	15	1	6	0	2	0	0	2	1	5
Medicaid												
Yes	187 (48.1)	105 (47.3)	82 (49.1)	1 (16.7)	31 (48.4)	4 (28.6)	10 (52.6)	0 ()	2 (33.3)	26 (56.5)	8 (57.1)	23 (47.9)
No	202 (51.9)	117 (52.7)	85 (50.1)	5 (83.3)	33 (51.6)	10 (71.4)	9 (47.4)	5 (100)	4 (66.7)	20 (43.5)	6 (42.9)	25 (52.1)
Missing	3	2	1	1	0	0	0	0	0	1	0	0
Urban/Rural												
Urban	236 (60.4)	137 (61.2)	99 (59.3)	4 (57.1)	43 (67.2)	9 (64.3)	7 (36.8)	5 (100)	2 (33.3)	33 (70.2)	7 (50.0)	27 (56.3)
Large rural	61 (15.6)	32 (14.3)	29 (17.4)	1 (14.3)	6 (9.4)	1 (7.1)	7 (36.8)	0 (0)	2 (33.3)	5 (10.6)	2 (14.3)	8 (16.7)
Small rural	46 (11.8)	28 (12.5)	18 (10.8)	1 (14.3)	7 (10.9)	2 (14.3)	3 (15.8)	0 (0)	0 (0)	7 (14.9)	3 (21.4)	5 (10.4)
Isolated rural	48 (12.3)	27 (12.1)	21 (12.6)	1 (14.3)	8 (12.5)	2 (14.3)	2 (10.5)	0 (0)	2 (33.3)	2 (4.3)	2 (14.3)	8 (16.7)
Missing	1	0	1	0	0	0	0	0	0	0	0	0

Table A23 Continued

	Number of Specimens (%)											
	Total (n=392)	**Positive (n=224)**	**Negative (n=168)**	**Ad (n=7)**	**HRV (n=64)**	**HBoV (n=14)**	**hMPV (n=19)**	**Flu A (n=5)**	**Flu B (n=6)**	**RSV (n=47)**	**All PIV [a] (n=14)**	**Coinfection (n=48)**
Smoke exposure												
None	107 (66.5)	63 (63.0)	44 (72.1)	3 (75.0)	16 (69.6)	4 (57.1)	3 (37.5)	2 (66.7)	1 (50.0)	14 (66.7)	6 (85.7)	14 (56.0)
Direct	17 (10.6)	9 (9.0)	8 (13.1)	0 (0)	1 (4.4)	0 (0)	2 (25.0)	0 (0)	1 (50.0)	1 (4.8)	0 (0)	4 (16.0)
Indirect	37 (23.0)	28 (28.0)	9 (14.8)	1 (25.0)	6 (26.1)	3 (42.9)	3 (37.5)	1 (33.3)	0 (0)	6 (28.6)	1 (14.3)	7 (28.0)
Missing	231	124	107	3	41	7	11	2	4	26	7	23

Note: Excludes 13 specimens for which medical record information was inaccessible. Percentages may not add to 100.0 due to rounding. Virus-specific estimates exclude coinfections.

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

Table A24 Mean age of children for specimens with accessible medical record information and with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI or concern for ARTI in the absence of traditional symptoms, without duplicates (n=392)

	Total (n=392)	Positive (n=224)	Negative (n=168)	Ad (n=7)	HRV (n=64)	HBoV (n=14)	hMPV (n=19)	Flu A (n=5)	Flu B (n=6)	RSV (n=47)	All PIV [a] (n=14)	Coinfection (n=48)
Age (years)												
Mean	2.09	2.03	2.17	2.04	2.19	2.08	1.87	4.44	4.35	1.28	1.86	2.11
Std deviation	2.52	2.37	2.71	2.99	2.65	1.99	1.97	2.60	2.85	1.62	1.91	2.56
Minimum	0.00	0.01	0.00	0.01	0.03	0.23	0.13	1.51	0.31	0.02	0.06	0.10
Maximum	9.79	9.73	9.80	8.64	9.73	6.94	6.13	8.59	7.31	7.44	6.71	9.62

Note: Excludes 13 specimens for which medical record information was inaccessible. Percentages may not add to 100.0 due to rounding. Virus-specific estimates exclude coinfections.

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

Table A25 Clinical characteristics (indicators of severity) associated with specimens with accessible medical record information from children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI or concern for ARTI in the absence of traditional symptoms, without duplicates (n=392)

	Number of Specimens (%)											
	Total (n=392)	**Positive (n=224)**	**Negative (n=168)**	**Ad (n=7)**	**HRV (n=64)**	**HBoV (n=14)**	**hMPV (n=19)**	**Flu A (n=5)**	**Flu B (n=6)**	**RSV (n=47)**	**All PIV[a] (n=14)**	**Coinfection (n=48)**
Inpatient												
Yes	305 (77.8)	170 (75.9)	135 (80.4)	6 (85.7)	50 (78.1)	14 (100)	19 (100)	1 (20.0)	1 (16.7)	34 (72.3)	10 (71.4)	35 (72.9)
No	87 (22.2)	54 (24.1)	33 (19.6)	1 (14.3)	14 (21.9)	0 (0)	0 (0)	4 (80.0)	5 (83.3)	13 (27.7)	4 (28.6)	13 (27.1)
ICU admission, if hospitalized												
Ever	117 (38.4)	44 (25.9)	73 (54.1)	1 (16.7)	15 (30.0)	7 (50.0)	4 (21.1)	0 (0)	1 (100)	12 (64.7)	0 (0)	4 (11.4)
Never	188 (61.6)	126 (74.1)	62 (45.9)	5 (83.3)	35 (70.0)	7 (50.0)	15 (79.0)	1 (100)	0 (0)	22 (35.3)	10 (100)	31 (88.6)
ICU at collection												
Yes	109 (35.7)	42 (24.7)	67 (49.6)	1 (16.7)	15 (30.0)	6 (42.9)	3 (15.8)	0 (0)	1 (100)	12 (35.3)	0 (0)	4 (11.4)
No	196 (64.3)	128 (75.3)	68 (50.4)	5 (83.3)	35 (70.0)	8 (57.1)	16 (84.2)	1 (100)	0 (0)	22 (64.7)	10 (100)	31 (88.6)
Mechanically ventilated												
Yes	65 (16.6)	22 (9.8)	43 (25.6)	1 (14.3)	7 (10.9)	3 (21.4)	2 (10.5)	0 (0)	0 (0)	8 (17.0)	0 (0)	1 (2.1)
No	327 (83.4)	202 (90.2)	125 (74.4)	6 (85.7)	57 (89.1)	11 (78.6)	17 (89.5)	5 (100)	6 (100)	39 (83.0)	14 (100)	47 (97.9)
Oxygen requirement												
Yes	176 (44.9)	89 (39.7)	87 (51.8)	2 (28.6)	21 (32.8)	11 (78.6)	10 (52.6)	0 (0)	1 (16.7)	23 (48.9)	3 (21.4)	18 (37.5)
No	216 (55.1)	135 (60.3)	81 (48.2)	5 (71.4)	43 (67.2)	3 (21.4)	9 (47.4)	5 (100)	5 (83.3)	24 (51.1)	11 (78.6)	30 (62.5)
Bronchodilator administered												
Yes	113 (28.8)	86 (38.4)	27 (16.1)	1 (14.3)	17 (26.6)	9 (64.3)	8 (42.1)	2 (40.0)	0 (0)	27 (57.5)	2 (14.3)	20 (41.7)
No	279 (71.2)	138 (61.6)	141 (83.9)	6 (85.7)	47 (73.4)	5 (35.7)	11 (57.9)	3 (60.0)	6 (100)	20 (42.6)	12 (85.7)	28 (58.3)
Oxygen saturation < 90%												
Yes	132 (33.7)	68 (30.4)	64 (38.1)	1 (14.3)	17 (26.6)	7 (50.0)	6 (31.6)	0 (0)	1 (16.7)	19 (40.4)	2 (14.3)	15 (31.3)
No	260 (66.3)	156 (69.6)	104 (61.9)	6 (85.7)	47 (73.4)	7 (50.0)	13 (68.4)	5 (100)	5 (83.3)	28 (59.6)	12 (85.7)	33 (68.8)

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

Table A26 Clinical characteristics (length of hospitalization) associated with specimens with accessible medical record information from children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI or concern for ARTI in the absence of traditional symptoms, without duplicates (n=392)

	Total (n=392)	Positive (n=224)	Negative (n=168)	Ad (n=7)	HRV (n=64)	HBoV (n=14)	hMPV (n=19)	Flu A (n=5)	Flu B (n=6)	RSV (n=47)	All PIV[a] (n=14)	Coinfection (n=48)
UIHC hospitalization Length of stay, days												
N	305	170	135	6	50	14	19	1	1	34	10	35
Median	4.00	3.00	8.00	3.50	3.00	4.50	6.00	5.00	153.00	2.50	2.50	2.50
Mean	22.33	15.49	30.95	3.17	12.36	23.93	34.58	5.00	153.00	14.62	2.90	9.17
Std deviation	47.06	42.11	51.51	1.83	31.48	42.49	88.90	NA	NA	27.89	1.66	28.70
Minimum	<1.00	<1.00	1.00	1.00	<1.00	<1.00	1.00	5.00	153.00	1.00	1.00	1.00
Maximum	377.00	369.00	377.00	5.00	204.00	140.00	369.00	5.00	153.00	112.00	6.00	172.00
Non-ICU days												
N	245	157	88	5	46	11	18	1	1	31	10	35
Median	3.00	2.00	3.00	3.00	2.00	3.00	5.00	5.00	153.00	2.00	2.50	2.50
Mean	6.97	7.40	6.19	2.80	5.20	3.55	28.78	5.00	153.00	3.52	2.90	5.97
Std deviation	24.87	30.53	7.91	1.79	11.45	3.70	85.69	NA	NA	4.33	1.66	11.48
Minimum	<1.00	<1.00	1.00	1.00	<1.00	<1.00	1.00	5.00	153.00	1.00	1.00	1.00
Maximum	369.00	369.00	55.00	5.00	77.00	12.00	369.00	5.00	153.00	19.00	6.00	67.00
ICU days												
N	117	44	73	1	15	7	4	0	0	12	0	4
Median	17.00	9.00	30.00	5.00	5.00	4.00	10.00	NA	NA	15.50	NA	2.50
Mean	43.65	33.45	49.79	5.00	25.27	42.29	54.97	NA	NA	32.3	NA	28.00
Std deviation	58.21	49.97	62.18	NA	51.89	55.68	2.00	NA	NA	39.70	NA	51.34
Minimum	<1.00	<1.00	1.00	5.00	<1.00	1.00	2.00	NA	NA	2.00	NA	2.00
Maximum	377.00	204.00	377.00	5.00	204.00	140.00	117.00	NA	NA	112.00	NA	105.00

Table A26 Continued

	Total (n=392)	Positive (n=224)	Negative (n=168)	Ad (n=7)	HRV (n=64)	HBoV (n=14)	hMPV (n=19)	Flu A (n=5)	Flu B (n=6)	RSV (n=47)	All PIV[a] (n=14)	Coinfection (n=48)
Total hospitalization, days[b]												
N	305	170	135	6	50	14	19	1	1	34	10	35
Median	5.00	3.00	8.00	4.00	3.00	4.50	6.00	5.00	153.00	3.00	2.50	3.00
Mean	23.14	16.72	31.23	3.50	15.7	24.64	34.68	5.00	153.00	14.88	4.40	9.29
Std deviation	48.01	44.16	51.50	2.17	40.20	42.49	88.95	NA	NA	27.81	5.68	28.85
Minimum	<1.00	<1.00	1.00	1.00	<1.00	<1.00	1.00	5.00	153.00	1.00	1.00	1.00
Maximum	377.00	369.00	377.00	6.00	204.00	140.00	369.00	5.00	153.00	112.00	20.00	173.00

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

[b] Includes non-UIHC hospitalizations when applicable.

Table A27 Clinical characteristics (antimicrobial use and inflammation markers) associated with specimens with accessible medical record information from children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI or concern for ARTI in the absence of traditional symptoms, without duplicates (n=392)

	Number of Specimens (%)											
	Total (n=392)	**Positive (n=224)**	**Negative (n=168)**	**Ad (n=7)**	**HRV (n=64)**	**HBoV (n=14)**	**hMPV (n=19)**	**Flu A (n=5)**	**Flu B (n=6)**	**RSV (n=47)**	**All PIV[a] (n=14)**	**Coinfection (n=48)**
Antimicrobial use												
Prior use[b]												
Yes	117 (29.9)	68 (30.4)	49 (29.2)	3 (42.9)	22 (34.4)	4 (28.6)	5 (26.3)	1 (20.0)	0 (0)	15 (31.9)	2 (14.3)	16 (33.3)
No	275 (70.2)	156 (69.6)	119 (70.8)	4 (57.1)	42 (65.6)	10 (71.4)	14 (73.7)	4 (80.0)	6 (100)	32 (68.1)	12 (85.7)	32 (66.7)
UIHC administered												
Yes	239 (61.0)	127 (56.7)	112 (66.7)	4 (57.1)	35 (54.7)	10 (71.4)	13 (68.4)	2 (40.0)	3 (50.0)	23 (48.9)	8 (57.1)	29 (60.4)
No	153 (39.0)	97 (43.3)	56 (3.3)	3 (42.9)	29 (45.3)	4 (28.6)	6 (31.6)	3 (60.0)	3 (50.0)	24 (51.1)	6 (42.9)	19 (39.6)
Take-home prescription												
Yes	104 (26.5)	69 (30.8)	35 (20.8)	2 (28.6)	17 (26.6)	4 (28.6)	8 (42.1)	2 (40.0)	1 (16.7)	10 (21.3)	6 (42.9)	19 (39.6)
No	288 (73.5)	155 (69.2)	133 (79.2)	5 (71.4)	47 (73.4)	10 (71.4)	11 (57.9)	3 (60.0)	5 (83.3)	37 (78.7)	8 (57.1)	29 (60.4)
Leukopenia												
Yes	71 (23.5)	38 (22.9)	33 (24.3)	1 (16.7)	8 (16.7)	0 (0)	5 (27.8)	1 (33.3)	3 (100)	10 (32.3)	3 (30.0)	7 (20.6)
No	231 (76.5)	128 (77.1)	103 (75.7)	5 (83.3)	40 (83.3)	13 (100)	13 (72.2)	2 (66.7)	0 (0)	21 (67.7)	7 (70.0)	27 (79.4)
Missing	90	58	32	1	16	1	1	2	3	16	4	14
Leukocytosis												
Yes	79 (26.2)	41 (24.7)	38 (27.9)	2 (33.3)	13 (27.1)	8 (61.5)	5 (27.8)	0 (0)	0 (0)	5 (16.1)	1 (10.0)	7 (20.6)
No	223 (73.8)	125 (75.3)	98 (72.1)	4 (66.7)	35 (72.9)	5 (38.5)	13 (72.2)	3 (100)	3 (100)	26 (83.9)	9 (90.0)	27 (79.4)
Missing	90	58	32	1	16	1	1	2	3	16	4	14
CRP > 0.5 mg/dl												
Yes	170 (67.5)	91 (69.5)	79 (65.3)	5 (100)	24 (61.5)	10 (83.3)	11 (73.3)	1 (100)	2 (100)	15 (57.7)	8 (88.9)	15 (68.2)
No	82 (32.5)	40 (30.5)	42 (34.7)	0 (0)	15 (38.5)	2 (16.7)	4 (26.7)	0 (0)	0 (0)	11 (42.3)	1 (11.1)	7 (31.8)
Missing	140	93	47	2	25	2	4	4	4	21	5	26

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

[b] Denotes antibiotics used prior to UIHC episode during which specimen was collected.

Table 28 Clinical characteristics (diagnoses) associated with specimens with accessible medical record information from children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI or concern for ARTI in the absence of traditional symptoms, without duplicates (n=392)

	Number of Specimens (%)											
	Total (n=392)	**Positive (n=224)**	**Negative (n=168)**	**Ad (n=7)**	**HRV (n=64)**	**HBoV (n=14)**	**hMPV (n=19)**	**Flu A (n=5)**	**Flu B (n=6)**	**RSV (n=47)**	**All PIV[a] (n=14)**	**Coinfection (n=48)**
ARTI												
None	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Physician diagnosed	156 (48.5)	134 (59.8)	56 (33.3)	5 (71.4)	33 (51.6)	7 (50.0)	15 (79.0)	3 (60.0)	1 (16.7)	35 (74.5)	5 (35.7)	30 (62.5)
Physician documented symptoms	190 (39.8)	78 (34.8)	78 (46.4)	2 (28.6)	27 (42.2)	6 (42.9)	4 (21.1)	2 (40.0)	4 (66.7)	8 (17.0)	8 (57.1)	17 (35.4)
Concern for ARTI without traditional symptoms	46 (11.7)	12 (5.4)	34 (20.2)	0 (0)	4 (6.3)	1 (7.1)	0 (0)	0 (0)	1 (16.7)	4 (8.5)	1 (7.1)	1 (2.1)
Diagnosis												
Bronchiolitis												
Yes	45 (11.5)	40 (17.9)	5 (3.0)	0 (0)	4 (6.3)	2 (14.3)	3 (15.8)	0 (0)	0 (0)	21 (44.7)	1 (7.1)	9 (18.8)
No	347 (88.5)	184 (82.1)	163 (97.0)	7 (100)	60 (93.8)	12 (85.7)	16 (84.2)	5 (100)	6 (100)	26 (55.3)	13 (92.9)	39 (81.3)
Pneumonia												
Yes	87 (22.2)	53 (23.7)	34 (20.2)	1 (14.3)	11 (17.2)	5 (35.7)	9 (47.4)	0 (0)	0 (0)	10 (21.3)	2 (14.3)	15 (31.3)
No	305 (77.8)	171 (76.3)	134 (79.8)	6 (85.7)	53 (82.8)	9 (64.3)	10 (52.6)	5 (100)	6 (100)	37 (78.7)	12 (85.7)	33 (68.8)
Respiratory tract infection												
Yes	106 (27.0)	65 (29.0)	41 (24.4)	5 (71.4)	25 (39.1)	3 (21.4)	7 (36.8)	1 (20.0)	1 (16.7)	7 (14.9)	5 (35.7)	11 (22.9)
No	286 (73.0)	159 (71.0)	127 (75.6)	2 (28.6)	39 (60.9)	11 (78.6)	12 (63.2)	4 (80.0)	5 (83.3)	40 (85.1)	9 (64.3)	37 (77.1)

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

Table A29 Clinical characteristics (symptoms) associated with specimens with accessible medical record information from children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI or concern for ARTI in the absence of traditional symptoms, without duplicates (n=392)

	Number of Specimens (%)											
	Total (n=392)	**Positive (n=224)**	**Negative (n=168)**	**Ad (n=7)**	**HRV (n=64)**	**HBoV (n=14)**	**hMPV (n=19)**	**Flu A (n=5)**	**Flu B (n=6)**	**RSV (n=47)**	**All PIV[a] (n=14)**	**Coinfection (n=48)**
Fever												
Yes	219 (55.9)	131 (58.5)	88 (52.4)	6 (85.7)	28 (43.8)	7 (50.0)	18 (94.7)	5 (100)	6 (100)	23 (48.9)	4 (28.6)	28 (58.3)
No	173 (44.1)	93 (41.5)	80 (47.6)	1 (14.3)	36 (56.3)	7 (50.0)	1 (5.3)	0 (0)	0 (0)	24 (51.1)	10 (71.4)	20 (41.7)
Nasal												
Yes	164 (41.8)	114 (50.9)	50 (29.8)	5 (71.4)	30 (46.9)	6 (42.9)	10 (52.6)	4 (80.0)	3 (50.0)	22 (46.8)	5 (35.7)	29 (60.4)
No	228 (58.2)	110 (49.1)	118 (70.2)	2 (28.6)	34 (53.1)	8 (57.1)	9 (47.4)	1 (20.0)	3 (50.0)	25 (53.2)	9 (64.3)	19 (39.6)
Cough												
Yes	216 (55.1)	150 (67.0)	66 (39.3)	5 (71.4)	35 (54.7)	8 (57.1)	17 (89.5)	5 (100)	4 (66.7)	28 (59.6)	9 (64.3)	39 (81.3)
No	176 (44.9)	74 (33.0)	102 (60.7)	2 (28.6)	29 (45.3)	6 (42.9)	2 (10.5)	0 (0)	2 (33.3)	19 (40.4)	5 (35.7)	9 (18.8)
Wheeze												
Yes	74 (18.9)	62 (27.7)	12 (7.1)	1 (14.3)	18 (28.1)	5 (35.7)	5 (26.3)	1 (20.0)	0 (0)	16 (34.0)	2 (14.3)	14 (29.2)
No	318 (81.1)	162 (72.3)	156 (92.9)	6 (85.7)	46 (71.9)	9 (64.3)	14 (73.7)	4 (80.0)	6 (100)	31 (66.0)	12 (85.7)	34 (70.8)
Tachypnea												
Yes	29 (7.3)	21 (9.4)	8 (4.8)	0 (0)	5 (7.8)	3 (21.4)	3 (15.8)	0 (0)	0 (0)	4 (8.5)	2 (14.3)	4 (8.3)
No	363 (92.6)	203 (90.6)	160 (95.2)	7 (100)	59 (92.2)	11 (78.6)	16 (84.2)	5 (100)	6 (100)	43 (91.5)	12 (85.7)	44 (91.7)
Increased work of breathing												
Yes	94 (24.0)	66 (29.5)	28 (16.7)	1 (14.3)	20 (31.3)	4 (28.6)	5 (26.3)	0 (0)	0 (0)	19 (40.4)	4 (28.6)	13 (27.1)
No	298 (76.0)	158 (70.5)	140 (83.3)	6 (85.7)	44 (68.8)	10 (71.4)	14 (73.7)	5 (100)	6 (100)	28 (59.6)	10 (71.4)	35 (72.9)
Gastrointestinal												
Yes	126 (32.1)	80 (35.7)	46 (27.4)	2 (28.6)	18 (28.1)	2 (14.3)	10 (52.6)	2 (40.0)	2 (33.3)	23 (48.9)	4 (28.6)	17 (35.4)
No	266 (67.9)	144 (64.3)	122 (72.6)	5 (71.4)	46 (71.9)	12 (85.7)	9 (47.4)	3 (60.0)	4 (66.7)	24 (51.1)	10 (71.4)	31 (64.6)

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

Table A30 Clinical characteristics (medical history) associated with specimens with accessible medical record information from children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI or concern for ARTI in the absence of traditional symptoms, without duplicates (n=392)

	Number of Specimens (%)											
	Total (n=392)	**Positive (n=224)**	**Negative (n=168)**	**Ad (n=7)**	**HRV (n=64)**	**HBoV (n=14)**	**hMPV (n=19)**	**Flu A (n=5)**	**Flu B (n=6)**	**RSV (n=47)**	**All PIV[a] (n=14)**	**Coinfection (n=48)**
Respiratory condition												
Any												
Yes	139 (35.5)	84 (37.5)	55 (32.7)	1 (14.3)	30 (46.9)	7 (50.0)	4 (21.1)	4 (80.0)	2 (33.3)	15 (31.9)	3 (21.4)	18 (37.5)
No	253 (64.5)	140 (62.5)	113 (67.3)	6 (85.7)	34 (53.1)	7 (50.0)	15 (79.0)	1 (20.0)	4 (66.7)	32 (68.1)	11 (78.6)	30 (62.5)
Asthma												
Yes	47 (12.0)	33 (14.7)	14 (8.3)	1 (14.3)	12 (18.8)	2 (14.3)	0 (0)	3 (60.0)	0 (0)	8 (17.0)	1 (7.1)	6 (12.5)
No	345 (88.0)	191 (85.3)	154 (91.7)	6 (85.7)	52 (81.3)	12 (85.7)	19 (100)	2 (40.0)	6 (100)	39 (83.0)	13 (92.9)	42 (87.5)
Structural defect												
Yes	74 (18.9)	47 (21.0)	27 (16.1)	0 (0)	17 (26.6)	4 (28.6)	3 (15.8)	0 (0)	0 (0)	9 (19.2)	2 (14.3)	12 (25.0)
No	318 (81.1)	177 (79.0)	141 (83.9)	7 (100)	47 (73.4)	10 (71.4)	16 (84.2)	5 (100)	6 (100)	38 (80.9)	12 (85.7)	36 (75.0)
Other medical condition												
Prematurity												
Yes	88 (22.5)	43 (19.2)	45 (26.8)	0 (0)	13 (20.3)	7 (50.0)	3 (15.8)	1 (20.0)	1 (16.7)	8 (17.0)	3 (21.4)	7 (14.6)
No	304 (77.6)	181 (80.8)	123 (73.2)	7 (100)	51 (79.7)	7 (50.0)	16 (84.2)	4 (80.0)	5 (83.3)	39 (83.0)	11 (78.6)	41 (85.4)
Cancer												
Yes	28 (7.1)	17 (7.6)	11 (6.6)	0 (0)	5 (7.8)	0 (0)	2 (10.5)	1 (20.0)	0 (0)	4 (8.5)	1 (7.1)	4 (8.3)
No	364 (92.9)	207 (92.4)	157 (93.5)	7 (100)	59 (92.2)	14 (100)	17 (89.5)	4 (80.0)	6 (100)	43 (91.5)	13 (93.9)	44 (91.7)
Transplant												
Yes	10 (2.6)	6 (2.7)	4 (2.4)	0 (0)	4 (6.3)	0 (0)	0 (0)	0 (0)	1 (16.6)	0 (0)	0 (0)	1 (2.1)
No	382 (97.5)	218 (97.3)	164 (97.6)	7 (100)	60 (93.8)	14 (100)	19 (100)	5 (100)	5 (83.3)	47 (100)	14 (100)	47 (97.9)
Immunocompromised[b]												
Yes	118 (30.1)	67 (29.9)	51 (30.4)	1 (14.3)	19 (29.7)	1 (7.1)	8 (42.1)	1 (20.0)	3 (50.0)	13 (27.7)	2 (14.3)	19 (39.6)
No	274 (69.9)	157 (70.1)	117 (69.6)	6 (85.7)	45 (70.3)	13 (92.9)	11 (57.9)	4 (80.0)	3 (50.0)	34 (72.3)	12 (85.7)	29 (60.4)

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

[b] Includes history of cancer, transplant, and chronic conditions that may lead to increased risk of ARTI (see Table 2).

Table A31 Laboratory characteristics of specimens with accessible medical record information from children with confirmed (physician diagnosed) or suspected (physician-documented symptoms) ARTI or concern for ARTI in the absence of traditional symptoms, without duplicates (n=392)

	Number of Specimens (%)											
	Total (n=346)	**Positive (n=224)**	**Negative (n=168)**	**Ad (n=7)**	**HRV (n=64)**	**HBoV (n=14)**	**hMPV (n=19)**	**Flu A (n=5)**	**Flu B (n=6)**	**RSV (n=47)**	**All PIV[a] (n=14)**	**Coinfection (n=48)**
Month												
Mar 08	19 (4.9)	14 (6.3)	5 (3.0)	0 (0)	4 (6.3)	1 (7.1)	1 (5.3)	0 (0)	1 (16.7)	2 (4.3)	3 (21.4)	2 (4.1)
Apr 08 - Jun 08	81 (20.7)	51 (22.8)	30 (17.9)	2 (28.6)	13 (20.3)	4 (28.6)	8 (42.1)	0 (0)	0 (0)	3 (6.4)	5 (35.7)	16 (33.3)
Jul 08 - Sep 08	28 (7.1)	15 (6.7)	13 (7.7)	1 (14.3)	12 (18.8)	1 (7.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.1)
Oct 08 - Dec 08	71 (18.1)	31 (13.8)	40 (23.8)	2 (28.6)	10 (15.6)	3 (21.4)	1 (5.3)	0 (0)	0 (0)	6 (12.8)	1 (7.1)	8 (16.7)
Jan 09 - Mar 09	126 (32.1)	75 (33.5)	51 (30.4)	1 (14.3)	12 (18.8)	3 (21.4)	7 (36.8)	5 (100)	4 (66.7)	34 (72.3)	1 (7.1)	8 (16.7)
Apr 09 - Jun 09	67 (17.1)	38 (17.0)	29 (17.3)	1 (14.3)	13 (20.3)	2 (14.3)	2 (10.5)	0 (0)	1 (16.7)	2 (4.3)	4 (28.6)	13 (27.1)
Source												
Nasal wash	333 (86.5)	203 (91.9)	130 (79.3)	6 (85.7)	51 (82.3)	11 (84.6)	17 (89.5)	5 (100)	6 (100)	45 (95.7)	14 (100)	48 (100)
Bronch lavage	12 (3.1)	3 (1.4)	9 (5.5)	0 (0)	3 (4.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Trach aspirate	32 (8.3)	12 (5.4)	20 (12.2)	0 (0)	6 (9.7)	2 (15.4)	2 (10.5)	0 (0)	0 (0)	2 (4.3)	0 (0)	0 (0)
Other[b]	8 (2.4)	3 (1.4)	5 (3.0)	1 (14.3)	2 (3.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Missing	7	3	4	0	2	1	0	0	0	0	0	0

Note: Excludes 13 specimens for which medical record information was accessible Percentages may not add to 100.0 due to rounding. Virus-specific estimates exclude coinfections.

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

[b] Other may include bronchial wash/biopsy, lung aspirate/biopsy, nasopharyngeal swab, nasal swab, THS, tissue biopsy.

Table A32 Available demographic characteristics of children with accessible medical record information from eligible specimens excluded from study due to unavailability of specimen, with duplicates (n=108)

	Number of Specimens (%)								
	Total (n=108)	**Positive (n=77)**	**Negative (n=31)**	**Ad (n=2)**	**Flu A (n=3)**	**Flu B (n=5)**	**RSV (n=57)**	**All PIV[a] (n=8)**	**Coinfection (n=2)**
Gender									
Female	40 (37.0)	31 (40.3)	9 (29.0)	0 (0)	2 (66.7)	4 (80.0)	22 (38.6)	2 (25.0)	1 (50.0)
Male	68 (63.0)	46 (59.7)	22 (71.0)	2 (100)	1 (33.3)	1 (20.0)	35 (61.4)	6 (75.0)	1 (50.0)
Age (years)									
0 to < 0.5	45 (41.7)	34 (44.2)	11 (35.5)	0 (0)	1 (33.3)	0 (0)	30 (52.6)	1 (12.5)	0 (0)
0.5 to < 1	23 (21.3)	18 (23.4)	5 (16.1)	0 (0)	1 (33.3)	0 (0)	17 (29.8)	0 (0)	0 (0)
1 to < 5	30 (27.8)	21 (27.3)	9 (29.0)	0 (0)	1 (33.3)	3 (60.0)	10 (17.5)	5 (62.5)	0 (0)
≥ 5	10 (9.3)	4 (5.2)	6 (19.4)	2 (100)	0 (0)	2 (40.0)	0 (0)	2 (.25)	1 (100)
Race									
Caucasian	74 (77.1)	55 (82.1)	19 (65.5)	1 (50.0)	3 (100)	1 (25.0)	42 (84.0)	7 (100)	1 (100)
African-American	9 (9.4)	4 (6.0)	5 (17.2)	1 (50.0)	0 (0)	0 (0)	3 (6.0)	0 (0)	0 (0)
Hispanic	5 (5.2)	2 (3.0)	3 (10.3)	0 (0)	0 (0)	1 (25.0)	1 (2.0)	0 (0)	0 (0)
Other	8 (8.3)	6 (9.0)	2 (76.9)	0 (0)	0 (0)	2 (50)	4 (8.0)	0 (0)	0 (0)
Missing	12	10	2	0	0	0	7	1	1
Urban/Rural									
Urban	85 (78.7)	59 (76.6)	26 (83.9)	2 (100)	2 (66.7)	5 (100)	44 (77.2)	4 (50.0)	2 (100)
Large rural	8 (7.4)	7 (9.1)	1 (3.2)	0 (0)	0 (0)	0 (0)	4 (7.0)	3 (37.5)	0 (0)
Small rural	9 (8.3)	7 (9.1)	2 (6.5)	0 (0)	0 (0)	0 (0)	6 (10.5)	1 (12.5)	0 (0)
Isolated rural	6 (5.6)	4 (5.2)	2 (6.5)	0 (0)	1 (33.3)	0 (0)	3 (5.3)	0 (0)	0 (0)
Missing	0	0	0	0	0	0	0	0	0

Note: Excludes 8 specimens for which medical record information was inaccessible. Percentages may not add to 100.0 due to rounding. Virus-specific estimates exclude coinfections.

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

Table A33 Mean age of children with accessible medical record information from eligible specimens excluded from study due to unavailability of specimen, with duplicates (n=108)

	Total (n=108)	Positive (n=77)	Negative (n=31)	Ad (n=2)	Flu A (n=3)	Flu B (n=5)	RSV (n=57)	All PIV[a] (n=8)	Coinfection (n=2)
Age (years)									
Mean	1.56	1.33	2.14	2.42	1.65	5.24	0.68	3.36	0.39
Std deviation	2.11	1.74	2.77	0.35	2.00	2.09	0.82	2.06	0.12
Minimum	0.01	0.01	0.04	2.17	0.44	3.43	0.01	0.47	0.30
Maximum	8.53	7.62	8.53	2.67	3.97	7.62	4.75	6.41	0.47

Note: Excludes 8 specimens for which medical record information was inaccessible. Percentages may not add to 100.0 due to rounding. Virus-specific estimates exclude coinfections.

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

Table A34 Available clinical characteristics (indicators of severity) associated with specimens with accessible medical record information from eligible children excluded from study due to unavailable specimen, with duplicates (n=108)

	Number of Specimens (%)								
	Total (n=108)	**Positive (n=77)**	**Negative (n=31)**	**Ad (n=2)**	**Flu A (n=3)**	**Flu B (n=5)**	**RSV (n=57)**	**All PIV[a] (n=8)**	**Coinfection (n=2)**
Inpatient									
Yes	50 (46.3)	36 (46.8)	14 (45.2)	2 (100)	1 (33.3)	0 (0)	26 (45.6)	7 (87.5)	0 (0)
No	58 (53.7)	41 (53.3)	17 (54.8)	0 (0)	2 (66.7)	5 (100)	31 (54.4)	1 (12.5)	2 (100)
ICU admission, if hospitalized									
Ever	16 (32.0)	7 (19.4)	9 (64.3)	0 (0)	0 (0)	NA	7 (26.9)	0 (0)	NA
Never	34 (68.0)	29 (80.6)	5 (35.7)	2 (100)	1 (100)	NA	19 (73.1)	7 (100)	NA

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

Table A35 Clinical characteristics (length of hospitalization) associated with specimens with accessible medical record information from eligible children excluded from study due to unavailable specimen, with duplicates (n=108)

	Total (n=108)	Positive (n=77)	Negative (n=31)	Ad (n=2)	Flu A (n=3)	Flu B (n=5)	RSV (n=57)	All PIV[a] (n=8)	Coinfection (n=2)
UIHC hospitalization Length of stay, days									
N	49	35	14	2	1	0	26	6	0
Median	3.00	2.00	14.00	3.00	2.00	NA	2.00	3.50	NA
Mean	12.61	7.43	25.57	3.00	2.00	NA	8.96	3.17	NA
Std deviation	20.92	16.11	26.15	2.83	NA	NA	18.50	1.94	NA
Minimum	<1.00	<1.00	1.00	1.00	2.00	NA	<1.00	1.00	NA
Maximum	93.00	93.00	63.00	5.00	2.00	NA	93.00	6.00	NA
Non-ICU days									
N	43	35	8	2	1	0	26	6	0
Median	2.00	2.00	1.50	3.00	2.00	NA	2.00	3.50	NA
Mean	4.47	4.06	6.25	3.00	2.00	NA	4.42	3.17	NA
Std deviation	6.33	5.26	10.07	2.83	NA	NA	6.00	1.94	NA
Minimum	<1.00	<1.00	1.00	1.00	2.00	NA	<1.00	1.00	NA
Maximum	29.00	28.00	29.00	5.00	2.00	NA	28.00	6.00	NA
ICU days									
N	16	7	9	0	0	0	7	0	0
Median	12.00	8.00	28.00	NA	NA	NA	8.00	NA	NA
Mean	26.63	16.86	34.22	NA	NA	NA	16.86	NA	NA
Std deviation	26.50	22.08	28.33	NA	NA	NA	22.08	NA	NA
Minimum	1.00	4.00	1.00	NA	NA	NA	4.00	NA	NA
Maximum	65.00	65.00	63.00	NA	NA	NA	65.00	NA	NA

Table A35 Continued

	Total (n=108)	Positive (n=77)	Negative (n=31)	Ad (n=2)	Flu A (n=3)	Flu B (n=5)	RSV (n=57)	All PIV[a] (n=8)	Coinfection (n=2)
Total hospitalization, days[b]									
N	49	32	14	2	1	0	26	6	0
Median	3.00	2.00	19.50	3.00	2.00	NA	2.00	3.50	NA
Mean	12.92	7.38	26.50	3.00	2.00	NA	9.04	3.17	NA
Std deviation	20.97	16.80	25.82	2.83	NA	NA	18.50	1.94	NA
Minimum	<1.00	<1.00	1.00	1.00	2.00	NA	<1.00	1.00	NA
Maximum	93.00	93.00	63.00	5.00	2.00	NA	93.00	6.00	NA

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

[b] Includes non-UIHC hospitalizations when applicable.

Table A36 Laboratory characteristics of specimens with accessible medical record information from eligible children excluded from study due to unavailable specimen, with duplicates (n=108)

	Number of Specimens (%)								
	Total (n=108)	**Positive (n=77)**	**Negative (n=31)**	**Ad (n=2)**	**Flu A (n=3)**	**Flu B (n=5)**	**RSV (n=57)**	**All PIV[a] (n=8)**	**Coinfection (n=2)**
Month									
Mar 08	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Apr 08 - Jun 08	19 (17.6)	8 (10.4)	11 (35.5)	0 (0)	0 (0)	1 (20.0)	6 (10.5)	1 (12.5)	0 (0)
Jul 08 - Sep 08	2 (1.9)	0 (0)	2 (6.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Oct 08 - Dec 08	13 (12.0)	10 (13.0)	3 (9.7)	1 (50.0)	0 (0)	0 (0)	7 (12.3)	1 (12.5)	1 (50.0)
Jan 09 - Mar 09	49 (45.4)	47 (61.0)	2 (6.5)	0 (0)	2 (66.7)	4 (80.0)	38 (66.7)	2 (25.0)	1 (50.0)
Apr 09 - Jun 09	25 (23.1)	12 (15.6)	13 (41.9)	1 (50.0)	1 (33.3)	0 (0)	6 (10.5)	3 (37.5)	0 (0)
Source									
Bronch wash	1 (0.9)	1 (1.3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.8)	0 (0)	0 (0)
NP swab	5 (4.6)	0 (0)	5 (16.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nasal swab	6 (5.6)	1 (1.3)	5 (16.1)	0 (0)	0 (0)	0 (0)	1 (1.8)	0 (0)	0 (0)
Nasal wash	88 (81.5)	73 (94.8)	15 (48.4)	2 (100)	3 (100)	5 (100)	54 (94.7)	7 (87.5)	2 (100)
Tissue biopsy	4 (3.7)	0 (0)	4 (12.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Trach aspirate	3 (2.8)	2 (2.6)	1 (3.23)	0 (0)	0 (0)	0 (0)	1 (1.8)	1 (12.5)	0 (0)
Pleural fluid	1(0.9)	0 (0)	1 (3.23)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Note: Excludes 8 specimens for which medical record information was inaccessible. Percentages may not add to 100.0 due to rounding. Virus-specific estimates exclude coinfections.

[a] The category All PIV combines frequencies for PIV 1-3 and PIV NOS.

Table A37 Demographic characteristics of children for HRV-tested specimens with accessible medical record information, with duplicates (n=529)

	Number of Specimens (%)					
	HRV-Positive (n=127)	HRV-Negative (n=402)	HRV A (n=38)	HRV C (n=40)	HRV Other[a] (n=6)	Coinfection with Any Virus (n=43)
Gender						
Female	59 (46.5)	188 (46.8)	15 (39.5)	24 (60.0)	2 (33.3)	18 (41.9)
Male	68 (53.5)	214 (53.2)	23 (60.5)	16 (40.0)	4 (66.7)	25 (58.1)
Age (years)						
0 to < 0.5	36 (28.4)	145 (36.1)	14 (36.8)	12 (30.0)	0 (0)	10 (23.3)
0.5 to < 1	26 (20.5)	60 (14.9)	6 (15.8)	8 (20.0)	1 (16.7)	11 (25.6)
1 to < 5	47 (37.0)	149 (37.1)	12 (31.6)	14 (35.0)	2 (50.0)	18 (41.9)
≥ 5	18 (14.2)	48 (11.9)	6 (15.8)	6 (15.0)	3 (33.3)	4 (9.3)
Race						
Caucasian	85 (73.9)	257 (71.2)	28 (84.9)	22 (59.5)	5 (83.3)	30 (76.9)
African-American	11 (9.6)	42 (11.6)	3 (9.1)	6 (16.2)	0 (0)	2 (5.1)
Hispanic	11 (9.6)	36 (10.0)	2 (6.1)	6 (16.2)	0 (0)	3 (7.7)
Other	8 (7.0)	26 (7.2)	0 (0)	3 (8.1)	1 (16.7)	4 (10.3)
Missing	12	41	5	3	0	4
Medicaid						
Yes	60 (47.2)	202 (50.9)	17 (44.7)	21 (52.5)	3 (50.0)	19 (44.2)
No	67 (52.8)	195 (49.1)	21 (55.3)	19 (47.5)	3 (50.0)	24 (55.8)
Missing	0	5	0	0	0	0
Urban/Rural						
Urban	78 (61.4)	231 (57.6)	26 (68.4)	24 (60.0)	5 (83.3)	23 (53.5)
Large rural	15 (11.8)	67 (16.7)	3 (7.9)	3 (7.5)	0 (0)	9 (20.9)
Small rural	17 (13.4)	55 (13.7)	6 (15.8)	5 (12.5)	1 (16.7)	5 (11.6)
Isolated rural	17 (13.4)	48 (12.0)	3 (7.9)	8 (20.0)	0 (0)	6 (14.0)
Missing	0	1	0	0	0	0

Table A37 Continued

	Number of Specimens (%)					
	HRV-Positive (n=127)	HRV-Negative (n=402)	HRV A (n=38)	HRV C (n=40)	HRV Other[a] (n=6)	Coinfection with Any Virus (n=43)
Smoke exposure						
None	35 (67.3)	100 (62.5)	7 (53.9)	11 (78.6)	2 (50.0)	15 (71.4)
Direct	5 (9.6)	19 (11.9)	1 (7.7)	1 (7.1)	0 (0)	3 (14.3)
Indirect	12 (23.1)	41 (25.6)	5 (38.5)	2 (14.3)	2 (50.0)	3 (14.3)
Missing	75	242	25	26	2	22

Note: Excludes 30 specimens for which medical record information was inaccessible. Percentages may not add to 100.0 due to rounding. Virus-specific estimates exclude coinfections.

[a] The category HRV Other includes 1 HRV B and 5 non-typeable HRVs.

Table A38 Mean age of children for HRV-tested specimens with accessible medical record information, with duplicates (n=529)

	HRV-Positive (n=127)	HRV-Negative (n=400)	HRV A (n=38)	HRV C (n=40)	HRV Other[a] (n=6)	Coinfection with Any Virus (n=43)
Age (years)						
Mean	2.12	1.98	2.20	1.96	4.65	1.84
Std deviation	2.53	2.36	2.52	2.44	3.54	2.36
Minimum	0.03	0	0.04	0.03	0.79	0.11
Maximum	9.98	9.80	9.98	9.73	9.29	9.62

Note: Excludes 33 specimens for which medical record information was inaccessible. Percentages may not add to 100.0 due to rounding. Virus-specific estimates exclude coinfections.

[a] The category HRV Other includes 1 HRV B and 5 non-typeable HRVs.

Table A39 Clinical characteristics (indicators of severity) associated with HRV-tested specimens with accessible medical record information, with duplicates (n=529)

	Number of Specimens (%)					
	HRV-Positive (n=127)	HRV-Negative (n=402)	HRV A (n=38)	HRV C (n=40)	HRV Other[a] (n=6)	Coinfection with Any Virus (n=43)
Inpatient						
Yes	98 (77.2)	322 (80.1)	33 (86.8)	30 (75.0)	4 (66.7)	31 (72.1)
No	29 (22.8)	80 (19.9)	5 (13.2)	10 (25.0)	2 (33.3)	12 (27.9)
ICU admission, if hospitalized						
Ever	24 (24.5)	150 (46.6)	13 (39.4)	7 (23.3)	0 (0)	4 (12.9)
Never	74 (75.5)	172 (53.4)	20 (60.6)	23 (76.7)	4 (100)	27 (87.1)
ICU at collection						
Yes	24 (24.5)	136 (42.2)	13 (39.4)	7 (23.3)	0 (0)	4 (12.9)
No	74 (75.5)	186 (57.8)	20 (60.6)	23 (76.7)	4 (100)	27 (87.1)
Mechanically ventilated						
Yes	11 (8.7)	85 (21.1)	9 (23.7)	1 (2.5)	0 (0)	1 (2.33)
No	116 (91.3)	317 (78.9)	29 (76.3)	39 (97.5)	6 (100)	42 (97.7)
Oxygen requirement						
Yes	49 (38.6)	199 (49.5)	19 (50.0)	10 (25.0)	2 (33.3)	18 (41.9)
No	78 (61.4)	203 (50.5)	19 (50.0)	30 (75.0)	4 (66.7)	25 (58.1)
Bronchodilator administered						
Yes	46 (36.2)	104 (25.9)	7 (18.4)	16 (40.0)	2 (33.3)	21 (48.8)
No	81 (63.8)	298 (74.1)	31 (81.6)	24 (60.0)	4 (66.7)	22 (51.2)
Oxygen saturation < 90%						
Yes	43 (33.9)	143 (35.6)	15 (39.5)	10 (25.0)	2 (33.3)	16 (37.2)
No	84 (66.1)	259 (64.4)	23 (60.5)	30 (75.0)	4 (66.7)	27 (62.8)

[a] The category HRV Other includes 1 HRV B and 5 non-typeable HRVs.

Table A40 Clinical characteristics (length of hospitalization) associated with HRV-tested specimens with accessible medical record information, with duplicates (n=529)

	HRV-Positive (n=127)	HRV-Negative (n=402)	HRV A (n=38)	HRV C (n=40)	HRV Other[a] (n=6)	Coinfection with Any Virus (n=43)
UIHC hospitalization Length of stay, days						
N	98	322	33	30	4	31
Median	3.00	6.50	4.00	2.50	3.00	3.00
Mean	10.51	34.69	16.24	5.13	6.00	10.19
Std deviation	28.28	60.28	37.45	9.92	6.06	30.40
Minimum	<1.00	<1.00	<1.00	<1.00	2.00	1.00
Maximum	204.00	377.00	204.00	53.00	15.00	172.00
Non-ICU days						
N	92	247	29	28	4	31
Median	3.00	3.00	3.00	2.00	3.00	3.00
Mean	5.76	8.83	7.86	2.64	6.00	6.58
Std deviation	11.02	25.62	14.64	2.30	6.06	12.08
Minimum	<1.00	<1.00	1.00	<1.00	2.00	1.00
Maximum	77.00	369.00	77.00	11.00	15.00	67.00
ICU days						
N	24	150	13	7	0	4
Median	3.00	34.00	3.00	4.00	NA	2.50
Mean	20.83	59.97	23.69	11.43	NA	28.00
Std deviation	45.65	67.22	55.52	18.72	NA	51.34
Minimum	<1.00	1.00	<1.00	1.00	NA	2.00
Maximum	204.00	377.00	204.00	53.00	NA	105.00

Table A40 Continued

	HRV-Positive (n=127)	HRV-Negative (n=402)	HRV A (n=38)	HRV C (n=40)	HRV Other[a] (n=6)	Coinfection with Any Virus (n=43)
Total hospitalization, days[b]						
N	98	322	33	30	4	31
Median	3.00	7.00	4.00	3.00	3.00	3.00
Mean	12.23	35.01	21.24	5.2	6.00	10.26
Std deviation	33.59	60.27	48.08	9.91	6.06	30.57
Minimum	<1.00	<1.00	<1.00	<1.00	2.00	1.00
Maximum	204.00	377.0	204.00	53.00	15.00	173.00

[a] The category HRV Other includes 1 HRV B and 5 non-typeable HRVs.

[b] Includes non-UIHC hospitalizations when applicable.

Table A41 Clinical characteristics (antimicrobial use and inflammation markers) associated with HRV-tested specimens with accessible medical record information, with duplicates (n=529)

	Number of Specimens (%)					
	HRV-Positive (n=127)	HRV-Negative (n=402)	HRV A (n=38)	HRV C (n=40)	HRV Other[a] (n=6)	Coinfection with Any Virus (n=43)
Antimicrobial use						
Prior use[b]						
Yes	38 (29.9)	115 (28.6)	15 (39.5)	9 (22.5)	2 (33.3)	12 (27.9)
No	89 (70.1)	287 (71.4)	23 (60.5)	31 (77.5)	4 (66.7)	31 (72.1)
UIHC administered						
Yes	72 (56.7)	256 (63.7)	23 (60.5)	22 (55.0)	4 (66.7)	23 (53.5)
No	55 (43.3)	146 (36.3)	15 (39.5)	18 (45.0)	2 (33.3)	20 (46.5)
Take-home prescription						
Yes	38 (29.9)	95 (23.6)	11 (29.0)	12 (30.0)	0 (0)	15 (34.9)
No	89 (70.1)	307 (76.4)	27 (71.5)	28 (70.0)	6 (100)	28 (65.1)
Leukopenia						
Yes	12 (12.4)	90 (28.1)	5 (15.2)	4 (14.3)	1 (20.0)	2 (6.5)
No	85 (87.6)	230 (71.9)	28 (84.9)	24 (85.7)	4 (80.0)	29 (93.6)
Missing	30	82	5	12	1	12
Leukocytosis						
Yes	31 (32.0)	83 (25.9)	7 (21.2)	13 (46.4)	3 (60.0)	8 (25.8)
No	66 (68.0)	237 (74.1)	26 (78.8)	15 (53.6)	2 (40.0)	23 (74.2)
Missing	30	82	5	12	1	12
CRP > 0.5 mg/dl						
Yes	52 (68.4)	183 (68.5)	19 (67.9)	17 (68.0)	3 (100)	13 (65.0)
No	24 (31.6)	84 (31.5)	9 (32.1)	8 (32.0)	0 (0)	7 (35.0)
Missing	51	135	10	15	3	23

[a] The category HRV Other includes 1 HRV B and 5 non-typeable HRVs.

[b] Denotes antibiotics used prior to UIHC episode during which specimen was collected.

Table A42 Clinical characteristics (diagnoses) associated with HRV-tested specimens with accessible medical record information, with duplicates (n=529)

	Number of Specimens (%)					
	HRV-Positive (n=127)	HRV-Negative (n=402)	HRV A (n=38)	HRV C (n=40)	HRV Other[a] (n=6)	Coinfection with Any Virus (n=43)
ARTI						
None	3 (2.4)	16 (4.0)	0 (0)	1 (2.5)	0 (0)	2 (4.7)
Physician diagnosed	68 (53.5)	166 (41.3)	20 (52.6)	22 (55.0)	1 (16.7)	25 (58.1)
Physician documented symptoms	51 (40.2)	156 (38.8)	17 (44.7)	14 (35.0)	5 (83.3)	15 (34.9)
Concern for ARTI without traditional symptoms	5 (3.9)	64 (15.9)	1 (2.6)	3 (7.5)	0 (0)	1 (2.3)
Diagnosis						
Bronchiolitis						
Yes	14 (11.0)	37 (9.2)	1 (2.6)	3 (7.5)	0 (0)	10 (23.3)
No	113 (89.0)	365 (90.8)	37 (97.4)	37 (92.5)	6 (100)	33 (76.7)
Pneumonia						
Yes	26 (20.5)	83 (20.6)	9 (23.7)	3 (7.5)	1 (16.7)	13 (30.2)
No	201 (79.5)	319 (79.4)	29 (76.3)	37 (92.5)	5 (83.3)	30 (69.8)
Respiratory tract infection						
Yes	46 (36.2)	86 (21.4)	16 (42.1)	19 (47.5)	0 (0)	11 (25.6)
No	81 (63.8)	316 (78.6)	22 (57.9)	21 (52.5)	6 (100)	32 (74.4)

[a] The category HRV Other includes 1 HRV B and 5 non-typeable HRVs.

Table A43 Clinical characteristics (symptoms) associated with HRV-tested specimens with accessible medical record information, with duplicates (n=529)

	Number of Specimens (%)					
	HRV-Positive (n=127)	HRV-Negative (n=402)	HRV A (n=38)	HRV C (n=40)	HRV Other[a] (n=6)	Coinfection with Any Virus (n=43)
Fever						
Yes	60 (47.2)	229 (57.0)	18 (47.4)	17 (42.5)	3 (50.0)	22 (51.2)
No	67 (52.8)	173 (43.0)	20 (52.6)	23 (57.5)	3 (50.0)	21 (48.8)
Nasal						
Yes	64 (50.4)	141 (35.1)	17 (44.7)	21 (52.5)	2 (33.3)	24 (55.8)
No	63 (49.6)	261 (64.9)	21 (55.3)	19 (47.5)	4 (66.7)	19 (44.2)
Cough						
Yes	85 (66.9)	203 (50.5)	18 (47.4)	29 (72.5)	3 (50.0)	35 (81.4)
No	42 (33.1)	199 (49.5)	20 (52.6)	11 (27.5)	3 (50.0)	8 (18.6)
Wheeze						
Yes	38 (29.9)	59 (14.7)	4 (10.5)	17 (42.5)	1 (16.7)	16 (37.2)
No	89 (70.1)	343 (85.3)	34 (89.5)	23 (57.5)	5 (83.3)	27 (62.8)
Tachypnea						
Yes	11 (8.7)	30 (7.5)	3 (7.9)	4 (10.0)	1 (16.7)	3 (7.0)
No	116 (91.3)	372 (92.5)	35 (92.1)	36 (90.0)	5 (83.3)	40 (93.0)
Increased work of breathing						
Yes	33 (26.0)	89 (22.1)	8 (21.1)	12 (30.0)	1 (16.7)	12 (27.9)
No	94 (74.0)	313 (77.9)	30 (78.9)	28 (70.0)	5 (83.3)	31 (72.1)
Gastrointestinal						
Yes	39 (30.7)	125 (31.1)	12 (31.6)	12 (30.0)	2 (33.3)	13 (30.2)
No	88 (69.3)	277 (68.9)	26 (68.4)	28 (70.0)	4 (66.7)	30 (69.8)

[a] The category HRV Other includes 1 HRV B and 5 non-typeable HRVs.

Table A44 Clinical characteristics (medical history) associated with HRV-tested specimens with accessible medical record information, with duplicates (n=529)

	Number of Specimens (%)					
	HRV-Positive (n=127)	HRV-Negative (n=402)	HRV A (n=38)	HRV C (n=40)	HRV Other[a] (n=6)	Coinfection with Any Virus (n=43)
Respiratory condition						
Any						
Yes	68 (53.5)	141 (35.1)	23 (60.5)	20 (50.0)	3 (50.0)	22 (51.2)
No	59 (46.5)	261 (64.9)	15 (39.5)	20 (50.0)	3 (50.0)	21 (48.8)
Asthma						
Yes	24 (18.9)	44 (11.0)	6 (15.8)	10 (25.0)	1 (16.7)	7 (16.3)
No	103 (81.1)	358 (89.0)	32 (84.2)	30 (75.0)	5 (83.3)	36 (83.7)
Structural defect						
Yes	44 (34.7)	78 (19.4)	14 (36.8)	12 (30.0)	2 (33.3)	16 (37.2)
No	83 (65.4)	324 (80.6)	24 (63.2)	28 (70.0)	4 (66.7)	27 (62.8)
Other medical condition						
Prematurity						
Yes	30 (23.6)	105 (26.1)	10 (26.3)	10 (25.0)	0 (0)	10 (23.3)
No	97 (76.4)	297 (73.9)	28 (73.3)	30 (75.0)	6 (100)	33 (76.7)
Cancer						
Yes	9 (7.1)	31 (7.7)	3 (7.9)	3 (7.5)	0 (0)	3 (7.0)
No	118 (92.9)	371 (92.3)	35 (92.1)	37 (92.5)	6 (100)	40 (93.0)
Transplant						
Yes	6 (4.7)	14 (3.5)	4 (10.5)	1 (2.5)	0 (0)	1 (2.3)
No	121 (95.3)	388 (96.5)	34 (89.5)	39 (97.5)	6 (100)	42 (97.7)
Immunocompromised[b]						
Yes	46 (36.2)	136 (33.8)	15 (39.5)	9 (22.5)	3 (50.0)	19 (44.2)
No	81 (63.8)	266 (66.2)	23 (60.5)	31 (77.5)	3 (50.0)	24 (55.8)

[a] The category HRV Other includes 1 HRV B and 5 non-typeable HRVs.

[b] Includes history of cancer, transplant, and chronic conditions that may lead to increased risk of ARTI (see Table 2).

Table A45 Laboratory characteristics of HRV-tested specimens with accessible medical record information, with duplicates (n=529)

	Number of Specimens (%)					
	HRV-Positive (n=127)	HRV-Negative (n=400)	HRV A (n=38)	HRV C (n=40)	HRV Other[a] (n=6)	Coinfection with Any Virus (n=43)
Month						
Mar 08	6 (4.7)	15 (3.7)	2 (5.3)	2 (5.0)	0 (0)	2 (4.7)
Apr 08 - Jun 08	25 (19.7)	72 (17.9)	7 (18.4)	7 (17.5)	1 (16.7)	10 (23.3)
Jul 08 - Sep 08	14 (11.0)	27 (6.7)	11 (29.0)	3 (7.5)	0 (0)	0 (0)
Oct 08 - Dec 08	23 (18.1)	73 (18.1)	5 (13.2)	9 (22.5)	2 (33.3)	7 (16.3)
Jan 09 - Mar 09	26 (20.5)	146 (36.3)	1 (2.6)	13 (32.5)	3 (50.0)	9 (20.9)
Apr 09 - Jun 09	33 (26.0)	69 (17.2)	12 (31.6)	6 (15.0)	0 (0)	15 (34.9)
Source						
Nasal wash	109 (87.2)	329 (83.3)	26 (68.4)	34 (89.5)	6 (100)	43 (100)
Bronch lavage	4 (3.2)	17 (4.3)	2 (5.3)	2 (5.3)	0 (0)	0 (0)
Trach aspirate	8 (6.4)	37 (9.4)	7 (18.4)	1 (2.6)	0 (0)	0 (0)
Other[b]	4 (3.2)	11 (2.8)	3 (7.9)	1 (2.6)	0 (0)	0 (0)
Missing	2	7	0	2	0	0

Note: Excludes 30 specimens for which medical record information was inaccessible. Percentages may not add to 100.0 due to rounding. Virus-specific estimates exclude coinfections.

[a] The category HRV Other includes 1 HRV B and 5 non-typeable HRVs

[b] Other may include bronchial wash/biopsy, lung aspirate/biopsy, nasopharyngeal swab, nasal swab, THS, tissue biopsy

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