Review

Viruses and asthma ☆

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ABSTRACT

Background: Viral respiratory infection has long been known to influence the occurrence of asthma exacerbations. Over the last 20 years much effort has been put into clarifying the role that viral respiratory infections play in the eventual development of asthma.
Scope of review: In this review we give a general background of the role of viruses in the processes of asthma exacerbation and asthma induction. We review recent additions to the literature in the last 3 years with particular focus on clinical and epidemiologic investigations of influenza, rhinovirus, bocavirus, respiratory syncytial virus, and metapneumovirus.
Major conclusions: The development of asthma emerges from a complex interaction of genetic predisposition and environmental factors with viral infection likely playing a significant role in the effect of environment on asthma inception. This article is part of a Special Issue entitled: Biochemistry of Asthma.
General significance: Further understanding of the role that viruses play in asthma exacerbation and inception will contribute to decreased asthma morbidity in the future. This article is part of a Special Issue entitled: Biochemistry of Asthma.

1. Introduction

Asthma is a complex disease regulated by both genetic and environmental factors and characterized by dyspnea, coughing, wheezing, reversible episodes of bronchoconstriction, airway hyperreactivity, chronic eosinophilic inflammation, and mucus hypersecretion [1]. The large number of asthma exacerbations each year and significant morbidity due to asthma highlight the need for increased understanding of the mechanisms and pathways that generate the asthma phenotype [2]. The contribution of infections to the occurrence of asthma exacerbations has been of broad interest for at least the last 100 years since William Osler remarked with respect to

asthma that "every fresh cold" could induce a paroxysm of disease [3]. Epidemiologic and cohort studies have also increased our understanding of the role that viral infections contribute to asthma inception in the past 20 years. With the advent of highly sensitive polymerase chain reaction (PCR) and DNA sequencing techniques, diagnostic yields have increased and new viruses have been discovered that impact asthma pathogenesis. These findings have altered our understanding of the relative contributions of different viruses to the acute exacerbation of asthma and the development of asthma.

2. Influenza

Influenza is a significant cause of respiratory viral illness in both children and adults [4–6]. In the past 10–15 years, studies have led to increased appreciation of influenza burden in young children with asthma [4,6,7]. The Advisory Committee on Immunization Practices (ACIP) defines asthma as a high-risk condition for developing illness from influenza and has recommended the administration of influenza vaccine to patients with asthma since 1964 [8]. However, the importance of influenza as a cause of acute wheezing and asthma exacerbation is debated in the literature [9]. We therefore review recent evidence regarding the role of seasonal influenza in morbidity due to asthma and in asthma exacerbation. We then briefly address recent information about asthma in patients infected with pandemic 2009 H1N1 influenza A.

2.1. Morbidity and asthma exacerbations related to influenza

Evidence implicating influenza as a significant cause of morbidity in asthmatic patients primarily comes from studies assessing medical care utilization. Several investigators have associated influenza with increased medical care utilization by patients with asthma. In both adults and children with chronic underlying medical conditions (the majority of which were asthma), a substantial proportion of hospitalizations were linked to influenza seroconversion [5]. In a Medicaid database of children under the age of 15 years, children aged 1–3 years with asthma had significantly increased acute cardiopulmonary hospitalization rates (defined as hospitalization due to pneumonia, influenza, acute respiratory tract infection, heart failure, or myocarditis), outpatient visits, and antibiotic courses during influenza season compared to a predefined peri-influenza season [10]. Children aged 3–15 years with asthma did not demonstrate a significant increase in hospitalization rates due to acute cardiopulmonary disease during influenza season. However, rates of outpatient visits and antibiotic courses were markedly increased in this age group [10]. In a similar study, children with medical conditions placing them at high risk of complications from influenza – in whom asthma accounted for an average of 79% of the high-risk medical conditions per year – had increased incidence of hospitalization and outpatient visits compared with otherwise healthy patients during influenza season [11]. These studies are limited by retrospective assessment as well as reliance on diagnostic codes and virus-seasonality determinations to define influenza-attributable rates for their variables of interest. Diagnosis of asthma in children under 2 years of age is often difficult given the frequency with which recurrent wheezing occurs in the absence of atopy in this age group. In spite of these limitations, the studies suggest that asthmatic patients are at risk for significant morbidity related to influenza infection.

Prospective population-based surveillance has confirmed the above association between asthma and increased influenza-attributable hospitalization rates and outpatient clinic visits. From 2000 to 2004, children aged 6–59 months were prospectively assessed when presenting in either the inpatient (over four consecutive seasons) or outpatient (over two consecutive seasons) setting with acute respiratory illnesses or fever [12]. Influenza infection was defined as a viral culture or reverse transcriptase polymerase chain reaction (RT-PCR) positive for influenza A or B from nasal or throat swabs obtained at enrollment. Asthma was defined by parental report with systematic medical record review and discharge diagnosis code review. In this population, children aged 6–23 months with asthma had a significantly higher influenza-attributable hospitalization rate than did healthy children of the same age group (2.8 vs. 0.6 cases per 1000 children; $p < 0.05$). Children aged 24–59 months did not have a significantly different hospitalization rate. Outpatient surveillance during the 2003–2004 season identified higher influenza-attributable outpatient visits for both the 6–23 month age (316 cases per 1000 children) and the 24–59 month age groups (188 cases per 1000 children) vs. healthy children (152 and 102 cases per 1000 children respectively by age group). This pattern was not seen in the 2002–2003 season. These findings along with the preceding retrospective studies indicate a role for influenza in increased health care utilization in asthmatic patients in younger age groups and suggest an important role for influenza vaccination in preventing this morbidity.

Although the above studies demonstrate substantial morbidity associated with influenza in asthmatic patients, prospective studies aimed specifically at viral detection in patients with acute asthma exacerbation have not supported influenza as a cause of asthma exacerbation. An observational case–control study of 142 children aged 2–5 years with persistent asthma compared viral detection in children with asthma exacerbation with viral detection in children with well-controlled asthma [13]. Influenza was not detected in either group during the year of this study. In a study aimed primarily at

evaluating human bocavirus (HBoV) in children aged 3 months to 15 years (median: 1.6 years) with acute wheezing, influenza was detected in 3% of 259 children with acute wheezing. In only one of these cases was influenza identified as the sole virus detected from the specimen [14]. In contrast, the two most frequently isolated viruses – RSV and rhinovirus – were each identified in 28% of children. In a study of human rhinovirus (HRV) in children hospitalized for asthma exacerbation, influenza was co-detected with HRV in 2.4% of children [15]. In another study of 128 children aged 2–16 years with a prior diagnosis of asthma and presenting for acute asthma exacerbation, only one child had influenza detected from an isolate that was also positive for HRV and metapneumovirus [16]. Finally, in 40 patients with acute asthma exacerbation who were part of a larger study of viruses in acute wheezing, 8% of patients had influenza detected, all of which were co-detections with additional respiratory viruses [17]. These studies were performed primarily, if not exclusively, using inpatients and collectively suggest that influenza is not a significant cause of asthma exacerbation requiring hospitalization.

A recent study has suggested that influenza may play a greater role in asthma exacerbation in the outpatient setting than previously appreciated [18]. In this prospective study, children older than 18 months of age previously diagnosed with asthma and presenting to a single institution emergency department with acute asthma exacerbation were recruited. Viral detection was performed by direct immunofluorescence and viral culture. Viral detection was compared between patients requiring hospital admission and those discharged from the emergency department (ED). Three-hundred thirty-nine patients were included in the study, 68.5% of whom were hospitalized and 31.5% of whom were discharged from the ED. Patients discharged home had a greater frequency of influenza detection than those admitted (14.1% vs. 2.6%; $p < 0.001$). Although a separate preliminary study of 78 children with asthma detected influenza in only 5% of asthma exacerbation not requiring hospitalization [19], the results above implicate a role for influenza in less severe asthma exacerbations.

Studies examining the effectiveness of influenza vaccination in decreasing the number of asthma exacerbation are few and conflicting in their results. A retrospective cohort study evaluating HMO medical and vaccination records for children aged 1–6 years with asthma showed a decreased risk of asthma exacerbation following receipt of influenza vaccine [20]. This study was limited by its use of self-control analysis in which rates of asthma exacerbation before and after influenza vaccination were compared on an individual basis. A more recent randomized, double-blind, placebo-controlled trial of inactivated influenza vaccination in children age 6–18 years with asthma was performed in the Netherlands [21]. Influenza was detected in 42 asthma exacerbations in the study. Although asthma exacerbations related to influenza were of significantly shorter duration in recipients of the influenza vaccine, no difference was found in number or severity of influenza-related asthma exacerbations between vaccine and placebo groups [21].

2.2. Asthma and 2009 H1N1 influenza A

With the emergence of the novel 2009 H1N1 influenza A virus, numerous epidemiologic studies detected asthma as a frequent comorbid condition in patients infected with 2009 H1N1 influenza A with prevalence of asthma ranging from 6 to 50% (Table 1). Two of these studies noted that the prevalence of asthma in patients infected with 2009 H1N1 influenza A was increased over that noted in historical controls infected with influenza A (41% vs. 20%, $p < 0.001$; and 22% vs. 6%, $p < 0.001$) [22,23]. An association of asthma diagnosis with markers of illness severity such as hospital admission, ICU admission, and mortality in 2009 H1N1 influenza A infected patients has also been found [23–25]. In an evaluation by the Centers for

Table 1
Prevalence of asthma in patients with 2009 H1N1 Influenza A and asthma associated risk from selected studies.

Location	Time period	Asthma prevalence		Asthma-associated morbidity			Significance	Citation
		Pediatric	Adult	Risk factor	Outcome	Risk quantification		
Buenos Aires	May 1–July 31, 2009	6%		asthma	ICU admission	OR, 4.92	$p = 0.002$	[25]
				asthma	mortality	OR, 3.69 [a]	$p = 0.02$	
Toronto	May 8–July 22, 2009	22%		ICU admission	Asthma	42% vs. 7% [b]	$p = 0.017$	[23]
United States	May 1–June 9, 2009	29%	27%					[107]
Minnesota	May 2–August 31, 2009	40%	41%					[22]
New York	April 25–May 24, 2009	50%	46%					[108]
Seattle	April 29–August 1, 2009	15.8%		asthma	hospitalization	OR, 2.8	$p = 0.005$	[109]

ICU, intensive care unit.
[a] Risk attributable to chronic lung disease with asthma included as part of this.
[b] Comparison of asthma prevalence in 2009 H1N1 infected ICU patients vs. historical controls.

Disease Control and Prevention (CDC) of mortality from 2009 H1N1 influenza, the American Indian/Alaska Native (AI/AN) population had 3 times the mortality from influenza than did other groups. Of patients who died from their infection, 31% of AI/AN patients had a diagnosis of asthma whereas only 14.1% of other groups had been previously diagnosed with asthma [26]. While these data are limited by their use of historical controls and small sample sizes, they do suggest increased severity of novel influenza virus infection in patients with asthma and emphasize the importance of vigilance in distribution of influenza vaccine to asthmatic patients.

Thus, although a diagnosis of asthma is associated with increased morbidity from influenza, a direct role for influenza in asthma exacerbation is not well described. Further study is needed to clarify whether influenza might play a greater role in less severe asthma exacerbations.

3. Rhinovirus

Human rhinoviruses are members of the *Picornaviridae* family and as such are nonenveloped viruses with a single-stranded RNA genome [27]. Following their isolation in the 1950 s, HRVs became well documented as a cause of the common cold [28–30]. Recent recognition of their ability to replicate in the bronchial epithelium and of their association with pneumonia, bronchiolitis, and wheezing has led to greater understanding of its role in lower respiratory tract illness [31–36]. The ability of highly sensitive PCR techniques to detect HRV RNA has enabled greater appreciation of the role HRVs play in acute asthma exacerbations [37]. The recent discovery of a previously unrecognized species, human rhinovirus C (HRVC), has led to increased insight into the role that HRVs play in asthma exacerbation and their importance in predisposition to asthma [38,39]. In this section we will review (1) newer literature regarding the role of HRV infection in acute asthma exacerbation with attention to HRVC and (2) important cohort studies describing the association between HRV infections and eventual development of asthma.

3.1. Role of HRV in asthma exacerbations

Detection of HRV has long been associated with acute exacerbation of asthma in both children and adults [40–42]. Lower respiratory tract infections with HRV in people with asthma are more severe and longer lasting than in people unaffected by asthma [43]. Several recent studies have confirmed and extended these prior findings. A case–control study of children aged 2–17 years with asthma exacerbation or with well-controlled asthma was performed using age and seasonal matching of cases and controls. HRV was the most prevalent virus in asthma exacerbation (60% in cases vs. 18.2% in controls) and was the only virus significantly associated with asthma exacerbations (OR, 6.8; 95% CI, 3.2–14.3) [13]. This association was stronger for symptomatic infections and led the authors to conclude that HRV infections could account for as many as 30% of asthma exacerbations

in children. Similar findings were recently demonstrated in children aged 3–18 years with asthma exacerbation in Hong Kong (OR for asthma exacerbation with positive HRV detection, 2.38; 95% CI, 1.09–5.32) [44]. In both of these studies the majority of patients with acute asthma exacerbation were hospitalized (72% [13] and 97% [44]). In an outpatient pilot study assessing HRV point prevalence in acute asthma exacerbations, HRV was detected in 52.6% of nasopharyngeal aspirate specimens [19]. A study performed in the Carribbean noted the association of HRV infection with acute asthma exacerbation in a season-independent manner [45]. Thus, HRV detection continues to be well associated with both severe and non-severe asthma exacerbation in outpatient and inpatient settings.

Multicenter collaborative studies have contributed to further understanding of the role of HRV in asthma exacerbation. Through the New Vaccine Surveillance Network (NVSN), a CDC-initiated collaboration intended to provide precise burden estimates of acute respiratory infection due to either vaccine preventable or potentially preventable diseases, prospective surveillance of HRV infections in children under 5 years has defined rates of HRV-associated hospitalization. In children under 5 admitted to two different children's hospitals with acute respiratory symptoms or fever (ARI/F), the overall HRV-associated hospitalization rate was 4.8 hospitalizations per 1000 children with the highest rate occurring in children age 0–5 months (17.6 hospitalizations per 1000 children) [46]. Notably, a history of wheezing or asthma was significantly associated with increased HRV-associated hospitalization (+ wheezing/asthma: 25.3 hospitalizations per 1000 children; −wheezing/asthma: 3.1 hospitalizations per 1000 children; $p<0.001$) and was independently associated with detection of HRV in children with ARI/F compared with ARI/F in which the virus was not detected (OR, 1.8; $p=0.02$).

Peak HRV infections typically occur in the late spring and early fall seasons [47–49]. Numerous studies have also described seasonal epidemics of asthma exacerbation in children that occur in September, generally following the beginning of a new school year, and have been colloquially termed "the September asthma epidemic" (Fig. 1) [50]. One recent study has suggested that HRV may be the cause of this temporal epidemic. A Canadian group prospectively evaluated viral etiologies in a case–control study of children age 5–15 years presenting to the emergency department with acute asthma exacerbation compared to age and asthma severity matched controls without acute exacerbation [51]. To focus on this early fall period the study was limited to recruitment in September. Viruses were detected in 62% of cases and 41% of controls ($p=0.011$) with human picornaviruses detected in 52% of cases and 29% of controls ($p=0.002$). This temporal association implicates HRV, at least partly, in the occurrence of this yearly, seasonal increase in asthma exacerbations.

More recently, the occurrence of asthma exacerbations in children during these peak HRV seasons has been linked to prior allergen sensitization. Using prospective viral surveillance over 5-week periods in 58 asthmatic children during September and April in two consecutive
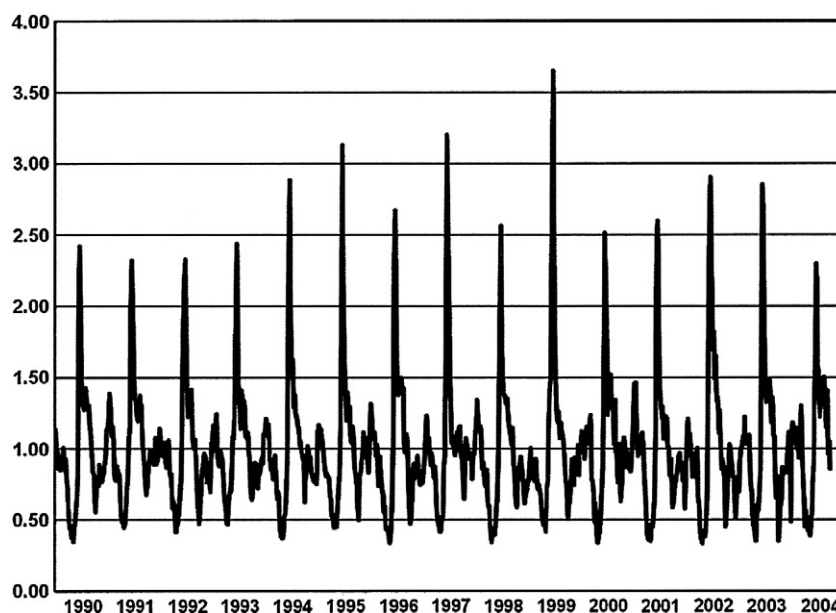
Fig. 1. Cyclical pattern of asthma hospitalization in children (2–15 years of age) over 15 years with yearly peak occurring in September. Asthma hospitalization rates are depicted as multiples of weekly mean hospitalizations. (Reprinted from J Allergy Clin Immunol, Vol. 120; Sears MR and Johnston NW. Understanding the September asthma epidemic, pp. 526–9, 2007, with permission from Elsevier).

years, 72–99% of detected viruses were HRV [52]. Virus detection was associated with increased duration and severity of asthma symptoms. Although no difference in viral detection was noted between sensitized and non-sensitized children, those sensitized to at least one allergen had more symptomatic virus-associated illnesses per season. Moreover, viral infections in these children were significantly more likely to cause moderate or severe asthma symptoms than in non-sensitized children (Fig. 2) [52]. These findings support a hypothesis that prior allergen sensitization and viral infection act in concert to increase risk for acute asthma exacerbations [53].
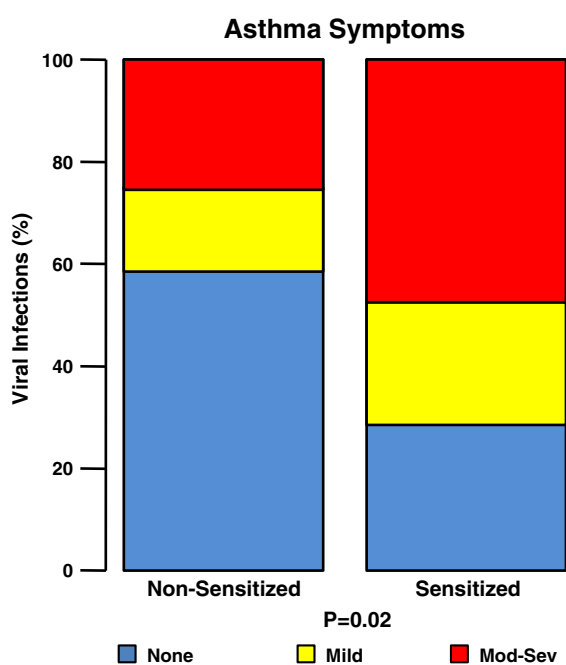

Fig. 2. Percentage viral infections determined to be asymptomatic, mild, or moderate to severe depending on allergic sensitization. (Reprinted from J Allergy Clin Immunol, Vol. 125; Olenec JP et al. Weekly monitoring of children with asthma for infections and illness during common cold seasons, pp. 1001–6, 2010, with permission from Elsevier).

Prior to 2007 HRV was classified into two phylogenetic groups – HRVA and HRVB. Recently, several research groups detected a novel group of HRV now named group C [38,39,54,55]. Studies have shown an association between human HRVC and asthma exacerbations. Children less than 5 years of age were prospectively identified through the NVSN upon presentation with ARI/F over the span of 2 years [15]. Nasal and throat swabs were obtained, RT-PCR was performed on HRV-positive samples to amplify a specific portion of the viral protein 4/viral protein 2 region, and sequences were evaluated to determine HRV grouping of each isolate. HRVC comprised 46% of HRVs detected. Children in whom HRVC was detected were more likely to be high-risk as defined by ACIP, with the majority of high-risk conditions being asthma, and more likely to have a discharge diagnosis of asthma than children in whom HRVA or HRVB were detected [15]. Prospective study performed in Jordan found an association between HRVC and parental report of wheezing [56]. Retesting of samples from a previously published study of viral respiratory tract infections in children with asthma noted a significant association between acute asthma exacerbation and HRVC detection [13,57].

HRVC infection may also be associated with increased severity of asthma exacerbation compared to other HRVs [16]. In a prospective evaluation of children (age 2–16 years) presenting with an acute asthma exacerbation to a single emergency department, illness severity was scored according to a modified NIH scale and nasal aspirate samples were tested by direct fluorescent antibody (DFA) and/or RT-PCR for respiratory viruses. Severity scores for children with HRVC were significantly greater than for children infected with either HRVA or HRVB as well as for children infected with any other virus (mean severity score 10.4 vs. 9.5; $p = 0.018$, and vs. 9.4; $p = 0.016$, respectively). These results may have been influenced by the high rate of detection of HRV in patients (87.5% of 128 total cases were HRV+) and the high degree of asthma severity in the patient population assessed (85.2% of cases with moderate to severe asthma exacerbation and 98.9% were admitted) [16].

HRV has a clear association with acute asthma exacerbation. Further study is required to determine the relative contribution of HRVC to asthma morbidity. Further study is also required to delineate the role of environment and allergic sensitization in occurrence of acute asthma exacerbation in response to HRV infection.

3.2. Role of HRV in asthma inception

Three cohort studies performed in the last 10 years provide important information about the relationship between HRV infection in infancy and eventual development of asthma (Table 2). In a study performed in Finland, 100 children aged 1–23 months with respiratory viral wheezing were prospectively enrolled and nasopharyngeal aspirates were obtained [58]. Six years after the initial virologic evaluation of these samples, residual frozen samples were tested for HRVs. At that time follow up information and frozen samples were available for 66 of the original 100 patients. Using this data, the authors identified that cases in which HRV alone was isolated during wheezing respiratory illness requiring hospitalization had an odds ratio for development of asthma of 4.14 (95% CI, 1.02–16.77, $p = 0.047$) when compared to HRV negative cases [59].

The Childhood Origins of Asthma Study (COAST) birth cohort has provided similar information regarding the risk that HRV infection represents for eventual development of asthma. In the COAST birth cohort, 289 newborns with a family history of atopy (history of respiratory allergies diagnosed by aeroallergen skin test or physician-diagnosed asthma in either parent) were prospectively followed with nasal swabs obtained at regular intervals and respiratory illnesses determined by parental report and discussion with study personnel. Two-hundred seventy-five patients were available at 3 years of age for follow up [60]. At that age, patients with a preceding moderate to severe respiratory illness had increased risk of continued wheezing at 3 years of age when all viral etiologies were evaluated together regardless of whether or not wheezing was present during the original illness. The strongest relationship was noted with HRV infection in infancy (OR for wheezing at 3 years, 2.3 with wheezing-negative RV illness in infancy; OR, 10 with wheezing-positive RV illness in infancy) [60]. These findings were independent of the number of infections in infancy.

In the same birth cohort, 259 children were available for follow up at 6 years of age [61]. Asthma was diagnosed in 28% of children on the basis of formal criteria. Having had a prior HRV infection associated with wheezing was strongly associated with the eventual development of asthma regardless of whether the wheezing HRV illness occurred in the 1st, 2nd, or 3rd year of life (Table 3). While children with wheezing illnesses with both RV and RSV in the first 3 years also had significant risk of developing asthma, children who wheezed with RSV alone were only at increased risk of asthma if their illness occurred in the third year of life. The increased risk of asthma with HRV wheezing episodes also held true when children with HRV wheezing (either RV alone or RV + RSV) were compared to those children who wheezed only with RSV [61].

In a prospective birth cohort from Australia, newborns at high risk of asthma (parent with physician-diagnosed history of hay fever, asthma, or eczema) were enrolled and clinical and virologic information was obtained for all respiratory illnesses in the first year of life. The occurrence of wheezing illness and diagnosis of asthma were assessed yearly until the age of 5 years and atopy was evaluated at 6 months, 2 years, and 5 years. These investigators

Table 2
Important prospective cohort studies evaluating relationship of human rhinoviruses to asthma inception.

Design	Inclusion	Viral detection method	Input	n in study/ median age at follow up	Outcome of interest	Risk for outcome	Citation
Prospective cohort study with retrospective virologic evaluation	Children aged 1–23 months with respiratory infection associated with wheezing and respiratory distress requiring hospital admission	direct antigen detection: RSV, parainfluenza, influenza A and B, adenovirus RT-PCR: rhinovirus, enterovirus, and coronavirus	Respiratory illness requiring admission to hospital between 1 and 23 months of age	82 children median age: 7.2 years	i) asthma related maintenance medication ii) specific symptoms/ symptom frequency suggestive of asthma	Illness with RV alone: OR 4.14	[58,59]
Prospective birth cohort	At least one parent with skin test confirmed respiratory allergy AND/OR physician-diagnosed asthma	viral culture: RSV, influenza A and B, parainfluenza, rhinovirus, enteroviruses, adenovirus immunofluorescence: RSV, influenza A and B, parainfluenza and enteroviruses RT-PCR: rhinovirus	Moderate to severe respiratory illness with or without wheezing in 1st, 2nd, or 3rd year of life	275 children 3 years	wheezing at age 3 years: parental questionnaire at 3-year visit asking whether child had wheezed in prior year.	i) RV illness without wheezing: OR 2.3 ii) RV illness with wheezing: OR 10 iii) RSV illness with wheezing: OR 3.0	[60]
				259 children 6 years	current asthma i) physician diagnosis ii) use of albuterol for coughing or wheezing iii) use of daily controller medicine iv) step up plan including short term inhaled corticosteroid v) use of prednisone for asthma exacerbation	i) 1st year RV illness with wheezing: OR 2.7 ii) 2nd year RV illness with wheezing: OR 6.5 iii) 3rd year RV illness with wheezing: OR 31.7	[61]
Prospective birth cohort	At least one parent with physician-diagnosed history of hay fever, asthma, or eczema	RT-PCR: rhinovirus, enterovirus, coronavirus, influenza A and B, parainfluenza, adenovirus, human metapneumovirus	nonwheezy lower respiratory tract infection OR wheezy lower respiratory tract infection (wLRI) in first year of life	198 children 5 years	i) Asthma-physician-diagnosed asthma ever in the 5 years ii) Current asthma – asthma and wheeze in 12 months prior to 5-year visit	wLRI – with RV: i) OR 2.9 for persistent wheeze ii) OR 2.5 for current wheeze iii) OR 2.9 for current asthma	[62]

identified that HRV detection in the setting of a lower respiratory tract infection accompanied by wheezing was significantly associated with physician diagnosis of asthma (OR, 2.9; $p = 0.02$) as well as the occurrence of persistent wheezing (OR, 2.9; $p = 0.02$) at 5 years of age. In this cohort the occurrence of a wheezing illness with RSV was found also to be significantly associated with persistent wheeze (OR, 2.7; $p = 0.04$), but not with a diagnosis of asthma [62].

The relationship between antecedent HRV infection and asthma inception has also been evaluated using retrospective birth cohort information from a Medicaid database. Using database information and ICD-9 codes the authors identified children in the first year of life with no health care visit for bronchiolitis and those with a first visit for bronchiolitis [63]. Children were classified on the basis of whether this first bronchiolitis visit occurred during a winter virus season (November–April or December–February) or during a non-winter virus season (May–October or August and September). The narrower time frames were used to select for a primarily RSV season (December–February) or a primarily HRV season (August and September). Similar to the findings in the above studies, the risk of eventual development of asthma was significantly higher in the children with bronchiolitis during the non-winter virus season (RR, 2.22; 95% CI, 2.08–2.38) than in those children with bronchiolitis during the winter virus season (RR, 1.94; 95% CI, 1.86–2.03) when compared to children who did not have bronchiolitis in the first year of life. When compared directly, children with bronchiolitis in the HRV specific season were significantly more likely to develop asthma at the age of 4–5.5 years than those who had bronchiolitis during the RSV specific season (RR, 1.25; 95% CI, 1.13–1.38). Based on the seasonal differences in emergence of RSV and HRV, the authors conclude that this effect of bronchiolitis season on asthma development suggests a stronger role for HRV than RSV in eventual development of asthma. Although these findings are limited by the lack of viral detection and the possible misclassification of illness, these limitations would likely lead to underestimation of the effect rather than overestimation. Taken together, the above studies support an association between the occurrence of RV lower respiratory tract illness in infancy and the eventual development of asthma, an association that appears to be stronger for RV than for RSV.

4. Bocavirus

Human bocavirus (HBoV) is a newly discovered human parvovirus first identified in 2005 using molecular virus sequencing [64]. At present HBoV can only be detected using PCR techniques. Following identification of HBoV numerous studies were published reporting detection of the virus primarily in children with respiratory tract infection [65–69]. While causality for HBoV in acute respiratory tract infection has been difficult to determine, several trends have emerged – including highest rates of detection in younger age children (<2 years) and high frequency of co-detection with other respiratory viruses (Table 4).

Evaluation of the role of HBoV in asthma exacerbations is generally limited to studies primarily performed to detect HBoV in patients with

Table 3
Odds ratios for diagnosis of asthma at age 6 years by year and type of viral infection (data from [61]).

Year of viral infection	OR for asthma at 6 years [a]		
	Wheeze only with RV	Wheeze with RV + RSV	Wheeze only with RSV
1st year	2.9	2.7	1.2 (NS)[b]
2nd year	5.6	12.6	1.3 (NS)
3rd year	42.6	25.6	13.6
All 3 years	9.8	10.0	2.6

[a] Compared to children who did not wheeze with RV or RSV.
[b] All p values<0.05, unless marked as nonsignificant (NS).

acute respiratory symptoms. In one study performed shortly after discovery of HBoV, nasopharyngeal aspirate specimens from patients originally enrolled in a study to evaluate the effect of corticosteroids on wheezing were evaluated for HBoV [14]. Patients in this study ranged from 3 months to 16 years of age (61% with diagnosis of bronchiolitis; 39% acute asthma) [70]. Samples were obtained from non-asthmatic asymptomatic control patients by nasal swab. HBoV was detected in 49 patients (19%) of the 259 patients with a specimen available for testing. While HBoV was the sole virus in only 24% of HBoV-positive specimens, it was detected with greater frequency in patients with acute wheezing than asymptomatic controls (19% vs. 0%; $p<0.001$) [14]. Further, the authors defined non-overlapping populations of high and low HBoV quantitative viral load and found that, in patients with a high viral load, HBoV was more prevalent in children who did not have other viruses detected (i.e., "illness of otherwise unexplained etiology").

In a prospective study of HBoV and asthma exacerbation, 166 children aged 2–15 years with a history of asthma presenting to a single institution emergency department with severe asthma exacerbation were enrolled and a single nasopharyngeal aspirate was performed [71]. HBoV was detected in 16% of children 2–5 years old and 9% of children aged 5–15 years. Compared to a non-concurrently enrolled control population of children with stable asthma and no acute exacerbation, children with acute asthma exacerbation were significantly more likely to have HBoV detected (OR, 7; $p = 0.031$). Viral co-detection was only noted in four HBoV-positive cases. In spite of these findings this study was limited by several features. Detection of HRV, well described in association with asthma exacerbations, was not performed. Further, HBoV detection was performed by PCR whereas detection of other viruses was performed by viral culture as well as immunofluorescence. Both of these features may have limited the detection of other viruses in HBoV-positive specimens.

In a prospective birth cohort study in which detection of HBoV was similar between symptomatic and asymptomatic patients, a family history of asthma was noted as a risk factor for HBoV detection (OR, 2.20; 1.20–6.10; $p = 0.017$) [72]. Another study performed PCR for HBoV on specimens otherwise negative for respiratory viruses. Low rates of HBoV detection were noted but of the 16 patients with HBoV detection and with clinical data available, 28% of patients had wheezing and two patients had a clinical diagnosis of asthma [73]. Finally, in a retrospective study from Italy, nasopharyngeal specimens from 22 adult patients with severe asthma were available for testing. HBoV DNA was detected in none of these patients. This finding comes with the caveat that HBoV is primarily isolated from young children [74]. While these studies indicate a possible role for HBoV in acute asthma exacerbation, conclusions are hindered by high viral co-detection rates and lack of longitudinal prospective studies dealing specifically with acute asthma exacerbations.

More recently the association of HBoV detection with respiratory symptomatology has been investigated by prospective, longitudinal analysis [75]. Although this study did not specifically address asthma exacerbations, its findings provide insight into the relevance of HBoV detection in respiratory illness and have implications for study of HBoV and asthma. In this evaluation, 119 children between the ages of 6 and 24 months were prospectively enrolled if they attended one of three daycares for 20 h or more per week. Nasal swab samples were obtained at study enrollment and then with every respiratory illness for up to 2 years. Surveillance was performed both passively (parent or daycare staff contacted study staff with new or worsening illness in a child) and actively (by on-site study nurse). Illness symptoms were assessed by both study nurse interview of parents and by daily symptom diaries completed by parents. Comprehensive testing of nasal samples for 14 respiratory viruses was performed by PCR with testing for HBoV DNA performed retrospectively. Samples were obtained once weekly in a child until the sample was negative for all viruses and the child was symptomatically improving. Several

Table 4
Prevalence of human bocavirus detection and viral codetection rates from selected studies.

Citation	HBoV-positive specimen prevalence (%)	HBoV-positive specimens with viral codetection (%)	HBoV codetection by virus (% of HBoV-positive specimens)					
			RV	Enterovirus	RSV	Adenovirus	hMPV	Other
[14]	19.0%	76.0%	28.6%	14.3%	14.3%	16.3%	NA	2.0% [a]
[71]	12.7	23.8	[b]	–	4.8	–	4.8	14.3 [c]
[72]	8.2 [d]	47.4	14.0	–	8.8	8.8	1.8	14.1 [e]
[75]	33.3 [d]	72	34.9	–	[f]	31.1	[f]	[g]

[a] Unidentified in article.
[b] Detection for RV not performed in this study.
[c] Mycoplasma pneumoniae detected.
[d] Prevalence in patients with respiratory symptoms.
[e] 12.3% coronavirus; 1.8% parainfluenza virus.
[f] Codetections noted but specific numbers not reported.
[g] Influenza, parainfluenza, and coronavirus also detected but numbers not reported.

findings of this study point to a lack of association between HBoV detection and the presence of respiratory illness. While HBoV was second only to RV in frequency of detection in this study (106 of 318 study illnesses), the rate of co-detection was high with 72% of HBoV-positive illnesses having one or more other viruses detected. Detection of HBoV was not strongly associated with illness onset or with symptomatology by several markers. At study enrollment, HBoV was detected in samples from 44% of asymptomatic enrollees and there was no significant difference in detection between symptomatic and asymptomatic patients at enrollment. In 21% of HBoV-positive illnesses the initial detection of HBoV occurred at or after the second week of illness symptoms. Furthermore, in 20 'shedding events' with HBoV detected repeatedly in individual patients, HBoV detection spanned the occurrence and resolution of multiple respiratory illnesses. Finally, there was no difference in viral load of HBoV between symptomatic and asymptomatic patients. The findings of this study argue against an important role for HBoV in the pathogenesis of respiratory illnesses, and by extension, asthma.

While the role of HBoV in respiratory diseases and in asthma remains to be fully elucidated, the recent successful culturing of HBoV from human airway epithelial cells will allow more complete study of its putative role in both of these settings [76]. Increased use of serologic assays within these studies may also shed increased light on the role that HBoV plays in respiratory tract infections [77–80]. Prospective longitudinal studies utilizing these techniques will hopefully increase our understanding of what, if any, role human bocavirus plays in asthma.

5. Respiratory syncytial virus

Respiratory syncytial virus (RSV) is a non-segmented negative-strand RNA virus of the family *Paramyxoviridae* that is well described as a significant cause of acute respiratory infections and bronchiolitis in children [81]. Seasonal outbreaks of RSV are responsible for significant worldwide morbidity and mortality [82]. Although RSV is a significant cause of bronchiolitis and wheezing in infants and younger children, it does not emerge as a prominent cause of asthma exacerbation in studies of older children [13]. Therefore, in this section we will focus on studies evaluating the connection between RSV infection in infancy and eventual development of asthma.

A relationship between RSV bronchiolitis and the eventual development of asthma has long been postulated and evaluated [83]. In spite of the numerous studies directed at evaluating this relationship over the past 30 years, debate continues over whether RSV bronchiolitis in infancy causes an aberrant immune response resulting in development of asthma or is rather a marker of underlying genetic predisposition to the eventual development of asthma. In the late 1980s and early 1990s the Tucson Children's Respiratory Study, a prospective birth cohort, defined that a subset of infants with early childhood wheezing develop persistent wheezing

episodes later in life and that a family history of asthma is a risk factor for this persistent wheezing [84]. Both the frequency of RSV infection in infancy and the recognition in this study that many episodes of bronchiolitis and wheezing in infancy were caused by RSV [85] led to further intensive evaluations of the relationship between RSV infection in infancy and the development of asthma [86,87]. Recent studies designed to evaluate the nature and direction of this association are listed in Table 5. Several large prospective cohort and retrospective database studies have informed the debate over a causal role for RSV in asthma development. In this section we will review more recent studies from these groups in light of their prior contributions.

In 1995 a group from Boras, Sweden published the first in a series of studies evaluating the prevalence of asthma following episodes of RSV bronchiolitis requiring hospitalization in infants [88]. Their original cohort consisted of 47 RSV-infected infants with a mean age of 3.5 months and 93 date-of-birth, sex, and residence-matched control infants. Subsequent studies have indicated increased risk of asthma and allergic sensitization in the RSV-infected infants at 3, 7½, and 13 years with 28% of children in the RSV group carrying a current diagnosis of asthma at 13 years of age (RR, 8.7; $p < 0.001$) compared to the control group [87–89]. Follow up information from this group at 18 years of age has recently been published [90]. At this time point, 46 of the original 47 RSV-infected subjects and 92 of the 93 control subjects were available for study. Importantly, RSV-infected and control groups did not have significant differences in family history of asthma, allergic rhinoconjunctivitis, or atopic dermatitis. As previously noted, the RSV-infected cohort had increased prevalence of current asthma (33% vs. 7%, $p < 0.001$) and allergic sensitization defined by skin-prick testing (33% vs. 11%, $p = 0.005$) compared to the control cohort [90]. The authors evaluated multiple risk factors for current asthma using multivariate logistic regression and determined that only prior RSV (OR, 7.2) and current allergic rhinoconjuncitivitis (OR, 4.4) were significant independent risk factors for current asthma. While the power in the study was inadequate to specifically assess the effect of differences in parental history of asthma in the RSV group on current diagnosis of asthma, a significant trend was noted for the combined effect of both RSV and parental asthma history on current asthma and allergic sensitization. This study provides interesting information regarding the persistence of asthma following RSV bronchiolitis into early-adulthood and suggests that the effect may be more prolonged than previously noted. A similar persistence of asthma has also been found in a cohort of children with RSV bronchiolitis prior to the age of 2 years [91].

The Tennessee Asthma Bronchiolitis Study (TABS) is a population-based retrospective birth cohort of over 90,000 children identified from a Medicaid database with linked vital records files. Using information from health care visits, pharmacy data, and demographic data available through these databases, investigators have evaluated the relationship between winter virus infection and asthma [63,92,93]. In an earlier

Table 5
Studies evaluating the impact of bronchiolitis, RSV bronchiolitis, and genetic predisposition on development of asthma.

Citation	Design	Year	Inpatient/Outpatient [a]
Murray et al. [110]	PC	1992	Inpatient
Martinez et al. [84]	PBC	1995	Inpatient/Outpatient
Noble et al. [111]	PCC	1997	Inpatient
Castro-Rodriguez et al. [112]	PBC	1999	Inpatient/Outpatient
Piippo-Savolainen et al. [91]	PBC	2004	Inpatient
Fjaerli et al. [113]	RCC	2005	Inpatient
Wu et al. [92]	RC	2008	Inpatient/Outpatient
Carroll et al. [63,93]	RC	2009	Inpatient/Outpatient
Pullan et al. [83]	PCC	1982	Inpatient
Sigurs et al. [87–90]	PCC	1995, 2000, 2005, 2010	Inpatient
Stein et al. [86]	PBC	1999	Inpatient/Outpatient
Bont et al. [114]	PC	2004	Inpatient
Henderson et al. [115]	PBC	2005	Inpatient
Kusel et al. [62]	PBC	2007	Outpatient
Simoes et al. [116,117]	PC	2007, 2010	Inpatient/Outpatient
Lee et al. [118]	PBC	2007	Outpatient
Goetghebuer et al. [119]	PC	2004	Inpatient
Stensballe at al. [120]	RCC	2006	Inpatient
Thomsen et al. [96]	RC-T	2008	Inpatient
Stensballe et al. [95]	RC-T	2009	Inpatient
Thomsen et al. [97]	RC-T	2009	Inpatient
Poorisrisak et al. [94]	RC-T	2010	Inpatient
Thomsen et al. [98,121]	RC-T	2010	No viral infection

Abbreviations: PBC – prospective birth cohort; PC - prospective cohort; RCC – retrospective case–control; PCC – prospective case–control; RC – retrospective cohort; RC-T – retrospective cohort, twin study.
[a] Location of patients at occurrence of viral infection.

study using this database, this group determined an association between infant birth timing in relationship to winter virus season and the development of childhood asthma between 3.5 and 5 years of age [92]. Weekly frequencies of bronchiolitis hospitalizations were used to determine the 'winter virus peak' during the time period of the study. Using this data, the authors found that infant birth timing with regard to winter virus peak was predictive of infants developing bronchiolitis with the peak risk of bronchiolitis at 122 days of age. Timing of infant birth was also predictive of development of childhood asthma with children 121 days of age having the highest risk. Children at this age had a statistically significant increase in likelihood of developing asthma compared to those infants born 12 months prior to peak winter virus time (adjusted OR, 1.29; 95% CI, 1.19–1.40). This relationship held when other possible interactions were taken into account (smoking during pregnancy, maternal asthma, infant race, gender, birth weight, gestational age, living siblings, region of residence, and maternal education). The authors point out that a purely genetic effect in the development of asthma while still allowing a seasonal development of bronchiolitis in these infants would not result in a seasonal effect on asthma.

In more recent study, this group used the same Medicaid database to establish a severity-dependent relationship between bronchiolitis occurrence in infancy and eventual diagnosis of asthma [93]. Severity of bronchilitis was determined by the location at which a patient received care for their illness (outpatient visit, emergency department visit, hospital stay). Patients with increased level of care associated with an asthma ICD-9 code had significantly increased risk of asthma development (OR, 1.86, 2.41, and 2.28, for outpatient, emergency department, and hospitalization, respectively) compared to children without any medical visit for bronchiolitis. This relationship was noted whether a familial predisposition to asthma, defined by presence of maternal asthma, was present. While this study does not establish causality, the relationship between bronchiolitis severity and asthma development and the persistence of this effect independent of maternal history of asthma is suggestive of a role for viral

infection in the development of asthma that is distinct from genetic contributions to risk.

Registry-based twin studies have contributed information indicating a genetic component in the relationship between RSV bronchiolitis in infancy and the development of asthma [94–97]. These studies were performed using the Danish National Patient Registry and the Danish Twin Registry. Previously, these investigators evaluated the associations between RSV and asthma in a bidirectional manner. Using the twin registry, they found that while the occurrence of RSV bronchiolitis did result in increased risk of subsequent asthma, this increased risk was time-dependent and decreased significantly over the following 1–2 years. Looking at the opposite direction, the occurrence of asthma (defined from the registry as asthma-related hospitalization or asthma-related corticosteroid use) was associated with an increased risk of subsequent RSV bronchiolitis that remained significant over time [95]. Although the authors speculated that these findings are accounted for by a predisposition to severe RSV infection in asthmatics, it is important to note that the majority of asthma diagnoses and corticosteroid use in their study occurred in the first 2 years of life when transient early wheeze is a frequent occurrence that does not necessarily represent asthma.

Most recently, asthma outcomes were evaluated in a group of monozygotic twins who were discordant for documented hospitalization due to RSV. In this way the effect of RSV on eventual asthma was assessed independent of any genetic differences. The investigators evaluated lung function, bronchial responsiveness, asthma diagnosis, and use of asthma medications at a mean age of 7.6 years and found no differences between the RSV hospitalized twins and the non-hospitalized twin in these measures [94]. While limited by a small sample size of 37 twin-pairs, these results contradict those of the TABS group in which increased severity of bronchiolitis resulted in increased risk of asthma, and instead support the critical role of genetic factors in predisposition to asthma. Additional investigation by this group has reported a genetic effect on occurrence of severe RSV and the age of diagnosis of asthma and further determined that a model in which asthma 'caused' RSV hospitalization fit the twin registry data better and with statistical significance than did a model in which RSV hospitalization 'caused' asthma [96–98].

6. Human metapneumovirus

Human metapneumovirus (hMPV), a paramyxovirus closely related to RSV, was first isolated in 2001 and has been well described to cause respiratory tract infections in children [99–101]. Early studies defined that as many as 14% of children admitted with LRTI due to hMPV were diagnosed with asthma exacerbation [101]. Other studies have supported this observation when investigating children under 5 years [102–104]. When including children aged 2–17 years, hMPV was however not associated with asthma exacerbation [13]. hMPV also appears to play an etiologic role in asthma exacerbation in adults [105]. More recently prospective surveillance by the NVSN of hospitalized children under the age of 5 years with acute respiratory infection or fever documented population-based incidence rates for hMPV in this age group [99]. Peak incidence rates occurred in the 0–5 month (4.9 infections/1000 children) and 6–11 month (2.9 infections//1000 children) age groups with overall incidence of 1.2 infections//1000 children 0–5 years of age [99]. Finally, few studies have evaluated the role of hMPV in development of asthma. In the sole study directed primarily at this question, the occurrence of hMPV bronchiolitis under 2 years of age was significantly associated with asthma diagnosis between the ages of 3 and 5 years (OR for asthma diagnosis, 15.9 for hMPV). In this study the association of hMPV and asthma diagnosis actually exceeded that seen for RSV bronchiolitis (OR, 10.1) [106].

7. Concluding remarks

Despite the abundance of studies addressing the role of viral infections in the development of asthma, definitive conclusions cannot yet be draw about the causal nature of the relationship. From the available evidence, the development of asthma emerges from a complex interaction of genetic predisposition and environmental factors with viral infection likely playing a significant role in the effect of environment on asthma inception. The discovery of new viruses such as HRVC and human bocavirus continue to provide intriguing avenues for further research into the relationship of viruses to asthma. Continued evaluation of this interaction with epidemiologic investigation, cohort studies, animal models, and in vitro evaluation is required to gain new insights and answers to these issues.

Acknowledgement

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