Rhinovirus infections in infancy and early childhood

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Abstract

Rhinovirus (RV) infections occur early and recurrently in life, imposing a significant burden of disease on infants and young children. They are the most frequent causative agents of both upper and lower respiratory tract infections in this age group and are associated with a broad variety of clinical outcomes, ranging from asymptomatic infections to severe respiratory disease requiring hospitalisation. In addition to their impact on short-term morbidity, RVs are also debated as important pathogens in the development of recurrent wheeze and/or asthma. Several studies in infants at high-risk for atopy and asthma and in hospitalised children have demonstrated that recurrent wheezing illnesses induced by RVs in early life are a risk factor for asthma development later in childhood. Underlying mechanisms, however, are poorly understood. The question whether RVs are directly involved in the development of childhood wheeze and asthma, or whether symptomatic RV infections only represent a proxy for infants prone to develop obstructive lung diseases, is still open. In this review we provide an overview on the role of RVs as important disease-causing agents from infancy to early childhood and discuss their contribution to the subsequent development of childhood wheeze and/or asthma.
**Definition of abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ARTI</td>
<td>Acute respiratory tract infection</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>ICAM-1</td>
<td>Intercellular adhesion molecule-1</td>
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<td>LDLR</td>
<td>Low-density lipoprotein receptor</td>
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<td>LRTI</td>
<td>Lower respiratory tract infection</td>
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<td>OR</td>
<td>Odds ratio</td>
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<td>PCR</td>
<td>Polymerase chain reaction</td>
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<td>RNA</td>
<td>Ribonucleic acid</td>
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<td>RSV</td>
<td>Respiratory syncytial virus</td>
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<tr>
<td>RV</td>
<td>Rhinovirus</td>
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<tr>
<td>URTI</td>
<td>Upper respiratory tract infection</td>
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</table>
Introduction

Acute respiratory tract infections (ARTIs) are the most frequent infections worldwide and represent a major public health problem. They are the leading cause of acute illnesses in all age groups and a major contributing factor of childhood morbidity and mortality [1, 2]. Infants and young children are particularly vulnerable to ARTIs as their immunity is still developing and not fully in place to defend against most of the respiratory pathogens they are exposed to. ARTI in young children are very common and usually of viral origin due to the abundance of circulating viruses and their easy transmission among hosts. Viral ARTIs in childhood result in a wide range of disease severity – from the common cold to severe life-threatening respiratory tract infections [3]. Thus, they impose considerable burden on health care systems and account for a large proportion of emergency visits and hospitalisations [4].

A large number of community-based studies have characterised the frequency, seasonality, age specificity and clinical features of viral ARTI in childhood and have determined the most commonly involved pathogens in children [5-7]. These are respiratory syncytial virus (RSV) [8], influenza virus [9], parainfluenza virus [10], adenovirus [11], rhinovirus (RV) [12] and coronavirus [13]. Recent advances in the development of diagnostic techniques, and specifically of molecular biology tools [14-16], have led to the identification of additional viruses associated with ARTI in childhood, amongst them human metapneumovirus [17], the coronaviruses NL63 and HKU1 [18, 19], bocavirus [20] and different subgroups of RVs [21], and of emerging viruses such as SARS coronavirus [22] and the H5N1 and H1N1 influenza viruses [23, 24]. Whereas the role of RSV, influenza virus, parainfluenza virus, adenovirus and more recently human metapneumovirus in causing ARTI in infants and children has been intensively studied and is widely accepted [6, 25], the contribution of RVs to respiratory morbidity in childhood is subject to debate [26, 27].
The aim of this review is to provide an overview of the increasingly recognized role of RVs as important disease-causing agents from infancy to early childhood, to portray their impact on short-term and long-term morbidity, and to depict their role in the development of childhood wheeze and asthma.

**Characteristics, epidemiology and detection of rhinoviruses**

First discovered in the 1950s, RVs belong to the family *Picornaviridae*. They are small, non-enveloped viruses with a single-stranded, positive-sense RNA genome. To date, there are more than 100 identified serotypes, which are classified according to the receptor they bind at the surface of epithelial cells of the respiratory tract [28]. Strains binding to intercellular adhesion molecule-1 (ICAM-1) belong to the so-called major-group RVs, in contrast to the minor-group RVs, which consist of approximately ten strains and bind to the low-density lipoprotein receptor (LDLR) [29]. According to sequence variations, RVs are further classified into two main phylogenetic species, RV-A and RV-B [30, 31]. Recently, a novel RV species distributed worldwide, namely RV-C, was identified [21, 32-35]. One of the striking characteristics of RVs compared to many other respiratory viruses is that they replicate rapidly and demonstrate high mutation rates, resulting in distinct genetic diversity [36, 37]. Infections caused by certain genetic RV sublineages seem to be more prevalent in the general population, occur at specific seasons, and are also more often associated with symptomatic respiratory disease in children compared to other sublineages [38, 39]. *E.g.* RV-C was shown to cause nearly half of all RV-induced ARTIs with clinical and age-related differences as compared to RV-A or RV-B [40, 41].

The mode of RV transmission has been vividly discussed. Most probably, RVs are transmitted both by direct or indirect contact [28]. Infections with RVs have been shown to occur throughout the year [42, 43], but most reports suggest that there is a seasonal variability with peaks during cold and rainy seasons. The peak incidence of RV infections varies
annually and geographically [44], most probably depending on the seasonal distribution of specific strains [45-47]. Compelling evidence shows higher rates of RV infection during crowding of children at return to school after holidays [48-51]. Observations on virus transmission, infection patterns and immune responses suggest that due to a temporary lack of exposure during holidays, a transitory window of susceptibility to RV infections develops afterwards [52].

There are four principal ways in which RVs can be diagnosed: virus culture [53, 54], serology [55], immunofluorescence [56, 57] and nucleic acid / polymerase chain reaction (PCR)-based tests. Virus culture is labor-intensive and time-consuming, and culture results may only be available when clinical symptoms have already disappeared. Serology, which has long been the main diagnostic tool for RV infections, relies on the detection of an immune response towards the virus and thus only provides a delayed and indirect picture of the infection itself. Further, serology is insensitive, as some RVs serotypes lack a common group antigen, making the possibility of broadly reacting antibodies unlikely [58, 59]. Therefore, it is not longer used in routine diagnostics but only for studies purposes, such as epidemiological studies aimed at following the natural course of an infection [55]. Due to the lack of sensitive detection methods, the prevalence of RV infections has been under-estimated in early studies. The availability of new PCR-based molecular diagnostic techniques for virus detection [60], has provided evidence that RVs are the leading agents of the common cold and wheezing illnesses in infants and young children compared to any other virus affecting the respiratory tract [61-67]. However, the high sensitivity of PCR is also a limitation, as the presence of virus nucleic acid in respiratory secretions of a patient with respiratory symptoms does not prove that the virus is the cause of the symptoms. PCR may overestimate RV burden because of a high proportion of positive results in asymptomatic children [64, 68-71]. Further, PCR may detect remnants of previous virus infections or replication defective virus sequences. Indeed, RV
genome may be detected by PCR even weeks after an acute viral infection [65]. Finally, a high co-detection rate, with on average about 20% of respiratory samples being positive for two or more viruses during ARTI [3, 72], adds to the difficulty of differentiating RVs as true pathogens from innocent bystanders. Due to its lower sensitivity and possibly higher specificity for clinically relevant RV infections, rapid RV detection with immunofluorescence as been proposed as an alternative to PCR both for clinical and research applications [43, 57, 73, 74].

Clinical features of rhinovirus infections

Rhinoviruses and their impact on short-term morbidity: upper respiratory tract infection and the “common cold”

RVs are the most common pathogens associated with ARTI in all age groups, and they account for the vast majority of upper respiratory tract infections (URTIs) [75-78]. Together with coronaviruses, they are the main causative agents of the common cold [44, 78]. The common cold is the colloquial expression for a self-limited URTI of a median duration of nine to ten days with the most prevalent symptoms being a running nose, nasal stuffiness, sneezing, a sore throat and cough. Besides the common cold, RVs can also cause other URTIs with a range of mild to more severe symptoms, such as acute otitis media, sinusitisitis, pharyngitis and croup [4, 78, 79].

Rhinoviruses and their role in lower respiratory tract infections: more than just a “common cold”

Rhinoviruses replicate best at temperatures slightly below body temperature (33-34°C), and therefore RV infections were long assumed to be restricted to the upper airways. Recent breakthroughs in molecular diagnostics have provided data on RVs as important causes of lower respiratory tract infections (LRTIs) and of acute virus-induced wheeze in children. RVs
were shown to have the capacity to infect the lower respiratory tract and to replicate effectively in lower airway cells even at core temperatures of 37°C, although greater viral yields are obtained at lower temperatures [80-83]. In line with these findings, studies using sensitive molecular viral detection methods have shown that RVs are a common cause of LRTI in infants and young children including wheezing disorders, bronchiolitis and pneumonia, with potential subsequent hospitalisations [65-67, 84-92]. Both prevalence and severity of LRTI induced by RV are further increased in high-risk groups, especially in infants and young children with underlying chronic lung disease such as those with bronchopulmonary dysplasia [93, 94], asthma [66, 90, 95, 96] and cystic fibrosis [97-101]. Co-infection with other viruses, mainly with RSV, occurs in about one third of RV-infected children and has been linked to more severe respiratory symptoms [40, 86, 102, 103].

Rhinoviruses and their role in the very young

Infections with RV occur very early in life. Whereas older children experience on average one RV infection per year, this occurs up to two to three times more frequently in infants and younger children [42, 47]. As reported in several studies including in- and outpatient follow-up [47, 62-64, 67, 86, 87, 89, 90, 92, 104-107], as well as in prospective birth cohorts of otherwise healthy infants [66, 91, 108-111], RVs represent the most common pathogens associated with URTI, LRTI and wheeze in the first year of life (Table 1). The mean age at the first symptomatic RV infection is four to six months compared to more than six months for other viruses, such as RSV [67, 91]. By the age of six months, more than 20% of children have already experienced their first RV infection, by the age of two years RV can be identified in almost 80% of children with ARTI, and 90% of children have antibodies against RV [108]. Re-infections occur regularly and are usually caused by different virus strains [67]. Up to 30% of all hospitalisations due to respiratory symptoms in children below five years of age are caused by RVs (this relates to five hospitalisations per 1000 children) [90]. The
highest incidence was found in children with a personal history of wheeze and/or suspected asthma with up to 45%, only second to RSV in children younger than twelve months of age [62, 86, 87, 89, 106]. At the same frequency and especially among atopic infants older than six months, RV infections were found to be associated with ARTI or wheeze [66, 107, 110, 112]. This was also confirmed in studies from developing countries, which showed increased prevalence of RV infection and frequent association with wheeze in infants from two to six months of age [105, 111]. All these studies highlight the predominant role of RV as a respiratory pathogen in early life.

**Rhinoviruses and their role during asthma development: causing or unmasking asthma?**

*Current evidence*

RV infections not only constitute the most common cause of acute illnesses and wheezing during infancy, but they have also been debated [113-116] as important pathogens with regard to the development of subsequent recurrent wheeze and asthma [104, 110, 112, 117-120, 121] (Table 2). In the Childhood Origins of Asthma (COAST) study, a birth cohort study of high-risk infants (at least one parent with a history of doctor-diagnosed hay fever, asthma or eczema), Lemanske et al. [112] and Jackson et al. [110] identified moderate to severe RV-induced wheezing illnesses in the first years of life as strongest predictors and risk factors for subsequent wheeze at the age of three and six years, respectively. Almost 90% of high-risk children who wheezed with RVs at the age of three years had asthma at school-age [110]. These findings are corroborated by data of an Australian birth cohort study of children at high risk for asthma development, in which Kusel et al. [119, 121] found that RV-induced wheezing illnesses in infancy were associated with asthma at age five and ten years. Also Finnish studies [117, 118, 120] showed that infants hospitalised because of RV-induced wheezing exhibited a considerably higher risk for childhood and adolescent asthma as compared to infants hospitalised because of LRTI associated with other viruses. Taken
together, high frequency and severe RV infections during infancy, especially in high-risk infants with an atopic background, seem to increase the risk for subsequent wheeze/asthma in childhood.

_Possible mechanisms_

The precise mechanisms through which RV-induced illnesses are involved in the pathogenesis of subsequent childhood wheeze and the development of asthma are unknown. Although the majority of children are infected with RV at the age of two years, only one third of infants undergoing recurrent RV-induced illnesses will go on to develop asthma later in life [28]. The question whether RV infections are directly involved in the development of childhood wheeze and asthma, for instance through damage of the airway epithelium and the induction of inflammatory and remodelling processes, or whether they rather unveil infants prone to develop obstructive lung diseases, is subject to debate [122]. In fact, both scenarios are not mutually exclusive.

As RVs have the ability to invade lower airways and escape immunity [58], they may promote exaggerated inflammatory responses towards further stimuli such as allergens, and lead to enhanced airway responsiveness, possibly promoting the development of asthmatic features [123-126]. Evidence from animal studies further suggests that viral infections are important environmental stimuli for airway inflammation, injury and remodelling [126-128]. Exact pathophysiological mechanisms of viral infections and atopy in asthma have been previously reviewed extensively [129]. Infancy is a period of profound growth and development of the pulmonary and immune systems [130, 131], and recurrent RV infections and associated inflammatory and remodelling processes during this time may thus inter- and disrupt normal processes of lung growth. Infants repeatedly undergoing severe RV infection might therefore develop recurrent wheezing as a consequence of airway remodelling and impaired lung growth.
On the other hand, symptomatic RV infections might only represent a proxy for infants prone to develop obstructive lung diseases. Indeed, important determinants for the occurrence of wheezing illness including RV-associated wheezing during the first year of life have been recently described. An already reduced premorbid lung function shortly after birth was shown to predispose infants to more frequent and severe LRTI [132-134]. Further studies have demonstrated that timing and frequency of RV-induced wheezing illnesses, respectively, play an important role in asthma pathogenesis [110, 135, 136]. The age at which RV-induced wheeze occurs has a prognostic value, with later wheeze playing a more important role than early wheeze [110, 112].

**Interplay with other risk factors for asthma development**

Several risk factors for asthma development, including non-viral ones, have been identified in clinical and population-based studies. Intrinsic factors include epigenetic [137, 138] and genetic factors [138-140], the stage of infant development, airway size [132-134, 139], immune function [139], male gender [139], stress [141], disease severity [121], airway hyperresponsiveness and atopic predisposition [139, 142-145]. Amongst extrinsic factors, environmental and lifestyle factors, such as various exposures *in utero* and in early life, e.g. indoor and outdoor air pollutants [139, 146, 147], environmental and parental/maternal tobacco smoke [139, 145, 148, 149], older siblings and early daycare attendance [139, 144] are known to be relevant. It has been for example shown that traffic-related air pollution impairs lung development and influences the frequency of asthma exacerbations in older children [150]. There is also evidence for a significant impact of air pollution and environmental tobacco smoke exposure on lung development during pregnancy and early life [151], with a clear connection to asthma development [150].

The interesting question is, which of these factors might denote a link to viral infections and their impact on asthma risk. One such factor is atopy. The highest risk to develop asthma was
observed for children having both recurrent viral infections during infancy and atopic features, such as atopic dermatitis or a family history of allergy [110, 112, 119, 152, 153]. Moreover, it was recently demonstrated that allergic sensitization precedes RV-associated wheezing [154], suggesting that allergic sensitization leads to more severe RV-induced illnesses. These findings support a causal role for allergic sensitization in this developmental pathway, but underlying mechanisms are poorly understood. It might be that the innate antiviral immune system of atopic children gets additionally activated in an atopy-dependent way upon respiratory viral infection, which would amplify and sustain airway inflammation via enhancement of atopy-associated immune cascades, e.g. by increasing up-regulation of specific high-affinity Immunglobulin E receptors involving T-helper type 2 cells [155]. Additional contributors and determinants of the risk might be polymorphisms in genes encoding cytokines or other mediators of the immune system [140], or genes that have been associated with asthma [156-159]. Some protective factors have been reported as well, in particular the allergy-protective farm exposure [160] and the presence of commensal bacteria [161]. Both factors are important for normal cellular immune maturation and further control of allergic airway inflammation. However, their role in preventing infants from RV-induced wheezing illnesses and further prevention of subsequent development of childhood asthma remains unclear. To summarize, viral aetiology, illness severity, timing, allergic sensitization and genetic predisposition probably all contribute as synergistic factors to the risk of developing asthma.

**Conclusion and outlook**

Recent advances in molecular diagnostic tools have led to a better understanding of the impact of RV infections in infancy and childhood. RV infections occur early and recurrently in life and impose a large burden of disease on the very young. RVs are not only the most frequent pathogens of URTI and LRTI in this age group, but have been shown to represent an
important pathogenic factor for the development of recurrent wheeze and asthma. However, most of the studies that have highlighted the role of RV in causing acute illness and as possible contributor to asthma development have been performed in hospitalised and high-risk infants or in infants from selected populations of a wide age-range. Thus, little is known about the true impact of RVs on both short- and long-term morbidity in otherwise healthy infants. In particular, knowledge about occurrence of asymptomatic RV infections early in life and their relationship with e.g. early bacterial acquisition or atopy is poor. Carefully conducted prospective and longitudinal population-based studies in unselected healthy infants and young children are needed to more precisely define underlying mechanisms of RV-induced wheezing episodes in early life and their complex interactions with atopy, age and maturity of the immune system on asthma development. A better understanding and characterisation of these relationships might enable identification and close follow-up of children at highest risk for severe RV infections and asthma development. This might also help to better target preventive and therapeutic measures for these conditions, such as immunisations or antiviral therapies against RV.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Country / Cohort</th>
<th>Study type</th>
<th>Study population</th>
<th>Study enrolment</th>
<th>Follow-up</th>
<th>Assessment of RV prevalence</th>
<th>RV prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midulla et al., 2011 [107]</td>
<td>Italy / n. m.</td>
<td>prospective cohort study</td>
<td>hospitalised infants¹ and controls³</td>
<td>&lt; 1 year of age</td>
<td>1st year</td>
<td>during hospitalisation regardless of symptoms</td>
<td>3.2% (without recurrent wheezing) 10.9% (with recurrent wheezing)</td>
</tr>
<tr>
<td>Van der Zalm et al., 2009 [109]</td>
<td>Netherlands / WHISTLER prospective birth cohort study</td>
<td>healthy infants</td>
<td>2-3 weeks of age</td>
<td>1st year</td>
<td>during symptoms of respiratory illness</td>
<td>73%</td>
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<tr>
<td>Peltola et al., 2009 [92]</td>
<td>Finland / n. m.</td>
<td>retrospective study</td>
<td>hospitalised infants²</td>
<td>&lt; 1 year of age</td>
<td>-</td>
<td>during acute respiratory infection</td>
<td>26%</td>
</tr>
<tr>
<td>Peltola et al., 2009 [92]</td>
<td>Finland / n. m.</td>
<td>prospective study</td>
<td>hospitalised infants²</td>
<td>≥ 1 month of age</td>
<td>3 weeks</td>
<td>during hospitalisation regardless of symptoms during first LRTI</td>
<td>28%</td>
</tr>
<tr>
<td>Regamey et al., 2008 [91]</td>
<td>Switzerland / BILD prospective birth cohort study</td>
<td>healthy infants</td>
<td>prenatally</td>
<td>1st year</td>
<td>during scheduled visits at 2-4-6-9-12 months of age (regardless of symptoms) and during respiratory illness</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>Jartti et al., 2008 [67]</td>
<td>USA / COAST prospective birth cohort study</td>
<td>high-risk infants¹</td>
<td>at birth</td>
<td>1st year</td>
<td>during scheduled visits at 2 weeks and 4-8-12 months of age (regardless of symptoms)</td>
<td>35-61%</td>
<td></td>
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<tr>
<td>Lee et al., 2007 [104]</td>
<td>Canada / CAPP intervention study</td>
<td>high-risk infants¹</td>
<td>prenatally</td>
<td>1st year</td>
<td>during scheduled visits at 2 weeks and 4-8-12 months of age (regardless of symptoms) and during respiratory illness</td>
<td>68%</td>
<td></td>
</tr>
<tr>
<td>Miller et al., 2007 [90]</td>
<td>USA / n. m.</td>
<td>prospective study</td>
<td>hospitalised infants²</td>
<td>&lt; 5 years of age</td>
<td>n. m.</td>
<td>during acute respiratory infection</td>
<td>26%</td>
</tr>
<tr>
<td>Kusel et al., 2006 [66]</td>
<td>Australia / n. m.</td>
<td>prospective birth cohort study</td>
<td>high-risk infants¹</td>
<td>prenatally</td>
<td>1st year</td>
<td>during symptoms of acute respiratory illness</td>
<td>48%</td>
</tr>
<tr>
<td>Jacques et al., 2006 [89]</td>
<td>France / n. m.</td>
<td>prospective study</td>
<td>hospitalised infants²</td>
<td>&lt; 36 months of age</td>
<td>n. m.</td>
<td>during acute respiratory infection</td>
<td>21%</td>
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<tr>
<td>Korppi et al., 2004 [87]</td>
<td>Finland / n. m.</td>
<td>prospective trial</td>
<td>hospitalised infants²</td>
<td>1-23 months of age</td>
<td>n. m.</td>
<td>during acute respiratory infection</td>
<td>52%</td>
</tr>
<tr>
<td>Heymann et al., 2004 [106]</td>
<td>USA / n. m.</td>
<td>case-control study</td>
<td>hospitalised infants² and controls³</td>
<td>2-36 months of age</td>
<td>n. m.</td>
<td>during hospitalisation regardless of symptoms</td>
<td>58% (wheezing infants) 26% (controls)</td>
</tr>
<tr>
<td>Camara et al., 2004 [105]</td>
<td>Brazil / n. m.</td>
<td>case-control study</td>
<td>hospitalised infants² and controls³</td>
<td>&lt; 2 years of age</td>
<td>n. m.</td>
<td>during hospitalisation regardless of symptoms</td>
<td>20.2% (wheezing infants) 10.0% (controls)</td>
</tr>
<tr>
<td>Van Benten et al., 2003 [64]</td>
<td>Netherlands / VIGALL prospective birth cohort study</td>
<td>high-risk infants¹</td>
<td>at birth</td>
<td>2nd year</td>
<td>during URTI</td>
<td>~ 40%</td>
<td></td>
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<tr>
<td>Souza et al., 2003 [111]</td>
<td>Brazil / n. m.</td>
<td>prospective study</td>
<td>healthy infants</td>
<td>2-24 months of age</td>
<td>n. m.</td>
<td>during symptoms of respiratory illness</td>
<td>48.3%</td>
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<tr>
<td>Blomqvist et al., 2002 [108]</td>
<td>Finland / FinOM prospective study</td>
<td>healthy infants</td>
<td>2 months of age</td>
<td>2nd year</td>
<td>during scheduled visits at 6-12-18-24 months of age (regardless of symptoms)</td>
<td>29%</td>
<td></td>
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<tr>
<td>Nokso-Koivisto et al., 2002 [63]</td>
<td>Finland / FinOM prospective study</td>
<td>healthy infants</td>
<td>2 months of age</td>
<td>2nd year</td>
<td>during acute upper respiratory tract infection</td>
<td>72%</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Design</td>
<td>Group Description</td>
<td>Age Range</td>
<td>Allergen History</td>
<td>Symptom Description</td>
<td>Symptom Incidence</td>
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<tr>
<td>Papadopoulos et al., 2002 [86]</td>
<td>Greece</td>
<td>Prospective Study</td>
<td>Hospitalised infants during acute respiratory infection (bronchiolitis)</td>
<td>&lt; 18 months of age</td>
<td>n. m.</td>
<td>29%</td>
<td></td>
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<tr>
<td>Rakes et al., 1999 [62]</td>
<td>USA</td>
<td>Cross-Sectional Case-Control Study</td>
<td>Hospitalised infants and controls during treatment of respiratory symptoms</td>
<td>&lt; 2 years of age</td>
<td>none</td>
<td>23% (wheezing infants) 25% (controls)</td>
<td></td>
</tr>
</tbody>
</table>

1 infants at high-risk for atopy (defined as at least one parent with a history of doctor-diagnosed asthma, hay fever or eczema); 2 infants hospitalised for respiratory tract infection-associated wheezing; 3 infants hospitalised for any reason unrelated to the respiratory system; RV = Rhinovirus; LRTI = lower respiratory tract infection; URTI = upper respiratory tract infection; n. m. = not mentioned
<table>
<thead>
<tr>
<th>Reference</th>
<th>Country / Cohort</th>
<th>Study type</th>
<th>Study population</th>
<th>Study enrolment</th>
<th>Assessment of RV infections</th>
<th>Age at assessment of wheeze/asthma</th>
<th>Type of assessment of wheeze/asthma</th>
<th>Atopic subjects among asthmatics</th>
<th>Association between RV-induced wheeze and subsequent development of wheeze/asthma [OR (95% CI)]</th>
</tr>
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<tbody>
<tr>
<td>Valkonen et al., 2009 [120]</td>
<td>Finland / n. m.</td>
<td>prospective trial</td>
<td>hospitalised infants&lt;sup&gt;2&lt;/sup&gt;</td>
<td>&lt; 2 years during hospitalisation</td>
<td>1-2-3 years after hospitalisation</td>
<td>doctor diagnosed, use of asthma specific medication</td>
<td>n. m.</td>
<td>wheeze during 1&lt;sup&gt;st&lt;/sup&gt; year: 6.6 (2.6; 16.5), wheeze during 2&lt;sup&gt;nd&lt;/sup&gt; year: 2.9 (1.7; 5.1) wheeze during 3&lt;sup&gt;rd&lt;/sup&gt; year: 3.4 (2.0; 5.7) reference: non-RV-induced wheezing</td>
<td>10.9 (2.5; 43.1)</td>
</tr>
<tr>
<td>Jackson et al., 2008 [110]</td>
<td>USA / COAST</td>
<td>birth cohort study</td>
<td>high-risk infants&lt;sup&gt;1&lt;/sup&gt;</td>
<td>at birth; additional follow-up at age of 3 years</td>
<td>6 years</td>
<td>doctor diagnosed, use of asthma specific medication</td>
<td>58 %</td>
<td>wheeze during 1&lt;sup&gt;st&lt;/sup&gt; year: 2.7 (1.4; 5.3) wheeze during 2&lt;sup&gt;nd&lt;/sup&gt; year: 6.5 (3.1; 13.7) wheeze during 3&lt;sup&gt;rd&lt;/sup&gt; year: 31.7 (10.6; 94.9) reference: asymptomatic RV infections</td>
<td>2.0 (1.0; 4.1)</td>
</tr>
<tr>
<td>Kusel et al., 2007 [119]</td>
<td>Australia/ n. m.</td>
<td>birth cohort study</td>
<td>high-risk infants&lt;sup&gt;1&lt;/sup&gt;</td>
<td>at birth</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; year (during symptoms of respiratory illness)</td>
<td>5 years</td>
<td>doctor diagnosed</td>
<td>~ 60 %</td>
<td>0.9 (0.3; 2.3)</td>
</tr>
<tr>
<td>Kusel et al., 2012 [121]</td>
<td>Australia/ n. m.</td>
<td>birth cohort study</td>
<td>high-risk infants&lt;sup&gt;1&lt;/sup&gt;</td>
<td>at birth</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; year (during symptoms of respiratory illness)</td>
<td>10 years</td>
<td>doctor diagnosed</td>
<td>59.9 %</td>
<td>2.9 (1.2; 7.1)</td>
</tr>
<tr>
<td>Lee et al., 2007 [104]</td>
<td>Canada / CAPP</td>
<td>intervention study</td>
<td>high-risk infants&lt;sup&gt;1&lt;/sup&gt;</td>
<td>prenatally</td>
<td>during scheduled visits at 2 weeks and 4-8-12 months of age (regardless of symptoms)</td>
<td>2 years</td>
<td>doctor diagnosed</td>
<td>n. m.</td>
<td>2.0 (1.0; 3.9)</td>
</tr>
<tr>
<td>Hyvärinen et al., 2005 [118]</td>
<td>Finland / n. m.</td>
<td>prospective trial</td>
<td>hospitalised infants&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1-23 months of age</td>
<td>during scheduled visits at 2 weeks and 4-8-12 months of age (regardless of symptoms)</td>
<td>11 years</td>
<td>see above</td>
<td>90 %</td>
<td>1.4 (0.4; 4.9)</td>
</tr>
<tr>
<td>Lemanske et al., 2005 [112]</td>
<td>USA / COAST</td>
<td>birth cohort study</td>
<td>high-risk infants&lt;sup&gt;1&lt;/sup&gt;</td>
<td>at birth</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; year (scheduled visits at 2-4-6-9-12 months of age and during symptoms of acute respiratory illness)</td>
<td>3 years</td>
<td>questionnaire</td>
<td>n. m.</td>
<td>10 (4.1; 26)</td>
</tr>
<tr>
<td>Finland / n. m.</td>
<td>prospective trial</td>
<td>hospitalised infants</td>
<td>1-23 months of age</td>
<td>during hospitalisation</td>
<td>6 years</td>
<td>questionnaire, use of asthma specific medication, asthma-suggestive symptoms, exercise challenge test</td>
<td>n. m.</td>
<td>4.1 (1.02; 16.7) reference: RV-negative cases</td>
<td></td>
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</tr>
</tbody>
</table>

1 infants at high-risk for atopy; defined as at least one parent with history of doctor-diagnosed asthma, hay fever or eczema; 2 infants hospitalised for respiratory tract infection-associated wheezing; RV = Rhinovirus; OR = Odds ratio; RR = Risk ratio; CI = Confidence interval; n. m. = not mentioned
References

52. Tovey ER, Rawlinson WD. A modern miasma hypothesis and back-to-school asthma exacerbations. Medical hypotheses. 2011 Jan;76(1):113-6.

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